VOLUME ONE

Second Edition

Handbook of Pharmaceutical Manufacturing Formulations

Compressed Solid Products

SARFARAZ K. NIAZI

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Pharmaceutical Scientist, Inc.
Deerfield, Illinois, USA

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Handbook of Pharmaceutical Manufacturing Formulations Second Edition

Volume Series

Sarfaraz K. Niazi

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Handbook of Pharmaceutical Manufacturing Formulations: Compressed Solid Products

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Handbook of Pharmaceutical Manufacturing Formulations: Uncompressed Solid Products

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Handbook of Pharmaceutical Manufacturing Formulations: Semisolid Products

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to the memory of Sidney Riegelman

Preface to the Series—Second Edition

The science and the art of pharmaceutical formulation keeps evolving as new materials, methods, and machines become readily available to produce more reliable, stable, and release-controlled formulations. At the same time, globalization of sourcing of raw and finished pharmaceuticals brings challenges to regulatory authorities and results in more frequent revisions to the current good manufacturing practices, regulatory approval dossier requirements, and the growing need for cost optimization. Since the publication of the first edition of this book, a lot has changed in all of these areas of importance to pharmaceutical manufacturers. The second edition builds on the dynamic nature of the science and art of formulations and provides an evermore useful handbook that should be highly welcomed by the industry, the regulatory authorities, as well as the teaching institutions.

The first edition of this book was a great success as it brought under one umbrella the myriad of choices available to formulators. The readers were very responsive and communicated with me frequently pointing out to the weaknesses as well as the strengths of the book. The second edition totally revised attempts to achieve these by making major changes to the text, some of which include:

1. Complete, revised errors corrected and subject matter reorganized for easy reference. Whereas this series has six volumes differentiated on the basis of the type of dosage form and a separate inclusion of the U.S. OTC products, ideally the entire collection is needed to benefit from the myriad of topics relating to formulations, regulatory compliance, and dossier preparation.
2. Total number of pages is increased from 1684 to 2726.
3. Total number of formulations is expanded by about 30% with many newly approved formulations.
4. Novel formulations are now provided for a variety of drugs; these data are collected from the massive intellectual property data and suggest toward the future trend of formulations. While some of these formulations may not have been approved in the United States or Europe, these do provide additional choices, particularly for the NDA preparation. As always, it is the responsibility of the manufacturer to assure that the intellectual property rights are not violated.
5. A significant change in this edition is the inclusion of commercial products; while most of this information is culled out from the open source such as the FOIA (http://www.fda.gov/foi/default.htm), I have made attempts to reconstruct the critical portions of it based on what I call the generally acceptable standards. The drug companies are advised to assure that any intellectual property rights are not violated and this applies to all information contained in this book. The freedom of information act (FOIA) is an extremely useful conduit for reliable information and manufacturers are strongly urged to make use of this information. Whereas this information is provided free of charge, the process of obtaining the information may be cumbersome, in which case, commercial sources of these databases can prove useful, particularly for the non-U.S. companies.
6. Also included are the new Good Manufacturing Guidelines (2007) with amendments (2008) for the United States and similar updates for European Union and WHO; it is strongly urged that the companies discontinue using all old documents as there are significant changes in the revised form, and many of them are likely to reduce the cost of GMP compliance.
7. Details on design of clean rooms is a new entry that will be of great use to sterile product manufacturers; whereas the design and flow of personnel and material flow is of critical nature, regulatory agencies view these differently and the manufacturer is advised always to comply with most stringent requirements.
8. Addition of a self-auditing template in each volume of the series. While the cGMP compliance is a complex issue and the requirements diversified across the globe, the basic compliance remains universal. I have chosen the European Union guidelines (as these are more in tune with the ICH) to prepare a self-audit module that I recommend that every manufacturer adopt as a routine to assure GMP compliance. In most instances reading the template by those responsible for compliance with keep them sensitive to the needs of GMP.
9. OTC products cross-referenced in other volumes where appropriate. This was necessary since the regulatory authorities worldwide define this class of drug differently. It is important to iterate that regardless of the prescription or the OTC status of a product, the requirements for compliance with the cGMP apply equally.
10. OTC monograph status is a new section added to the OTC volume and this should allow manufacturers to chose appropriate formulations that may not require a filing with the regulatory agencies; it is important to iterate that an approved OTC monograph includes details of formulation including the types and quantities of active drug and excipients, labeling, and presentation. To qualify the exemption, the manufacturer must comply with the monograph in its entirety. However, subtle modifications that are merely cosmetic in nature and where there is an evidence that the modification will not affect the safety and efficacy of the products can be made but require prior approval of the regulatory agencies and generally these approvals are granted.
11. Expanded discussion on critical factors in the manufacturing of formulations provided; from basic shortcuts to smart modifications now extend to all dosage forms. Pharmaceutical compounding is one of the oldest professions and whereas the art of formulations has been

relegated to more objective parameters, the art nevertheless remains. An experienced formulator, like an artist, would know what goes with what and why; he avoids the pitfalls and stays with conservative choices. These sections of the book present advice that is time tested, although it may appear random at times; this is intended for experienced formulators.

12. Expanded details on critical steps in the manufacturing processes provided but to keep the size of the book manageable, and these are included for prototype formulations. The reader is advised to browse through similar formulations to gain more insight. Where multiple formulations are provided for the same drug, it intended to show the variety of possibilities in formulating a drug and whereas it pertains to a single drug, the basic formulation practices can be extended to many drugs of same class or even of diversified classes. Readers have often requested that more details be provided in the Manufacturing Direction sections. Whereas sufficient details are provided, this is restricted to prototype formulations to keep the size of the book manageable and to reduce redundancy.
13. Addition of a listing of approved excipients and the level allowed by regulatory authorities. This new section allows formulators a clear choice on which excipients to choose; the excipients are reported in each volume pertaining to the formulation type covered. The listing is drawn from the FDA-approved entities. For the developers of an ANDA, it is critical that the level of excipients be kept within the range generally approved to avoid large expense in justifying any unapproved level. The only category for which the listing is not provided separately is the OTC volume since it contains many dosage forms and the reader is referred to dosage form–specific title of the series. The choice of excipients forms keeps increasing with many new choices that can provide many special release characteristics to the dosage forms. Choosing correct excipients is thus a tedious exercise and requires sophisticated multivariate statistical analysis. Whereas the formulator may choose any number of novel or classical components, it is important to know the levels of excipients that are generally allowed in various formulations to reduce the cost of redundant exercises; I have therefore included, as an appendix to each volume, a list of all excipients that are currently approved by the U.S. FDA along their appropriate levels. I suggest that a formulator consult this table before deciding on which level of excipient to use; it does not mean that the excipient cannot be used outside this range but it obviates the need for a validation and lengthy justification studies in the submission of NDAs.
14. Expanded section on bioequivalence submission was required to highlight the recent changes in these requirements. New entries include a comprehensive listing of bioequivalence protocols in abbreviated form as approved by the U.S. FDA; these descriptions are provided in each volume where pertinent. To receive approval for an ANDA, an applicant must generally demonstrate, among other things, equivalence of the active ingredient, dosage form, strength, route of administration and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. Bioequivalent drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 U.S.C. 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320. The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-specific BE studies, the U.S. FDA will be issuing product-specific BE recommendations (www.fda.gov/cder/ogd/index.htm). To make this vital information available, an appendix to each volume includes a summary of all currently approved products by the U.S. FDA where a recommendation on conducting bioequivalence studies is made available by the U.S. FDA. When filing an NDA or an ANDA, the filer is faced with the choice of defending the methods used to justify the bioavailability or bioequivalence data. The U.S. FDA now allows application for waiver of bioequivalence requirement; a new chapter on this topic has been added along with details of the dissolution tests, where applicable, approved for various dosage forms.
15. Dissolution testing requirements are included for all dosage forms where this testing is required by the FDA. Surrogate testing to prove efficacy and compliance is getting more acceptance at regulatory agencies; in my experience, a well-designed dissolution test is the best measure of continuous compliance. Coupled with chapters on waivers of bioequivalence testing, this information on dissolution testing should be great value to all manufacturers; it is recommended that manufacturers develop their own in-house specifications, more stringent than those allowed in these listings and the USP.
16. Best-selling products (top 200 prescription products) are identified with an asterisk and a brand name where applicable; in all instances, composition of these products is provided and formulation of generic equivalents. Despite the vast expansion of pharmaceutical sales and shifting of categories of blockbuster drugs, basic drugs affecting gastrointestinal tract, vascular system, and brain remain most widely prescribed.
17. Updated list of approved coloring agents in the United States, Canada, European Union, and Japan is included to allow manufactures to design products for worldwide distribution.
18. Tablet-coating formulations that meet worldwide requirements of color selection are included in the Volume 1 (compressed solids) and Volume 5 (OTC) because these represent the products often coated.
19. Guidelines on preparing regulatory filings are now dispersed throughout the series depending on where these guidelines are more crucial. However, the reader would, as before, need access to all volumes to benefit from the advice and guidelines provided.

As always, comments and criticism from the readers are welcomed and these can be sent to me at Niazi@pharmsci.com or Niazi@niazi.com. I would try to respond to any inquiries requiring clarification of the information enclosed in these volumes.

I would like to express deep gratitude to Sherri R. Niziolek and Michelle Schmitt-DeBonis at Informa, the publisher of

this work, for seeing an immediate value to the readers in publishing the second edition of this book and allowing me enough time to prepare this work. The diligent editing and composing staff at Informa, particularly Joseph Stubenrauch, Baljinder Kaur and others are highly appreciated. Regardless, all errors and omissions remain altogether mine.

In the first edition, I had dedicated each volume to one of my mentors; the second edition continues the dedication to these great teachers.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois, U.S.A.

Preface to the Series—First Edition

No industry in the world is more highly regulated than the pharmaceutical industry because of potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity (amortized over the cost of all molecules racing) to final regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. In the year 2004, it is anticipated that the industry will spend about $20 billion on research and development. The generic market of drugs as the new entities come off patent is one of the fastest growing segments of the pharmaceutical industry, with every major multinational company having a significant presence in this field.

Whereas many stages of new drug development are inherently constrained with time, the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced with appropriate knowledge by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the first major attempt to consolidate the available knowledge about formulations in a comprehensive, and by nature a rather voluminous, presentation.

The book is divided into six volumes, based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and OTC products. The separation of OTC products even though they may easily fall into one of the other five categories is made to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of product, and of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of products into these six categories.

Each volume includes a description of regulatory filing techniques for the formulations described. Also included are the current regulatory guidelines on cGMP compliance specific to the dosage form. Advice is offered on how to scale up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and cut the race to file short by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a close paradigm when it comes to selecting formulations—"not invented here" perhaps reigns in the mind of many seasoned formulations scientists subconsciously when they prefer to choose only a certain platform for development. It is expected that with the quick review of possibilities available to formulate made available in this book, scientists will benefit from the experience of others.

For the teachers of formulation sciences, this series offers a wealth of information. Whether it is a selection of a preservative system or the choice of a disintegrant, the series offers a wide choice to study and rationalize.

Many have assisted me in the development of this work that has taken years to compile, and I thank scores of my graduate students and colleagues for their help. A work of this size cannot be produced without errors, although I hope that these errors do not distract the reader from the utility of the book. I would sincerely appreciate if readers point out these mistakes for corrections in future editions.

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Preface to the Volume—First Edition

Compressed solids present one of the greatest challenges to formulation scientists, as they offer remarkable marketing opportunities to marketers. A solid oral dosage form is easy to ingest, is relatively more stable than other dosage forms (longer shelf life), and with it, opportunities to design delivery profiles to meet specific therapeutic requirements are offered. As a result, almost two-thirds of all dosage forms fall into this category. The challenge in formulating these products includes finding an optimum medium of compromises that will ensure releases of an active drug at the most desired and consistent rate. The formulation components and process of manufacturing thus take pivotal importance. As a result, the formulations provided in this volume offer a rare opportunity for formulators to start with an optimal composition. Described in this volume are formulations for over 200 of the most widely used drugs for all types of release profiles.

The most significant issues in the formulation of compressed solids are related to bioequivalence. Over the past quarter of a century, the science of evaluating equivalence of products has taken a greater emphasis on testing in human subjects. Although they are expensive to conduct, such trials are now routine, requiring frequent evaluation during the development phases and before marketing new entities. Most frequently, trials are required when establishing generic equivalences. The U.S. FDA may require additional biostudies if there is a change in the manufacturing site or even a change in the specification of a raw material. This aspect of formulation development clearly differentiates the compressed solids category; as a result, chapter 1 in the book deals with the guidelines for bioavailability and bioequivalence testing of pharmaceutical products. Noteworthy are the changes proposed in this guideline from what is the currently accepted methodology; for example, what was long considered necessary, the multiple-dose studies of modified release products, will yield to single-dose studies, which are considered more discriminating. The manufacturers are particularly reminded to understand the changes in the requirements of bioavailability and bioequivalence studies that are on the horizon.

The formulation of compressed solids involves a highly intricate series of events, from the characterization of the active pharmaceutical ingredient, to the choice of excipients, to the selection of processing, compression, and coating equipment and packaging systems appropriate for the specific drug and the dosage form. In chapter 2 of this volume, we highlight what the manufacturers need to be aware of in establishing a manufacturing process based on the formulations presented.

In other volumes of this series, details are provided on various other issues that pertain to the manufacturing of compressed solids, including validation issues, compliance with cGMP, laboratory guidelines, etc. The reader is referred to the other volumes for further understanding of the subject matter.

Compressed solids or tablets are usually applied with coatings, mainly aqueous film coatings, for many reasons, from aesthetics to imparting higher physical–chemical stability. Coating technology is a separate science. Fortunately, the major suppliers of equipment, such as Accela-Cota® and Glatt® and coating materials such as Colorcon® and Röhm®, are very helpful in establishing coating parameters and choosing the right coating materials and formulations. A large number of coating formulations are listed in a separate section in this book, including sugar coating, film coating, and enteric coatings. With such a wide variety available, coating steps are omitted from all formulations where coating is recommended. Instead, the reader is referred to the appropriate section of the book to make an appropriate choice.

The formulations are presented with a scale for each unit, per tablet; and quantities are expressed for 1000 tablets. It is customary for manufacturers to scale formulas for a specific weight, such as 100 or 1000 kg, to match mixing vessel requirements. This can be done roughly by multiplying the weight of each tablet by the quantity desired to calculate the size of the batch. Remember that the actual yield may be different because of differences in the scale and quantity, due to differences in the chemical forms of the drugs used, excesses added, and losses of moisture during manufacturing. Further, the adjustment of quantity based on the potency of the raw material, where pertinent, changes the quantity requirements.

A distinctive feature of this volume is the identification and inclusion of the most popular prescription products. The 200 most widely prescribed drugs (by brand name) are marked with a bracketed number to indicate their rankings. These data are derived from over 3 billion prescriptions filled during 2002 in the United States, comprising the majority of the U.S. prescription market. Because in some instances more than one brand name is prescribed, only the top brand is listed; therefore, the total number of chemical equivalents is less than 200. The compressed solids represent more than an 80% share of this list, therefore expounding the need to elaborate this list in this particular volume. Obviously, for a generic manufacturer, it would be advantageous to enter the market with products that have a wide market, not necessarily the largest margin, and this list will further help in the selection of products. It is noteworthy that in the preparation of an ANDA (Abbreviated New Drug Application), it is important for both regulatory and scientific reasons to keep the selection of excipients as close as possible to the innovator's product. The listing provided here includes every excipient used in the innovator listing. Whereas, in most instances, sufficient details are provided to assist in the formulation of a generic equivalent with exact quantities of excipients and conditions appropriate for processing, the examples provided for other drugs of similar types should be sufficient for an astute formulator to quickly develop these formulations. However, should there be a need for assistance in finalizing

the formulation, the reader is invited, without any obligation, to write to the author at niazi@pharmsci.com.

I am grateful to CRC Press for taking this lead in publishing what is possibility the largest such work in the field of pharmaceutical products. It has been a distinct privilege to have known Mr. Stephen Zollo, the senior editor at CRC Press, for many years. Stephen has done more than any editor can to encourage me to complete this work on a timely basis. The editorial assistance provided by the CRC Press staff was exemplary, particularly the help given by Erika Dery, Joette Lynch, and others at CRC Press. Although much care has gone into correcting errors, any errors remaining are altogether mine. I would appreciate it if the readers bring these errors to my attention so that they can be corrected in future editions of this volume (niazi@pharmsic.com).

This book is dedicated to Sidney Riegelman, who was born July 19, 1921, in Milwaukee, Wisconsin. He attended the University of Wisconsin, graduating with a Bachelor of Science degree in pharmacy in 1944 and a Ph.D. in pharmacy in 1948. Following his graduate work, Sid joined the faculty of the School of Pharmacy at the University of California at San Francisco. In 1958, Sid published a series of papers with graduate student Wilfred Crowell, which appeared in the scientific edition of the *Journal of the American Pharmaceutical Association* under the major heading of "The Kinetics of Rectal Absorption." For these studies, Sid was awarded the Ebert Prize in 1959, which recognized Sid's publications as the best work published in the journals of the American Pharmaceutical Association during the year 1958. Sid's contributions to pharmaceutical sciences, particularly in the field of pharmacokinetics, earned him a revered place in the profession. On April 4, 1981, Sid drowned while scuba diving with his wife at Salt Point, California, a coastal area just north of San Francisco. At the University of California, a plaque is dedicated to Sid "by his graduate students, who honor his scientific achievements and excellence, his inspirations and contagious enthusiasm in research and teaching. We shall always remember Sid as our mentor, scientific father and most importantly, as our beloved friend and confidant."

I had the distinct privilege, both during my graduate studies and later as a faculty member teaching biopharmaceutics and pharmacokinetics, to interact with Sid. When my book, *Textbook of Biopharmaceutics and Clinical Pharmcokinetics*, was published, Sid called to congratulate me. It was like receiving a call from God—that is how he was revered in the profession. I remember vividly how he would argue in seminars while appearing to be dozing off during the presentation. Sid was a giant: a scientist, a scholar, and, above all, a loving human being. When a professional crisis arose, I called Sid for advice. Instead of telling me what I should do, Sid told me a story about his childhood: "Sarf, my brother was much stronger than I and every time he would run into me, he would take a jab at me, and when I would return his jab, he would knock me down. I complained about this to my father, and my father advised me not to return the jabs. My brother became so frustrated, he started jabbing others." I have never forgotten his advice.

Sarfaraz K. Niazi, Ph.D.
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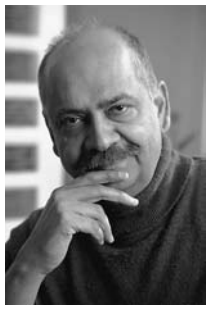
About the Author



Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 35 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents in the field of drug and dosage form delivery systems; he is also licensed to practice law before the U.S. Patent and Trademark Office. Having formulated hundreds of products from the most popular consumer entries to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science and art of formulating and regulatory filings of investigational new drugs (INDs) and new drug applications (NDAs). Dr. Niazi advises the pharmaceutical industry internationally on issues related to formulations, cGMP compliance, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (http://www.pharmsci.com). He can be contacted at Niazi@pharmsci.com

Contents

Part I

Regulatory and Manufacturing Considerations

1

Bioequivalence Testing Rationale and Principles

I. BACKGROUND

The bioavailability of a drug is controlled by three factors, namely:

- the rate and extent of release of the drug from the dosage form,
- its subsequent absorption from the solution state, and
- the biotransformation during the process of absorption.

In all quantitative determinations of bioavailability, concentration is measured in blood, plasma, and urine. Plasma concentrations following the oral administration of a drug assume four sequential phases depending on the magnitude of absorption and elimination:

1. Absorption > elimination
2. Absorption = elimination
3. Absorption < elimination
4. Absorption = elimination = 0

The shape of the plasma concentration profile depends on the relative rates of absorption and elimination and thus, the plasma concentration profiles may be quite different with different routes of administration. Intravenous and sometimes intramuscular routes yield an early peak due to fast or almost instantaneous absorption, whereas oral, subcutaneous, rectal, and other routes may show delayed peaks due to slower rates of absorption. It should be noted that the rate of elimination is considered constant since it depends primarily in the specific nature of the active drug ingredient.

The purpose of bioavailability studies is to demonstrate therapeutic equivalence. However, depending on the mechanism of action, more meaningful comparisons can be made from such parameters as peak plasma concentration or the time to reach peak plasma concentration. For example, in the case of antibiotics, it is important to know how soon the minimum inhibitory concentration is reached and maintained. The choice of single-dose versus multiple-dose study depends on the mechanism of drug action. For example, antidepressants like imipramine show delayed action, a characteristic of many psychotropic and antihypertensive agents. In these instances, a new product should be judged for its quality from repeated administration because in these examples the peak concentration or time for peak concentration is relatively unimportant. It is therefore important to isolate the clinically important parameter, but in all instances, the AUC must be monitored since it represents the proportionality to the total amount of drug eliminated from the body and hence absorbed.

The estimation of bioavailability from plasma concentration profiles requires a thorough understanding of the nature of plasma level profiles. For example, a higher or earlier peak does not necessarily mean greater overall absorption than from a product giving a smaller or delayed peak. The total absorption of drugs is, therefore, proportional not only to the plasma concentrations achieved but also to the length of time these concentrations persist in the blood. One parameter that characterizes this aspect is the area under the plasma concentration versus time profile.

The major contribution to the area under the curve (AUC) for a fast-absorbed formulation is due to the high, peak concentration; whereas for a slowly absorbed formulation, the area is mainly because of sustained or prolonged plasma concentration. It should be noted that the area under the plasma concentration versus time profile is only proportional to the total amount of drug absorbed and cannot be used to determine the actual amount of drug administered unless it is compared with a known standard, whereby the extent of absorption is either measured by other methods or assumed to be 100%, as in the case of intravenous administration.

The in vivo bioavailability of a drug product is measured if the product's rate and extent of absorption, as determined by comparison of measured parameters, for example, concentration of the active drug ingredient in the blood, urinary excretion rates, or pharmacological effects, do not indicate a significant difference from the reference material's rate and extent of absorption. For drug products that are not intended to be absorbed into the bloodstream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredient or active moiety becomes available at the site of action.

Statistical techniques used in establishing bioequivalence shall be of sufficient sensitivity to detect differences in rate and extent of absorption that are not attributable to subject variability.

A drug product that differs from the reference material in its rate of absorption, but not in its extent of absorption, may be considered to be bioavailable if the difference in the rate of absorption is intentional, is appropriately reflected in the labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug product.

Two drug products will be considered bioequivalent drug products if they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the active moiety under similar experimental conditions, either single dose or multiple dose. Some pharmaceutical equivalents or pharmaceutical alternatives may be equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on chronic use, and are considered medically insignificant for the particular drug product studied.

II. EVIDENCE TO MEASURE BIOEQUIVALENCE

In vivo bioequivalence may be determined by one of several direct or indirect methods. Selection of the method depends

upon the purpose of the study, the analytical method available, and the nature of the drug product. Bioequivalence testing should be conducted using the most appropriate method available for the specific use of the product.

The preferred hierarchy of bioequivalence studies (in descending order of sensitivity) is the blood-level study, pharmacologic end-point study, and clinical end-point study. When absorption of the drug is sufficient to measure drug concentration directly in the blood (or other appropriate biological fluids or tissues) and systemic absorption is relevant to the drug action, then a blood (or other biological fluid or tissue) level bioequivalence study should be conducted. The blood-level study is generally preferred above all others as the most sensitive measure of bioequivalence. The sponsor should provide justification for choosing either a pharmacologic or clinical end-point study over a blood-level (or other biological fluids or tissues) study.

When the measurement of the rate and extent of absorption of the drug in biological fluids cannot be achieved or is unrelated to drug action, a pharmacologic end-point (i.e., drug-induced physiologic change which is related to the approved indications for use) study may be conducted. Lastly, in order of preference, if drug concentrations in blood (or fluids or tissues) are not measurable or are inappropriate, and there are no appropriate pharmacologic effects that can be monitored, then a clinical end-point study may be conducted, comparing the test (generic) product to the reference (pioneer) product and a placebo (or negative) control.

Bioavailability may be measured or bioequivalence may be demonstrated by several in vivo and in vitro methods. FDA may require in vivo or in vitro testing, or both, to measure the bioavailability of a drug product or establish the bioequivalence of specific drug products. Information on bioequivalence requirements for specific products is included in the current edition of FDA's publication "Approved Drug Products with Therapeutic Equivalence Evaluations" and any current supplement to the publication. The selection of the method used to meet an in vivo or in vitro testing requirement depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. The following in vivo and in vitro approaches, in descending order of accuracy, sensitivity, and reproducibility, are acceptable for determining the bioavailability or bioequivalence of a drug product:

- An in vivo test in humans in which the concentration of the active ingredient or active moiety, and when appropriate, its active metabolite(s), in whole blood, plasma, serum, or other appropriate biological fluid is measured as a function of time. This approach is particularly applicable to dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution within the body.
- An in vitro test that has been correlated with and is predictive of human in vivo bioavailability data.
- An in vivo test in humans in which the urinary excretion of the active moiety, and when appropriate, its active metabolite(s), is measured as a function of time. The intervals at which measurements are taken should ordinarily be as short as possible so that the measure of the rate of elimination is as accurate as possible. Depending on the nature of the drug product, this approach may be applicable to highly metabolized drugs. This method is not appropriate where urinary excretion is not a significant mechanism of elimination.
- An in vivo test in humans in which an appropriate acute pharmacological effect of the active moiety, and when appropriate, its active metabolite(s), is measured as a function of time if such effect can be measured with sufficient accuracy, sensitivity, and reproducibility. This approach is applicable only when appropriate methods are not available for measurement of the concentration of the moiety, and when appropriate, its active metabolite(s), in biological fluids or excretory products but a method is available for the measurement of an appropriate acute pharmacological effect. This approach may be particularly applicable to dosage forms that are not intended to deliver the active moiety to the bloodstream for systemic distribution.
- Well-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. This approach is the least accurate, sensitive, and reproducible of the general approaches for measuring bioavailability or demonstrating bioequivalence. For dosage forms intended to deliver the active moiety to the bloodstream for systemic distribution, this approach may be considered acceptable only when analytical methods cannot be developed to permit use of one of the approaches outlined above are not available. This approach may also be considered sufficiently accurate for measuring bioavailability or demonstrating bioequivalence of dosage forms intended to deliver the active moiety locally, for example, topical preparations for the skin, eye, and mucous membranes; oral dosage forms not intended to be absorbed, for example, an antacid or radiopaque medium; and bronchodilators administered by inhalation if the onset and duration of pharmacological activity are defined.
- A currently available in vitro test acceptable to FDA (usually a dissolution rate test) that ensures human in vivo bioavailability.
- Any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence.

FDA may require in vivo testing in humans of a product at any time if the agency has evidence that the product

- may not produce therapeutic effects comparable to a pharmaceutical equivalent or alternative with which it is intended to be used interchangeably,
- may not be bioequivalent to a pharmaceutical equivalent or alternative with which it is intended to be used interchangeably, or
- has greater than anticipated potential toxicity related to pharmacokinetic or other characteristics.

A list of therapeutic, pharmacokinetic, and physicochemical factors has been compiled to classify which product needs demonstration of bioequivalence by in vivo testing (Table 1.1). A large number of drugs have been classified in this category (Table 1.2). All enteric-coated and -controlled release dosage forms of any solid oral dosage form require in vivo bioavailability testing. It is generally suggested that if there is more than 25% intrabatch or batch-to-batch variability in bioavailability is observed, in vivo tests will be required for batch certification. Any changes in the manufacturing process, including product formulation or dosage strength change, beyond that suggested in the NDA or ANDA and changes in labeling for a new indication or new dosage regimen also require in vivo bioavailability testing.

The pharmacotherapeutic nature of the drug plays an important role in the regulations regarding its bioavailability.

Table 1.1 Factors Determining the Establishment of Biequivalence Requirement by the FDA

1. Therapeutic factors evidence from
   a. clinical trials,
   b. controlled observations on patients, and
   c. well-controlled bioequivalence studies that
      i. the drug exhibits a low therapeutic ratio,
      ii. the drug requires careful dosage titration, and
      iii. bioinequivalence would produce adverse prophylacitc or therapeutic effects.
2. Pharmacokinetic factors evidence that the drug entity
   a. is absorbed from localized sites in the gastrointestinal tract,
   b. is subject to poor absorption,
   c. is subject to first-pass metabolism,
   d. requires rapid dissolution and absorption for effectiveness,
   e. is unstable in specific portions of the gastrointestinal tract, and
   f. is subject to dose-dependent kinetics in or near the therapeutic range.
3. Physiochemical factors evidence that the drug
   a. possesses low solubility in water or gastric fluids,
   b. is dissolved slowly from one or more of its dosage forms,
   c. particle size and/or surface area affects bioavailability,
   d. exhibits certain physical-structural characteristics e.g., polymorphism, solvates, etc. which modify its bioavailability,
   e. has a high ratio of excipients to active ingredients as formulated, and
   f. has a bioavailability which may be affected by the presence or absence of hydrophilic or hydrophobic excipients and lubricant.

Drugs which exhibit narrow therapeutic index, that is, less than a twofold difference in median lethal dose and median effective dose values (or less than a twofold difference in the minimum effective concentration and minimum toxic concentration in the blood), require careful demonstration of bioavailability and the consistency with which this requirement is met. Further consideration is needed in the type of side effects occurring if a toxic level is reached. For example, the therapeutic index (the U.S. FDA prefers to call this therapeutic range) for salicylates is smaller than cardiac glycosides; it does not mean that cardiac glycosides are less toxic. It merely signifies that the concentration of salicylates for therapeutic response is closer to the concentration where undesirable side effects start to appear. Another consideration along the same line is the potency of drug in question. Generally, highly potent drugs will require greater control of bioavailability than the one with lesser potency. Because of the logarithmic nature of the response, the curves flatten out at low and high doses. Thus a highly potent drug used in large doses will show lesser variability in response due to bioavailability factor than a low-potency drug used at a dose level where the response is log-linear. Any such comparison, however, should take into account the relative nature of the slope of the response to dose.

Table 1.2 Drugs with Potential Bioequivalency Problems

Acetazolamide	Hydrofluemthiazide	Propylthiouracil
Acetyldigitoxin	Imipramine	Pyrimethamine
Alseroxylon	Isoproterenol	Quinethiazide
Aminophyllin	Liothyronine	Quinidine
Aminosalicylic acid	Menadione	Rauwolfia serpentina
Bendrolflumethiazide	Mephenytoin	Rescinnamine
Benzthiazide	Methazolamide	Reserpine
Betamethasone	Methyclothizaide	Salicylazosulfapyridine
Bishydroxycoumarin	Methylprednisolone	Sodium sulfoxone
Chlorambucil	Methyltestosterone	Spironolactone
Chlorodiazepoxide	Nitrofurantoin	Sulfadiazine
Chloropromazine	Oxtriphylline	Sulfadimethoxine
Chlorothiazide	Para-aminosalicylic acid	Sulfamerazine
Cortisone acetate	Para-methadione	Sulfaphenazole
Deserpidine	Perphenazine	Sulfasomidine
Dexamethasone	Phenacemide	Sulfasoxazole
Dichlorphenamide	Phensuximide	Theophylline
Dienestrol	Phenylaminosalicylate	Thioridazine
Diethylstilbestrol	Phenytoin	Tolbutamide
Dyphylline	Pheytonadione	Triamcinolone
Ethinyl estradiol	Polythiazide	Trichlormethiazide
Ethosuxmide	Prednisolone	Triethyl melamine
Ethotoin	Primidone	Trifluoperazine
Ethoxzolamide	Probenecid	Triflupromazine
Fludrocortisone	Procainamide	Trimeprazine
Fluphenazine	Prochlorperazine	Trimethadione
Fluprednisolone	Promazine	Uracil mustand
Hydralazine	Promethazine	Warfarin
Hydrochlorothiazide		

The physicochemical evidence needed to establish a bioequivalence includes low water solubility, for example, less than 5 mg/mL, or if dissolution in the stomach is critical to absorption, the volume of gastric fluids required to dissolve the recommended dose (gastric fluid content is assumed to be 100 mL for adults and is prorated for infants and children). The dissolution rates are also taken into consideration if less than 50% of the drug dissolves in 30 minutes using official methods. Also included under physicochemical evidence are particle size and surface area of the active drug ingredient. Certain physical structural characteristics of the active drug ingredient, for example, polymorphism, solvation, etc., are also considered. Drug products which have a high ratio of excipients to active ingredients (e.g., greater than 5:1) may also be subjected to bioequivalency demonstration. Other evidence includes specific absorption sites or where the available dose is less than 50% of an administered dose. Drugs which are rapidly biotransformed in the intestinal wall or liver during absorption, and drugs which are unstable in specific portions of the gastrointestinal tract requiring special coating or formulations, are also subjected to bioequivalency requirements, as are drugs which show dose-dependent absorption, distribution, biotransformation, or elimination.

For some dosage forms, bioequivalency requirements can be waived such as with topical products, oral dosage forms not intended for absorption, inhalations, and solutions if there is sufficient evidence that the inactive ingredients do not affect the release and delivery of drugs from the dosage form.

III. PIVOTAL PARAMETERS FOR BLOOD-LEVEL BIOEQUIVALENCE

The sponsor is encouraged to calculate parameters using formulas which involve only the raw data (i.e., so-called model-independent methods).

A. Area Under the Curve Estimates

The extent of product bioavailability is estimated by the area under the blood concentration versus time curve (AUC). AUC is most frequently estimated using the linear trapezoidal rule. Other methods for AUC estimation may be proposed by the sponsor and should be accompanied by appropriate literature references during protocol development. For a single-dose bioequivalence study, AUC should be calculated from

time 0 (predose) to the last sampling time associated with quantifiable drug concentration AUC (0–LOQ). The comparison of the test and reference product value for this noninfinity estimate provides the closest approximation of the measure of uncertainty (variance) and the relative bioavailability estimate associated with AUC (0–INF), the full extent of product bioavailability. The relative AUC values generally change very little once the absorption of both products has been completed. However, because of the possibility of multifunctional absorption kinetics, it cannot always be determined when the available drug has been completely absorbed. Therefore, FDA recommends extending the duration of sampling until such time that AUC (0–LOQ)/AUC (0–INF) = 0.80. Generally, the sampling times should extend to at least 3 multiples of the drug's apparent terminal elimination half-life, beyond the time when maximum blood concentrations are achieved.

AUC (0–INF) should be used to demonstrate that the concentration time curve can be quantitated such that AUC (0–LOQ)/AUC (0–INF) $>=$ 0.80. The method for estimating the terminal elimination phase should be described in the protocol and the final study report. The AUC (0–LOQ)/AUC (0–INF) is calculated to determine whether AUC (0–LOQ) adequately reflects the extent of absorption.

The sponsor should consult with FDA if AUC (0–LOQ)/AUC (0–INF) is determined to be <0.80. If AUC (0–LOQ)/AUC (0–INF) is <<0.80, then a multiple-dose study to steady state may be needed to allow an accurate assessment of AUC (0–INF) (where AUC (0–INF) = AUC (0–t) at steady state and t is the dosing interval).

In a multiple-dose study, the AUC should be calculated over one complete dosing interval AUC (0–t). Under steady-state conditions, AUC (0–t) equals the full extent of bioavailability of the individual dose AUC (0–INF) assuming linear kinetics. For drugs which are known to follow nonlinear kinetics, the sponsor should consult with FDA to determine the appropriate parameters for the bioequivalence determination.

IV. RATE OF ABSORPTION

The rate of absorption will be estimated by the maximum observed drug concentration (C_{max}) and the corresponding time to reach this maximum concentration (T_{max}). When conducting a steady-state investigation, data on the minimum drug concentrations (trough values) observed during a single dosing interval (C_{min}) should also be collected. Generally, three successive C_{min} values should be provided to verify that steady-state conditions have been achieved. Although C_{min} most frequently occurs immediately prior to the next successive dose, situations do occur with C_{min} observed subsequent to dosing. To determine a steady-state concentration, the C_{min} values should be regressed over time and the resultant slope should be tested for its difference from zero.

V. DETERMINATION OF PRODUCT BIOEQUIVALENCE

Unless otherwise indicated by FDA during the protocol development for a given application, the pivotal bioequivalence parameters will be C_{max} and AUC (0–LOQ) (for a single-dose study) or AUC (0–t) (for a multiple-dose study). To be indicative of product bioequivalence, the pivotal metrics should be associated with confidence intervals which fall within a set of acceptability limits.

The sponsor and FDA should agree to the acceptable bounds for the confidence limits for the particular drug and formulation during protocol development. If studies or literature demonstrate that the pioneer drug product exhibits highly variable kinetics, then the generic drug sponsor may propose alternatives to the generally acceptable bounds for the confidence limits. T_{max} in single-dose studies and C_{min} in multiple-dose studies will be assessed by clinical judgment.

VI. ERRORS IN BE STUDIES

Erroneous conclusions can easily be made if the logic behind bioavailability studies is not clearly understood. The following are the important highlights of the most common errors:

1. When concentrations are monitored in the biologic fluids, the specificity of the assay methods is of utmost importance. This is especially applicable to single-dose studies in which small concentrations should be monitored in order to allow study of the complete elimination of the drug from the body.
2. It is generally assumed that the absorption rates of drugs are higher than the rates of elimination, but there can be exceptions, in which case the terminal plasma concentration profiles would represent both the absorption and elimination processes and the mathematical/statistical models used should take this into account.
3. The extrapolation of plasma or urinary concentration data to compensate for missing experimental points always introduces some error in the calculations; it is desirable to extend the study to at least three elimination half-lives when plasma concentration is monitored, and for at least seven half-lives when monitoring urinary excretion of drugs to estimate their bioavailability.
4. There is often lack of sufficient data points to characterize the plasma concentration profiles. Significant area can be lost if sufficient points are not collected during the peaking of the concentration. In general, there should be at least three data points before the peak occurs and at least four or five values after the peak, if possible.
5. The variation among individuals in the elimination rates of a drug should be considered. The proportionality between AUC and bioavailability is based on the assumption that the elimination rates are invariant; any deviation from the norm will result in significant error. Correction of this error can be made if the elimination rate constants are calculated for each subject and the AUC is corrected. If a drug is eliminated fast, K will be large, accounting for possible underestimation of the AUC.
6. Comparison of data for different studies which may not be well matched in terms of the characteristics of the subject population, study conditions, or routes of drug administration should be made with due consideration to these factors. It is ironic that such cross-study comparisons are both very common and very misleading.
7. When identical drug concentrations are obtained in the plasma following administration of equimolar doses from different formulations, these formulations are considered bioequivalent and the principle is referred to as the superimposition principle. In using this principle, one must choose a number of subjects in accordance with the statistical criteria which will demonstrate at least 20% differences in the means of values in order to make them clinically significant. This criterion can be applied to the concentration

at each sampling time, to the peak concentration, and to the time of the peak concentrations and the AUCs.

8. It should be noted that just because a drug product meets compendial standards of purity and other criteria, its bioavailability is not assured. In fact, compendial requirements fall far short of assuring the efficiency of dosage forms in releasing drugs. The latest edition of USP and NF requires demonstration of sufficient dissolution for many drugs where evidence of dissolution affecting bioavailability has been suggested. A large number of drugs remain to be included in this list and it is hoped that eventually demonstration of bioavailability will become a compendial requirement. The costs of performing bioavailability studies make such requirements impractical for some drugs. However, without such requirements it is difficult to justify the rejection of a product on the grounds that its chemical equivalence varies by more than 10%, when its biologic equivalent is allowed to vary to any degree.

VII. ABSORPTION PROFILING

The following are factors and oral drugs/drug products that should be considered when requesting a waiver of evidence of in vivo bioavailability or bioequivalence documentation. Generally, both in vivo and in vitro testing are necessary for orally administered drug products. In vivo testing is required for all generic drug products with certain exceptions. Based on scientific information, regulatory authorities may waive the requirement for bioavailability or bioequivalence.

1. For certain formulations and under certain circumstances, equivalence between two pharmaceutical products may be considered self-evident and no further documentation is required. For example:
   a. When multisource pharmaceutical or generic products are to be administered parenterally (e.g., intravenous, intramuscular, subcutaneous, intrathecal administration) as aqueous solutions and contain the same active substance(s) in the same concentration and the same excipients in comparable concentrations.
   b. When multisource pharmaceutical or generic products are solutions for oral use, contain the active substance in the same concentration, and do not contain an excipient that is known or suspected to affect gastrointestinal transit or absorption of the active substance.
   c. Gas-based multisource pharmaceutical or generic products.
   d. When the multisource pharmaceutical or generic products are powders for reconstitution as a solution and the solution meets either criterion (a) or criterion (b) above.
   e. *When multisource pharmaceutical or generic products are otic or ophthalmic products prepared as aqueous solutions, containing the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations.
   f. *When multisource pharmaceutical or generic products are topical products prepared as aqueous solutions, containing the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations.
   g. *When multisource pharmaceutical or generic products are inhalation or nasal spray products, tested to be administered with or without essentially the same device, prepared as aqueous solutions, and containing the same active substance(s) in the same concentration and essentially the same excipients in comparable concentrations. Special in vitro testing should be required to document comparable device performance of the multisource inhalation product.
2. In the event the applicant cannot provide this information about the reference product and the drug regulatory authority does not have access to these data or the data is protected under data exclusivity rights according to local regulations, in vivo studies should be performed.
3. For certain drug products, bioavailability or bioequivalence may be demonstrated by evidence obtained in vitro in lieu of in vivo data. Regulatory authorities should waive the requirement for the submission of evidence obtained in vivo demonstrating the bioavailability of the drug product if the drug product meets one of the following criteria:
   a. The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product manufactured at the same site for which the same manufacturer has obtained approval and the following conditions are met:
   b. The bioavailability of this other drug product has been demonstrated;
   c. Both drug products meet an appropriate in vitro test approved by a drug regulatory authority and/or accepted reference pharmacopeias, or has demonstrated in vivo–in vitro correlation (e.g., correlation level A, etc.).
   d. The applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients. That is, the ratio of active ingredients and excipients between strengths is essentially the same.
   e. The drug product is a reformulated product that is identical, except for a different color, flavor, or preservative that could not affect the bioavailability of the reformulated product, to another drug product for which the same manufacturer has obtained approval and the following conditions are met:
   f. The bioavailability of the other product has been demonstrated;
   g. Both drug products meet an appropriate in vitro test approved by the regulatory authority.
   h. Regulatory authorities, for good cause, may require evidence of in vivo bioavailability or bioequivalence for any drug product if the agency determines that any difference between the drug product and a listed drug may affect the bioavailability or bioequivalence of the drug product. The Bioavailability and Bioequivalence Working Group strongly recommends that in the case of antiretroviral drug products proof of pharmaceutical equivalence and bioequivalence be required to infer therapeutic equivalence.

VIII. PHARMACOKINETIC MEASURES OF SYSTEMIC EXPOSURE

Direct (e.g., rate constant, rate profile) and indirect (e.g., C_{max}, T_{max}, mean absorption time, mean residence time, C_{max}

*For elements (e), (f), and (g) above, it is incumbent upon the applicant to demonstrate that the excipients in the multisource product are essentially the same and in comparable concentrations as those in the reference product.

normalized to AUC) pharmacokinetic measures are limited in their abilities to assess rate of absorption. This guideline, therefore, recommends a change in focus from these direct or indirect measures of absorption rate to measures of systemic exposure. The C_{max} and AUC values can continue to be used as measures for product quality BA and BE, but more in terms of their capacity to assess exposure than their capacity to reflect the rate and extent of absorption. Reliance on systemic exposure measures should reflect comparable rates and extents of absorption, which, in turn, should achieve the underlying statutory and regulatory objective of ensuring comparable therapeutic effects. Exposure measures are defined relative to early, peak, and total portions of the plasma, serum, or blood concentration–time profile.

A. Early Exposure

For orally administered immediate-release drug products, BE may generally be demonstrated by measurements of peak and total exposure. An early exposure measure may be informative on the basis of appropriate clinical efficacy and safety trials or pharmacokinetic and pharmacodynamic studies that call for better control of drug absorption into the systemic circulation (e.g., to ensure rapid onset of an analgesic effect or to avoid an excessive hypotensive action of an antihypertensive). In this setting, the guidance recommends use of partial AUC as an early exposure measure. The partial area should be truncated at the population median of T_{max} values for the reference formulation. At least two quantifiable samples should be collected before the expected peak time to allow adequate estimation of the partial area.

B. Peak Exposure

Peak exposure should be assessed by measuring the peak drug concentration (C_{max}) obtained directly from the data without interpolation.

C. Total Exposure

For single-dose studies, the measurement of total exposure should be as follows:

- Area under the plasma/serum/blood concentration–time curve from time 0 to time t (AUC_{0-t}), where t is the last time point with measurable concentration for individual formulation.
- Area under the plasma/serum/blood concentration–time curve from time 0 to time infinity ($AUC_{0-\infty}$), where $AUC_{0-\infty} = AUC_{0-t} + C_t/l_z$, C_t is the last measurable drug concentration, and l_z is the terminal or elimination rate constant calculated according to an appropriate method; the terminal half-life ($t_{1/2}$) of the drug should also be reported.

For steady-state studies, the measurement of total exposure should be the area under the plasma, serum, or blood concentration–time curve from time 0 to time t over a dosing interval at steady state (AUC_{0-t}), where t is the length of the dosing interval.

IX. STATISTICAL ANALYSIS

The statistical models used in the evaluation of BE data have been evolving over the past few decades. The standard statistical method of null hypothesis were the first to be used where no difference is proved and rejection of null indicates statistically significant different ($p < 0.05$). A problem arises since small differences with $p < 0.05$ may be unimportant and large differences with $p > 0.05$ may be important. This prompted FDA to solve the problem by requesting power analysis confidence interval test of Schuirman where two one-sided comparisons are made; this also evolved in the use of the famous 75 to 125 rule to deal with individual effects.

FDA advocates the use of 90% confidence intervals, as the best available method for evaluating bioequivalence study data. The confidence interval approach should be applied to the individual parameters of interest (e.g., AUC and C_{max}). The sponsor may use untransformed or log-transformed data. However, the choice of untransformed or log-transformed data should be made by the sponsor with concurrence by FDA prior to conducting the study.

X. UNTRANSFORMED DATA

If we let T_1 be the mean for the test drug in period 1, T_2 the mean for the test drug in period 2, and R_1 and R_2 the respective means for the reference drug, then the estimates for the drugs averaged over both periods are $T = (1/2)(T_1 + T_2)$ for the test drug and $R = (1/2)(R_1 + R_2)$ for the reference drug. Although both sequence groups usually start with the same number of animals, the number of animals in each sequence group (n_A and n_B) that successfully finish the study may not be equal. The formulas above utilize the marginal or least squares estimates of μT and μR, the corresponding means in the target population. These means are not a function of the sample size in each sequence.

An analysis of variance is needed to obtain the estimate of σ^2, the error variance. The estimator, s^2, which will be used in the calculation of the 90% confidence interval should be obtained from the "error" mean square term found in the following ANOVA table.

Source	Degrees of freedom
Sequence	1
Animal (sequence)	$n_A + n_B - 2$
Period	1
Formulation	1
Error	$n_A + n_B - 2$
Total	$2n_A + 2n_B - 1$

Lower and upper 90% confidence intervals are then found by formulas based on Student's t-distribution.

$$L = (T - R) - t_{(n_A+n_B-2);0.05^s}\sqrt{\frac{1}{2}\left(\frac{1}{n_A} + \frac{1}{n_B}\right)} \quad (1)$$

$$U = (T - R) + t_{(n_A+n_B-2);0.05^s}\sqrt{\frac{1}{2}\left(\frac{1}{n_A} + \frac{1}{n_B}\right)} \quad (2)$$

The procedure of declaring two formulations bioequivalent, if the 90% confidence interval is completely contained in some fixed interval, is statistically equivalent to performing two one-sided statistical tests ($\alpha = 0.05$) at the end points of the interval.

Consider the following example with $L = 3$, $U = 17$, $T = 110$ and $R = 100$. By the traditional hypothesis testing approach, the result would be considered statistically significant since the confidence interval does not include 0. Using the confidence interval approach, the entire confidence interval lies within 17% of R. (The lower end of the confidence interval lies within $L/R = 3/100 = 3\%$ of R, while the upper end of the confidence interval lies within $U/R = 17/100 = 17\%$ of R.) If it were determined by FDA that only differences larger than 20% were biomedically important,

then using the confidence interval approach the results of this study would be considered adequate to demonstrate bioequivalence.

Now consider an example with $L = -4$, $U = 24$, $T = 110$, and $R = 100$. In this case, by the traditional hypothesis testing approach the result would not be considered statistically significant since the confidence interval includes 0. However, the confidence interval extends as far as 24% from R. (The lower end of the confidence interval lies within $L/R = -4/100 = -4\%$ of R, while the upper end of the confidence interval extends to $U/R = 24/100 = 24\%$ of R.) If it were determined by FDA that only differences larger than 20% were biomedically important, then the results of this study would be considered inadequate to demonstrate bioequivalence, since the entire confidence interval is not within 20% of R.

XI. LOGARITHMICALLY TRANSFORMED DATA

This section discusses how the 90% confidence interval approach should be applied to log-transformed data. In this situation the individual animal AUC and C_{max} values are log-transformed and the analysis is done on the transformed data. For a two-period crossover study, the ANOVA model used to calculate estimates of the error variance and the least square means are identical for both transformed and untransformed data. The procedural difference comes after the lower and upper 90% confidence intervals are found by formulas based on Student's t-distribution.

The lower and upper confidence bounds of the log-transformed data will then need to be back-transformed in order to be expressed on the original scale of the measurement. One thing to keep in mind when moving between the logarithm scale and the original scale is that the back-transformed mean of a set of data that has been transformed to the logarithm scale is not strictly equivalent to the mean that would be calculated from the data on the original scale of measurement. This back-transformed mean is known instead as the geometric mean.

It may help to see the calculations involved. If the AUC from each animal has been transformed to the logarithm scale, we can express the transformed AUC as lnAUC. Then the mean on the logarithm scale is as follows:

$$\bar{L}\bar{n}AUC_t = \sum_{i=1}^{N} LnAUC_t/n \tag{3}$$

where the subscript t represents the AUC determinations for the test article, i is the AUC of the ith animal, and n is the total number of animals receiving the test article. When this mean is back-transformed, it becomes the geometric mean: $e^{(\ln AUC_t)}$. This geometric mean will be on the original scale of the measurement. It will be close to but not exactly equal to the mean obtained on the original scale of the measurement. The back-transformation of the confidence bounds is accomplished in the following way:

Lower bound (expressed as a percentage) $= (e^{L} - 1) \times 100$
Upper bound (expressed as a percentage) $= (e^{U} - 1) \times 100$

Where L is the lower 90% confidence interval and calculated on the log-transformed data; U is the upper 90% confidence interval and calculated on the log-transformed data.

As an example, consider the data for AUC from a hypothetical crossover study in the following table:

		Reference article		Test article	
Animal	Crossover sequence	AUC	LogAUC	AUC	LogAUC
1	1	518.0	6.25	317.8	5.76
2	1	454.9	6.12	465.0	6.14
3	1	232.8	5.45	548.4	6.31
4	1	311.1	5.74	334.8	5.81
5	2	340.4	5.83	224.7	5.41
6	2	497.7	6.21	249.2	5.52
7	2	652.0	6.48	625.4	6.44
8	2	464.1	6.14	848.7	6.74
	MEAN	433.8	6.03	451.7	8602
	Standard Deviation	133.3	0.33	214.3	0.47
	Geometric Mean		414.7		

The statistics for AUC will be calculated from the log-transformed data. In this example, L, the lower 90% confidence interval calculated on the log scale is -0.395. U, the upper 90% confidence interval calculated on the log scale is 0.372. To back-transform these intervals and express them as percentages, we do the following:

Back-transformed lower bound:
$(e^{-0.395} - 1) \times 100 = (0.674 - 1) \times 100 = (-0.326) \times 100 = -32.6\%$
Back-transformed upper bound:
$(e^{0.372} - 1) \times 100 = (1.451 - 1) \times 100 = (0.451) \times 100 = 45.1\%$

Therefore, the lower end of the confidence bound lies within -32.6% of the geometric mean of the reference article, while the upper end of the confidence interval lies within 45.1% of the geometric mean of the reference article. If it were determined by FDA that the acceptable confidence bound was 80% to 125% of the geometric mean of the reference article in order to demonstrate bioequivalence, then the back-transformed lower bound can be as low as -20% and the back-transformed upper bound can be as high as 25%. In this example, we would determine that the study had not demonstrated an acceptable level of bioequivalence between the test article and the reference article.

The width of the confidence interval is determined by the within subject variance (between subject variance for parallel group studies) and the number of subjects in the study. In general, the confidence interval for untransformed data should be 80% to 120% (the confidence interval should lie within $\pm 20\%$ of the mean of the reference product). For logarithmically transformed data, the confidence interval is generally 80% to 125% (the confidence interval should lie within -20% to $+25\%$ of the mean of the reference product). The sponsor and FDA should determine the acceptable bounds for confidence limits for the particular drug and formulation during protocol development.

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2

Bioequivalence Testing Protocols-FDA-Compressed Dosage Forms

To receive approval for an ANDA, an applicant generally must demonstrate, among other things, that its product has the same active ingredient, dosage form, strength, route of administration, and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. Bioequivalent drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 USC 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320. The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-specific BE studies, the U.S. FDA will be issuing product-specific BE recommendations (www.fda.gov/cder/ogd/index.htm). Given below are the current recommendations for the products of relevance to this specific volume of the book:

- Abacavir Sulfate; Lamivudine; Zidovudine Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 300 mg/150 mg/300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 300 mg/150 mg/300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Abacavir, Lamivudine, and Zidovudine in plasma. Bioequivalence based on (90% CI): Abacavir, Lamivudine, and Zidovudine. Waiver request of in vivo testing: Not applicable.
- Abacavir Sulfate and Lamivudine Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 600 mg/300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 600 mg/300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Abacavir and lamivudine in plasma. Bioequivalence based on (90% CI): Abacavir and lamivudine. Waiver request of in vivo testing: Not applicable.
- Abacavir Sulfate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Abacavir in plasma. Bioequivalence based on (90% CI): Abacavir. Waiver request of in vivo testing: Not applicable.
- Acamprosate Calcium Delayed Release Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 333 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 333 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: Analytes to measure: Acamprosate in plasma Acamprosate exists completely dissociated in plasma. Therefore, BE measures may be reported in terms of acetylhomotaurine. Bioequivalence based on (90% CI): Acamprosate. Waiver request of in vivo testing: Not applicable.
- Acyclovir Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 800 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 800 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Acyclovir in plasma. Bioequivalence based on (90% CI): Acyclovir. Waiver request of in vivo testing: 400 mg based on (i) acceptable bioequivalence studies on the 800-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Alendronate Sodium Tablets/Oral. Recommended studies: 1 study. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 70 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Alendronate in urine. Bioequivalence based on (90% CI): Alendronate. The bioequivalence study should be based on urinary excretion data. The following pharmacokinetic parameters should be calculated: A_e (amount of drug excreted during each collection interval). Total A_e (0–48) (total amount of drug excreted over the entire period of sample collection), R_e (rate of drug excretion), R_{max} (maximum excretion rate), and T_{max} (time of the maximum excretion rate). All parameters should be calculated using a noncompartmental model. The statistical analysis using ANOVA should be performed on Total A_e (0–48) and R_{max}. The 90% confidence interval criteria should be applied to these parameters and should be within the limits of 80% to 125%. Waiver request of in vivo testing: 5 mg, 10 mg,

35 mg, and 40 mg based on (i) acceptable bioequivalence study on the 70-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Alfuzosin Hydrochloride Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Alfuzosin. Bioequivalence based on (90% CI): Alfuzosin. Waiver request of in vivo testing: Not applicable. In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.
- Almotriptan Malate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 12.5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 12.5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Almotriptan in plasma. Bioequivalence based on (90% CI): Almotriptan. Waiver request of in vivo testing: 6.25 mg based on (i) acceptable bioequivalence studies of the 12.5-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Alosetron Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 1 mg (base); Subjects: Normal, healthy females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 1 mg (base); Subjects: Normal, healthy females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Alosetron in plasma. Bioequivalence based on (90% CI): Alosetron. Waiver request of in vivo testing: 0.5 mg (base) based on (i) acceptable bioequivalence studies on the 1-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Alprazolam Tablet/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 1 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Alprazolam in plasma. Bioequivalence based on (90% CI): Alprazolam. Waiver request of in vivo testing: 0.25 mg, 0.5 mg, and 2 mg based on (i) acceptable bioequivalence studies on the 1-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Alprazolam Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 3 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 3 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Alprazolam in plasma. Bioequivalence based on (90% CI): Alprazolam. Waiver request of in vivo testing: 0.5 mg, 1 mg, and 2 mg based on (i) acceptable bioequivalence studies on the 3-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.
- Amlodipine Besylate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Amlodipine in plasma. Bioequivalence based on (90% CI): Amlodipine. Waiver request of in vivo testing: 2.5 mg and 5 mg based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Amoxicillin; Clavulanate Potassium Chewable Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 250 mg/62.5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 250 mg/62.5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Amoxicillin and clavulanic acid in plasma. Bioequivalence based on (90% CI): Amoxicillin and clavulanic acid. Waiver request of in vivo testing: 125 mg/31.25 mg, based on (i) acceptable bioequivalence studies on the 250-mg/62.5-mg strength, (ii) formulation proportionality across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Amoxicillin; Clavulanate Potassium Chewable Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 400 mg/57 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength:

400 mg/57 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Amoxicillin and clavulanic acid in plasma. Bioequivalence based on (90% CI): Amoxicillin and clavulanic acid. Waiver request of in vivo testing: 200 mg/28.5 mg, based on acceptable (i) bioequivalence studies on the 400-mg/57-mg strength, (ii) proportional similarity of the formulations, and (iii) acceptable in vitro dissolution testing of all strengths.

- Anastrozole Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 1 mg; Subjects: Please conduct the studies in postmenopausal subjects or surgically sterile females. Additional comments: Please do not include subjects who are using female hormone replacement therapies, thyroid hormone replacement therapies, or antihypertensive therapies in the study population. Anastrozole has a long terminal elimination half-life. Please ensure adequate washout periods between treatments in the crossover studies. You may also consider using a parallel study design due to anastrozole's long half-life. For long half-life drug products, an AUC truncated to 72 hours may be used in place of AUC0–t or AUC0–8. Please collect sufficient blood samples in the bioequivalence studies to adequately characterize the peak concentration (C_{max}) and time to reach peak concentration (T_{max}). 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 1 mg; Subjects: Please see comments above. Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Anastrozole in plasma. Bioequivalence based on (90% CI): Anastrozole. Waiver request of in vivo testing: Not applicable.
- Aripiprazole Tablets/Oral. Recommended studies: 3 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Dose and Tablet Strength: 10 mg; Subject: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Dose and Tablet Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 3. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Dose and Tablet Strength: 5 mg, if adequate exposure is not possible with a 5 mg dose, you may consider using a 10 mg dose (2 × 5 mg). Subjects: Normal, healthy males and females, general population. Additional comments: Notes: Life-threatening adverse events attributed to acute laryngeal dystonia have been reported following administration of a single dose of 30 mg aripiprazole to healthy volunteers in bioequivalence studies. Although such events have not been reported at doses lower than 30 mg, because of the life-threatening nature of these events, and because the dose response relationship is not known for this event, the following safety precautions are recommended for healthy volunteer studies of aripiprazole at all doses: Study protocols should specify standard procedures to diagnose and treat dystonic reactions should they occur. Subjects younger than 45 years should be excluded. There appears to be an inverse linear relationship between age and the incidence of acute dystonic reactions. Adults younger than 35 years were reported to have a 15-fold higher rate of neuroleptic-induced dystonia compared to a group of patients 60 to 80 years of age. The occurrence of dystonias appears to be rare at ages of approximately 45 years and higher. Protocols should include stringent drug screening procedures to ensure that subjects are free of illicit drugs at the time of administration of each study drug dose. The screening interview should include specific questions to exclude subjects with a prior personal or family history of dystonic reactions to medications. Prospective study subjects should also be specifically questioned about prior neuroleptic drug exposures. Aripiprazole has been poorly tolerated by healthy volunteers in some bioequivalence studies, particularly at the 15 and 30 mg dose levels. In several cases, adverse events have resulted in a high incidence of dropouts. Adverse events in aripiprazole studies have included nausea, vomiting, dizziness, syncope, insomnia, headache, fatigue, hypotension, hot flashes, weakness, diaphoresis, and confusion. To minimize the occurrence of adverse events, and to ensure the safety of healthy volunteer subjects in clinical trials of aripiprazole, the following is recommended: Subjects should be monitored in-house for at least 3 days after dosing and until adverse events have resolved. Subjects should be kept supine for at least 8 hours starting no longer than 15 minutes after each dose. Subjects should be asked to use the bathroom soon before dosing. Subjects should be encouraged to use urinals or bedpans during the first 8 hours after dosing and at any time after dosing if the subject is experiencing adverse events such as nausea, dizziness, or hypotension. If subjects do use the bathroom during the first 8 hours after dosing or while experiencing adverse events such as nausea, dizziness, or hypotension, they should be assisted to and from the bathroom by study personnel. At a minimum, routine 12-lead EKGs should be performed at 3 to 5 hours after dosing and at 8 to 12 hours after dosing. Continuous EKG monitoring during those time periods may be considered as an alternative. Vital signs monitoring should continue postdosing throughout the period that subjects are housed, commencing no later than 30 minutes following dosing. Vital signs should be monitored frequently (at least every 0.5–1 hour) for at least the first 8 hours after dosing and the first hour after subjects are allowed to rise from the supine position. Prespecified limits should be defined for reporting adverse events related to vital signs (e.g., hypotension, bradycardia, etc.). Vital sign readings that meet these predefined limits should be reported as adverse events, even if they are not performed during a scheduled assessment (e.g., vital signs performed as part of an assessment of an adverse event). The protocol should include standard procedures for the assessment and management of potential adverse events, including vital signs and EKG monitoring as appropriate for adverse events possibly associated with hypotension. Women of childbearing potential should be enrolled only if they are using effective contraceptives. A negative pregnancy test is needed within 24 hours prior to each dose. These subjects should also be informed of the potential teratogenicity of the study drug as part of the informed consent process. Nursing women should also be excluded. The protocol should include measures to prevent relative dehydration at the time of dosing, such as encouragement of water intake whenever possible prior to dosing. Consideration should be made to providing a standard meal just prior to the standard fasting period before dosing. During the informed consent process, subjects should be advised of the high incidence of adverse events that have occurred in some healthy volunteer studies of aripiprazole. Aripiprazole has a long terminal elimination half-life. Please ensure adequate washout periods between treatments in the crossover studies. You may also consider using a

parallel study design due to aripiprazole's long half-life. For long half-life drug products, an AUC truncated to 72 hours may be used in place of AUC0–t or AUC0–inf. Please collect sufficient blood samples in the bioequivalence studies to adequately characterize the peak concentration (C_{max}) and time to reach peak concentration (T_{max}). Analytes to measure (in appropriate biological fluid): Aripiprazole in plasma. Bioequivalence based on (90% CI): Aripiprazole. Waiver request of in vivo testing (assuming conduct of the three in vivo studies above): 2 mg, 15 mg, 20 mg, and 30 mg, based on (i) acceptable bioequivalence studies on the 5 mg, and 10-mg strengths (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Armodafinil Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 250 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 250 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Armodafinil in plasma. Bioequivalence based on (90% CI): Armodafinil. Waiver request of in vivo testing: 50 mg and 150 mg, based on acceptable (i) bioequivalence studies on the 250-mg strength, and (ii) proportional similarity of the formulations and (iii) acceptable in vitro dissolution testing of all strengths.
- Atorvastatin Calcium Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 80 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 80 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Atorvastatin, ortho-, and parahydroxylated metabolites of atorvastatin. The ortho- and parahydroxylated metabolites of atorvastatin are formed by presystemic metabolism and contribute meaningfully to efficacy. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Bioequivalence based on (90% CI): Atorvastatin. Waiver request of in vivo testing: 10 mg, 20 mg, and 40 mg based on (i) acceptable bioequivalence studies on the 80-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Atovaquone Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 250 mg; Subjects: Normal, healthy males and females, general population. Additional comments: You may also consider using a parallel study design due to atovaquone's long half-life. For long half-life drug products, an AUC truncated to 72 hours may be used in place of AUC0–t or AUC0–8. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 250 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure (in appropriate biological fluid): Atovaquone in plasma. Bioequivalence based on (90% CI): Atovaquone. Waiver request of in vivo testing: Not applicable. Atovaquone is known to be practically insoluble in both water and 0.1 M HCl (<0.0002 mg/mL at 25°C). Use of conventional aqueous dissolution media with and without surfactant has been found unsuccessful and not reproducible in some laboratories working with atovaquone tablet products. If encountering the same difficulty, you may consider developing a dissolution method similar to the method available in the Dissolution Database. Although the use of the high alcoholic medium is not considered conventional, it has been found justifiable by the FDA for this drug substance. You may develop an alternate dissolution testing method for the drug product and submit the dissolution testing results when the application is filed.
- Azithromycin Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 600 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 600 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Azithromycin. Bioequivalence based on (90% CI): Azithromycin. Waiver request of in vivo testing: 250 mg and 500 mg based on (i) acceptable bioequivalence studies on the 600-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Since Azithromycin tablets, 250 mg, 500 mg, and 600 mg, are the subject of three separate new drug applications (NDAs), three separate abbreviated new drug applications (ANDAs) must be submitted. You may request (a) Waiver of in vivo bioequivalence testing of the 250-mg and the 500-mg strengths if you meet the criteria. In addition, please cross-reference the in vivo bioequivalence studies conducted on the higher strength along with your Waiver request.
- Benzphetamine Hydrochloride Tablet/Oral. Recommended studies: Benzphetamine Hydrochloride Tablet is a DESI-effective drug product without known bioequivalence problems. Therefore, in vivo bioequivalence testing is not requested. Comparative dissolution testing on 12 dosage units of all strengths of the test and reference products is requested. You may request (a) Waiver of in vivo bioequivalence study requirements on this product under 21 CFR 320.22(c). Analytes to measure: Not applicable. Bioequivalence based on (90% CI): Not applicable. Waiver request of in vivo testing: 50 mg.
- Bicalutamide Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 50 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Female subjects should be excluded from the bioequivalence studies if they are pregnant. Bicalutamide has a long terminal elimination half-life. Please ensure adequate washout periods between treatments in the crossover studies. You may also consider using a parallel study design due to bicalutamide's long half-life. For long half-life drug products, an AUC truncated to 72 hours may be used in place of AUC0–t or AUC0–8. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 50 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. Analytes to measure: Bicalutamide, using an achiral assay. Bioequivalence based on (90% CI): Bicalutamide. Waiver request of in vivo testing: Not applicable.
- Bisoprolol Fumarate; Hydrochlorothiazide Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength:

10 mg/6.25 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 10 mg/6.25 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Bisoprolol and Hydrochlorothiazide in plasma. Bioequivalence based on (90% CI): Bisoprolol and Hydrochlorothiazide. Waiver request of in vivo testing: 2.5 mg/6.25 mg and 5 mg/6.25 mg based on (i) acceptable bioequivalence studies on the 10-mg/6.25-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Bisoprolol Fumarate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Bisoprolol in plasma. Bioequivalence based on (90% CI): Bisoprolol. Waiver request of in vivo testing: 5 mg based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Bupropion Hydrochloride Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 150 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 150 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Bupropion and Hydroxybupropion (active metabolite of bupropion) in plasma. Bioequivalence based on (90% CI): Bupropion. Waiver request of in vivo testing: 300 mg based on (i) acceptable bioequivalence studies on the 150-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Because of concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows: Testing Conditions: 900 mL, 0.1 N HCl, Apparatus I (basket) at 75 rpm, with and without the alcohol (see below): Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours. Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range, and %CV on both strengths.
- Candesartan Cilexetil; Hydrochlorothiazide Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 32 mg/12.5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Female subjects should be excluded from the bioequivalence studies if they are pregnant. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 32 mg/12.5 mg; Subjects: Normal, healthy males and females, general population Additional comments: Female subjects should be excluded from the bioequivalence studies if they are pregnant. Analytes to measure (in appropriate biological fluid): Candesartan and hydrochlorothiazide in plasma. Bioequivalence based on (90% CI): Candesartan and hydrochlorothiazide requests of Waivers of in vivo testing: 16 mg/12.5 mg, based on (i) acceptable bioequivalence studies on the 32-mg/12.5-mg strength, (ii) formulation proportionality across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Candesartan Cilexetil Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 32 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 32 mg; Subjects: Normal, healthy males and females, general population Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Candesartan in plasma. Bioequivalence based on (90% CI): Candesartan requests for Waivers of in vivo testing: 4 mg, 8 mg, and 16 mg based on (i) acceptable bioequivalence studies on the 32-mg strength, (ii) acceptable dissolution testing of all strengths, and (iii) proportional similarity in the formulations of all strengths.
- Carbamazepine Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 400 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 400 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Carbamazepine in plasma. Bioequivalence based on (90% CI): Carbamazepine. Waiver request of in vivo testing: 100 mg and 200 mg, based on acceptable (i) bioequivalence studies on the 400 mg tablet, (ii) proportional similarity of the formulations, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at

50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

- Carbidopa; Entacapone; Levodopa Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo. Strength: (37.5 mg, 200 mg, and 150 mg) Carbidopa; Entacapone; Levodopa. Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional Comments: 2. Type of study: Fasting Design: single-dose, two-way crossover in vivo. Strength: (12.5 mg, 200 mg, and 50 mg) Carbidopa; Entacapone; Levodopa. Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: Analytes to measure (in appropriate biological fluid): Carbidopa, Entacapone, and Levodopa in plasma. Bioequivalence based on (90% CI): Carbidopa, Entacapone, and Levodopa. Waiver request of in vivo testing: (25 mg, 200 mg, and 100 mg) Carbidopa, Entacapone and Levodopa tablets, based on (i) acceptable bioequivalence study on the 37.5 mg; 200 mg; 150 mg tablet, (ii) formulation proportionality across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Carvedilol Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 12.5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Due to safety concerns, the OGD recommends that you conduct the bioequivalence studies using Carvedilol Tablets, 12.5 mg, instead of the 25-mg strength. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 12.5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure: Carvedilol and 4-hydroxyphenyl-carvedilol metabolite of Carvedilol in plasma. Bioequivalence based on (90% CI): Carvedilol. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Waiver request of in vivo testing: 3.125 mg, 6.25 mg, and 25 mg based on (i) acceptable bioequivalence studies on the 12.5-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Cefditoren Pivoxil Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Cefditoren (not the prodrug cefditoren pivoxil) in plasma. Bioequivalence based on (90% CI): Cefditoren. Waiver request of in vivo testing: Not applicable.
- Cetirizine Hydrochloride; Pseudoephedrine Hydrochloride Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 5 mg/120 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 5 mg/120 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Cetirizine and Pseudoephrine in plasma. Bioequivalence based on (90% CI): Cetirizine and Pseudoephrine. Waiver request of in vivo testing: Not applicable. For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 tablets.
- Cetirizine Hydrochloride Chewable Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Cetirizine in plasma. Bioequivalence based on (90% CI): Cetirizine. Waiver request of in vivo testing: 5 mg based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Cilostazol Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Patients should be advised to take Cilostazol at least one-half hour before or 2 hours after food. Therefore, a fed study is not recommended. 2. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 50 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. Analytes to measure: Cilostazol in plasma. Bioequivalence based on (90% CI): Cilostazol. Waiver request of in vivo testing: Not applicable.
- Cinacalcet Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 90 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 90 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: Analytes to measure (in appropriate biological fluid): Cinacalcet in plasma. Bioequivalence based on (90% CI): Cinacalcet. Waiver request of in vivo testing:

60 mg and 30 mg based on (i) acceptable bioequivalence studies on the 90-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Ciprofloxacin; Ciprofloxacin Hydrochloride Extended Release Tablets/Oral. Recommended studies: 3 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 1000 mg (425.2 mg; EQ 574.9 mg base); Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 1000 mg (425.2 mg; EQ 574.9 mg base); Subjects: Normal, healthy males and females, general population. 3. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 500 mg (212.6 mg; EQ 287.5 mg base); Subjects: Normal, healthy males and females, general population. Analytes to measure: Ciprofloxacin. Bioequivalence based on (90% CI): Ciprofloxacin. Waiver request of in vivo testing: The 500-mg strength of ciprofloxacin extended-release tablets is NOT eligible for (a) Waiver of in vivo testing based on an acceptable in vivo bioequivalence study of the 1000-mg strength. For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 tablets.
- Ciprofloxacin Hydrochloride Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Ciprofloxacin in plasma. Bioequivalence based on (90% CI): Ciprofloxacin. Waiver request of in vivo testing: Not applicable. In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.
- Clarithromycin Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Clarithromycin in plasma. Bioequivalence based on (90% CI): Clarithromycin. Waiver request of in vivo testing: Not applicable. For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 tablets.
- Clonidine Hydrochloride Tablets/Oral. Recommended studies: 1 study. 1. Type of study: fasting Design: single-dose, two-way crossover in vivo; Strength: 0.3 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Clonidine in plasma. Bioequivalence based on (90% CI): Clonidine. Waiver request of in vivo testing: 0.1 mg and 0.2 mg based on (i) acceptable bioequivalence study on the 0.3-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Clopidogrel Bisulfate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 75 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 75 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Clopidogrel in plasma. Bioequivalence based on (90% CI): Clopidogrel. Waiver request of in vivo testing: Not applicable. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Darifenacin Hydrobromide Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 15 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 15 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure (in appropriate biological fluid): Darifenacin in plasma. Bioequivalence based on (90% CI): Darifenacin. Waiver request of in vivo testing: 7.5 mg based on (i) acceptable bioequivalence studies on the 15-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Darunavir Ethanolate Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: single-dose of 600 mg (2 × 300 mg); Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: single-dose of 600 mg (2 × 300 mg); Subjects: Normal, healthy males and females, general population. Additional

comments: Analytes to measure (in appropriate biological fluid): Darunavir in plasma. Bioequivalence based on (90% CI): Darunavir. Waiver request of in vivo testing: Not applicable.

- Delavirdine Mesylate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Analytes to measure (in appropriate biological fluid): Delavirdine in plasma. Bioequivalence based on (90% CI): Delavirdine. Waiver request of in vivo testing: 100 mg based on (i) acceptable bioequivalence studies on the 200-mg strength, (ii) proportional similarity of the 100 mg formulation to the 200-mg strength, and (iii) acceptable in vitro dissolution testing of all strengths.
- Desloratadine Orally Disintegrating Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Desloratadine and the active metabolite, 3-hydroxydesloratadine in plasma. Please submit the metabolite data as supportive evidence of the comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Bioequivalence based on (90% CI): Desloratadine. Waiver request of in vivo testing: 2.5 mg based on (i) acceptable bioequivalence studies on the 5-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Desloratadine Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Desloratadine and its metabolite, 3-hydroxydesloratadine. Bioequivalence based on (90% CI): Desloratadine. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Waiver request of in vivo testing: Not applicable.
- Dexmethylphenidate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Dexmethylphenidate in plasma. Bioequivalence based on (90% CI): Dexmethylphenidate. Waiver request of in vivo testing: 2.5 mg and 5 mg based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Diclofenac Sodium; Misoprostol Delayed Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 75 mg/0.2 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Female subjects should be excluded from the bioequivalence study if they are pregnant. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 75 mg/0.2 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Female subjects should be excluded from the bioequivalence study if they are pregnant. Analytes to measure: Diclofenac and misoprostol's metabolite, misoprostol acid in plasma. Bioequivalence based on (90% CI): Diclofenac and misoprostol's metabolite, misoprostol acid. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Waiver request of in vivo testing: 50 mg/ 0.2 mg based on (i) acceptable bioequivalence studies on the 75-mg/0.2-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Didanosine Chewable Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 2 × 200 mg (400 mg dose); Subjects: Normal, healthy males and females, general population Additional comments: Analytes to measure (in appropriate biological fluid): Didanosine in plasma using an achiral method. Bioequivalence based on (90% CI): Didanosine. Waiver request of in vivo testing: 25 mg, 50 mg, 100 mg, and 150 mg, based on (i) acceptable bioequivalence study on the 200-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Digoxin Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 0.25 mg; Subjects: Normal, healthy males and females, general population Additional comments: If reliable blood drug levels cannot be obtained using a 1 × 0.25 mg dose, you may use a single dose of 2 × 0.25 mg tablets. Please carefully monitor the study subjects for adverse events. A washout period of about 2 weeks is suggested. Please continue sample collection for approximately 6 days, that is, at least three or more terminal half-lives of the drug. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 0.25 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see above comments. Analytes to measure (in appropriate biological fluid): Digoxin in plasma. Bioequivalence based on (90% CI): Digoxin. Waiver request of in vivo testing: 0.125 mg based on (i) acceptable bioequivalence studies on the 0.25-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution

testing on 12 dosage units of all strengths of the test and reference products.

- Diltiazem Hydrochloride Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way, crossover in vivo; Strength: 420 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way, crossover in vivo; Strength: 420 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Diltiazem and the active metabolites desacetyldiltiazem and desmethyldiltiazem in plasma. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Bioequivalence based on (90% CI): Diltiazem. Waiver request of in vivo testing: 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg based on (i) acceptable bioequivalence studies on the 420-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 tablets.
- Dipyridamole Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 75 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Dipyridamole in plasma. Bioequivalence based on (90% CI): Dipyridamole. Waiver request of in vivo testing: 25 mg and 50 mg based on (i) acceptable bioequivalence study on the 75-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Divalproex Sodium Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way, crossover in vivo; Strength: 500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-way, crossover in vivo; Strength: 500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. Analytes to measure: Valproic acid in plasma. Bioequivalence based on (90% CI): Valproic acid. Waiver request of in vivo testing: 250 mg based on (i) acceptable bioequivalence studies on the 500-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 tablets.
- Donepezil Hydrochloride Orally Disintegrating Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Donepezil in plasma. Bioequivalence based on (90% CI): Donepezil. Waiver request of in vivo testing: 5 mg based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Donepezil Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way, crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way, crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Donepezil in plasma. Bioequivalence based on (90% CI): Donepezil. Waiver request of in vivo testing: 5 mg based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Doxazosin Mesylate Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 8 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 8 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: Analytes to measure (in appropriate biological fluid): Doxazosin in plasma. Bioequivalence based on (90% CI): Doxazosin. Waiver request of in vivo testing: 4 mg based on (i) acceptable bioequivalence studies on the 8-mg strength, (ii) proportionally similar across both strengths, and (iii) acceptable in vitro dissolution testing of both strengths. In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

- Doxycycline Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way, crossover in vivo; Strength: 150 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way, crossover in vivo; Strength: 150 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Doxycycline in plasma. Bioequivalence based on (90% CI): Doxycycline. Waiver request of in vivo testing: 50 mg, 75 mg, and 100 mg based on (i) acceptable bioequivalence studies on the 150-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Drospirenone; Estradiol Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 0.5 mg and 1 mg; Subjects: Normal, healthy postmenopausal women. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 0.5 mg and 1 mg; Subjects: Normal, healthy postmenopausal women. Additional comments: Analytes to measure (in appropriate biological fluid): Drospirenone and unconjugated estradiol, unconjugated estrone, and total estrone in plasma. Bioequivalence based on (90% CI): Drospirenone and baseline-adjusted total estrone. Statistical analysis should be performed on data both with and without baseline adjustment. Bioequivalence acceptance criteria will be based on baseline-adjusted results only. Baseline adjustment: Data of each subject and period should be adjusted for the mean of −1 hour, −0.5 hour, and predose levels for that same subject and period. If, after adjustment, any negative concentrations result, they should be set equal to zero. Waiver request of in vivo testing: Not applicable.
- Efavirenz Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 600 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Efavirenz in plasma. Bioequivalence based on (90% CI): Efavirenz. Waiver request of in vivo testing: Not applicable.
- Entacapone Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way, crossover in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Due to the high inter- and intrasubject variability observed with this product, you may want to consider using a replicate study design. Since the drug product is to be used predominantly in the elderly, please include as many subjects of 60 years of age or older as possible. 2. Type of study: Fed Design: single-dose, two-way, crossover in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. Analytes to measure: Entacapone in plasma. Bioequivalence based on (90% CI): Entacapone. Waiver request of in vivo testing: Not applicable.
- Entecavir Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 1 mg; Subjects: Normal, healthy males and females, general population. Additional comments: As an option, due to the relatively long half-life, the firm may wish to conduct this study using a parallel design. As an additional option for either the crossover or parallel design, the firm may wish to truncate the AUC at 72 hours. Analytes to measure (in appropriate biological fluid): Entecavir in plasma. Bioequivalence based on (90% CI): Entecavir. Waiver request of in vivo testing: 0.5 mg based on (i) acceptable bioequivalence studies on the 1-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Eplerenone Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 50 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of Study: Fed Design: single-dose, two-way crossover in vivo; Strength: 50 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Eplerenone in plasma. Bioequivalence based on (90% CI): Eplerenone. Waiver request of in vivo testing: 25 mg based on (i) acceptable bioequivalence studies on the 50-mg strength, (ii) proportionally similar to the 50-mg strength, and (iii) acceptable in vitro dissolution testing.
- Eprosartan Mesylate; Hydrochlorothiazide Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 600 mg/25 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Please include provisions for appropriate monitoring and intervention in the case of possible drug-related adverse events (e.g., subjects complaining of dizziness/lightheadedness should have blood pressure/heart rate assessed). 2. Type of Study: Fed Design: single-dose, two-way crossover in vivo; Strength: 600 mg/25 mg; Subjects: Normal, healthy males and females, general population. Additional Comments: Please see comment above. Analytes to measure (in appropriate biological fluid): Eprosartan and Hydrochlorothiazide in plasma. Bioequivalence based on (90% CI): Eprosartan and Hydrochlorothiazide. Waiver request of in vivo testing: 600 mg/12.5 mg, based on (i) acceptable bioequivalence studies on the 600-mg/25-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Erlotinib Hydrochloride Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 150 mg; Subjects: Normal, healthy males and females, general population. Additional Comments: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Any subject experiencing an adverse event should be followed until the adverse event has completely resolved. Analytes to measure (in appropriate biological fluid): Erlotinib in plasma. Bioequivalence based on (90% CI): Erlotinib. Waiver request of in vivo testing: 100 mg and 25 mg based on (i) acceptable bioequivalence studies on the 150-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Escitalopram Oxalate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Escitalopram, using an achiral assay. Bioequivalence based on (90% CI):

Escitalopram. Waiver request of in vivo testing: 5 mg and 10 mg based on (i) acceptable bioequivalence studies on the 20-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Esterified Estrogens Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 2.5 mg; Subjects: Normal, healthy post menopausal or surgically sterile females. Additional comments: Analytes to measure (in appropriate biological fluid): Estrone sulfate and Equilin sulfate in plasma. 1. Please provide baseline correction for endogenous estrone sulfate in the analysis. Please measure baseline estrone sulfate levels at −1, −0.5, and 0 hours. The mean of the predose estrone sulfate levels should be used for the baseline adjustment of the postdose levels. Any negative values obtained from baseline correction should be designated as zero (0) and any subject with baseline-adjusted predose concentrations (at time 0 hour) greater than 5% of their C_{max} should be excluded from the bioequivalence statistical analysis and the 90% confidence interval based on the remaining subjects. 2. The selected blood-sampling schedule should include sufficient time points around T_{max} for the best estimate of C_{max}, and should be sufficiently long for the best characterization of the elimination phase of both analytes (at least 96 hours). 3. The analytical assay method selected should be sufficiently sensitive and specific to measure estrone sulfate and equilin sulfate concentrations in plasma and should have a lower limit of quantitation (LLOQ) of 50 pg/mL or less for both analytes. 4. Based on the estimated half-life of the two analytes, the washout duration should be greater than five times the half-life, therefore at least a 2-week washout period between doses is recommended. Bioequivalence based on (90% CI): Estrone sulfate and Equilin sulfate. Waiver request of in vivo testing: 0.3 mg, 0.625 mg, and 1.25 mg based on (i) acceptable bioequivalence studies on the 2.5-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Eszopiclone Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 3 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 3 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Eszopiclone in plasma. Bioequivalence based on (90% CI): Eszopiclone. Waiver request of in vivo testing: 1 mg and 2 mg, based on acceptable (i) bioequivalence studies on the 3-mg tablet, and (ii) proportional similarity of the formulations and (iii) acceptable in vitro dissolution testing of all strengths.
- Ethambutol Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 400 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 400 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Ethambutol in plasma. Bioequivalence based on (90% CI): Ethambutol. Waiver request of in vivo testing: 100 mg, based on acceptable (i) bioequivalence studies on the 400-mg strength, and (ii) proportional similarity of the formulations and (iii) acceptable in vitro dissolution testing of all strengths.
- Ethinyl Estradiol and Levonorgestrel Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 0.03 mg/0.15 mg tablet of ethinyl estradiol and levonorgestrel; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 0.01 mg tablet of ethinyl estradiol; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Ethinyl estradiol and levonorgestrel in plasma for the combination tablets. Only ethinyl estradiol for the single component tablet. Bioequivalence based on (90% CI): Ethinyl estradiol and levonorgestrel. Waiver request of in vivo testing: Bioequivalence studies conducted on Seasonique® (ethinyl estradiol and levonorgestrel) tablets, 0.03 mg/0.15 mg, may be referenced to support a request for (a) Waiver of evidence of in vivo bioequivalence for Seasonale® (ethinyl estradiol and levonorgestrel) tablets, 0.03 mg/0.15 mg. Please submit separate applications for each RLD.
- Ethinyl Estradiol and Levonorgestrel Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 0.03 mg/0.15 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Ethinyl estradiol and levonorgestrel in plasma. Only ethinyl estradiol for the single component tablet in Seasonique. Bioequivalence based on (90% CI): Ethinyl estradiol and levonorgestrel. Waiver request of in vivo testing: Bioequivalence studies conducted on Seasonique (ethinyl estradiol and levonorgestrel) Tablets, 0.03 mg/0.15 mg, may be referenced to support a request for (a) Waiver of evidence of in vivo bioequivalence for Seasonale (ethinyl estradiol and levonorgestrel) Tablets, 0.03 mg/0.15 mg. Please submit separate applications for each RLD.
- Etidronate Disodium Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 400 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Etidronate in plasma. Bioequivalence based on (90% CI): Etidronate. Waiver request of in vivo testing: 200 mg based on (i) acceptable bioequivalence study on the 400-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Exemestane Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way, crossover in vivo; Strength: 25 mg; Subjects: Normal, healthy postmenopausal women, general population. Additional comments: This product is indicated for use in postmenopausal women. Because of teratogenicity concerns with this product, females in these studies should not be of childbearing potential. We recommended that you attempt to include as many postmenopausal women as possible. 2. Type of study: Fed Design: single-dose, two-way, crossover in vivo; Strength: 25 mg; Subjects: Normal, healthy postmenopausal women, general population.

Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Exemestane in plasma. Bioequivalence based on (90% CI): Exemestane. Waiver request of in vivo testing: Not applicable.

- Famotidine Orally Disintegrating Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Famotidine in plasma. Bioequivalence based on (90% CI): Famotidine. Waiver request of in vivo testing: 20 mg based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Famotidine Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way, crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way, crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Famotidine in plasma. Bioequivalence based on (90% CI): Famotidine. Waiver request of in vivo testing: 10 mg and 20 mg based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Note: Separate applications should be submitted for the prescription (Rx) and over-the-counter (OTC) products. You may request (a) Waiver of in vivo bioequivalence testing for the OTC product; if you conduct the studies on the Rx product, submit acceptable dissolution data on all strengths and the formulations of the products are proportional. Please cross-reference in the OTC application the studies conducted for the Rx product. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Felbamate Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: Multipledose, two-way steady-state crossover in vivo; Strength: 600 mg; Subjects: Male and nonpregnant female epilepsy patients. Additional comments: Please also consider the following additional safety monitoring: (a) If any evidence of bone marrow (hematologic) depression occurs, felbamate treatment should be discontinued and a hematologist consulted to ensure appropriate medical care. (b) Additional criteria for exclusion from the study relative to baseline be practiced including: (i) twofold increase in the highest, 2-day prestudy seizure frequency, (ii) single generalized, tonic–clonic seizure if none occurred during pretreatment screening, and/or (iii) significant prolongation of generalized, tonic–clonic seizures. Analytes to measure: Felbamate in plasma. 1. Measurements of felbamate are requested on at least two consecutive days immediately prior to pharmacokinetic analysis days 7 and 14 to confirm steady-state concentrations of felbamate (i.e., additional consecutive measures on days 5, 6, 12, and 13). 2. Because felbamate is rapidly absorbed and reaches a peak plasma concentration within 1 to 3 hours postconsumption, please also include blood sampling at 0.25 hours after drug dosing to accurately measure the absorption/distribution phases of the felbamate pharmacokinetic profile. 3. Patients who receive multiples of 600 mg tablets of felbamate per day (1200–4800 mg/day) would be eligible for the study by continuing their established maintenance dose. Because patients will be administered different dosing regimens, the dose needs to be included in the analysis of variance (ANOVA) statistical model. Dose normalization is not advised. 4. No washout period is necessary between treatment periods. 5. You are encouraged to submit protocols for the in vivo bioequivalence studies to be conducted at steady state in patients already taking the RLD at a therapeutic dose for review prior to initiating the studies. Bioequivalence based on (90% CI): Felbamate. Waiver request of in vivo testing: 400 mg based on (i) acceptable bioequivalence studies on the 600-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Fenofibrate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 145 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 145 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Due to the difficulties with the fenofibrate assay, only the metabolite, fenofibric acid, should be measured. Bioequivalence based on (90% CI): Fenofibric Acid. Waiver request of in vivo testing: 48 mg based on (i) acceptable bioequivalence studies on the 145-mg strength, (ii) proportional similarity of the formulations 48 mg and 145-mg strengths, and (iii) acceptable in vitro dissolution testing of 48-mg and 145-mg strengths.
- Fexofenadine Hydrochloride Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 180 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Fexofenadine in plasma. Bioequivalence based on (90% CI): Fexofenadine. Waiver request of in vivo testing: 30 mg and 60 mg based on (i) acceptable bioequivalence study on the 180-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Flavoxate Hydrochloride Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Flavoxate and the metabolite, 3-methylflavone-8-carboxylic acid in plasma. Bioequivalence based on (90% CI): Flavoxate or the metabolite, 3 methyl-flavone-8-carboxylic acid. If flavoxate can be reliably measured, a confidence interval approach for bioequivalence determination should be used for flavoxate. If flavoxate cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for 3-methylflavone-8-carboxylic acid. Waiver request of in vivo testing: Not applicable.
- Fluconazole Tablet/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Fluconazole in plasma. Bioequivalence based on (90% CI): Fluconazole. Waiver request of in vivo testing: 50 mg, 100 mg, and 150 mg based on (i) acceptable bioequivalence study on the 200-mg strength, (ii) proportional similarity of the

formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Fluvastatin Sodium Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 80 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Due to the teratogenicity concerns with fluvastatin sodium, female subjects enrolled in these studies should not be pregnant. 2. Type of study: Fed Design: single-dose, two-way, crossover in vivo; Strength: 80 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Fluvastatin in plasma (achiral assay). Bioequivalence based on (90% CI): Fluvastatin. Waiver request of in vivo testing: Not applicable. For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 tablets.
- Fosamprenavir Calcium Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 700 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of Study: Fed Design: single-dose, two-way crossover in vivo; Strength: 700 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Amprenavir (not the prodrug fosamprenavir) in plasma. Bioequivalence based on (90% CI): Amprenavir. Waiver request of in vivo testing: Not applicable.
- Fosinopril Sodium; Hydrochlorothiazide Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 20/12.5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Female subjects should be excluded from the studies if they are pregnant. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 20/12.5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Female subjects should be excluded from the studies if they are pregnant. Analytes to measure (in appropriate biological fluid): The metabolite of fosinopril, fosinoprilat and hydrochlorothiazide in plasma. Bioequivalence based on (90% CI): Fosinoprilat and Hydrochlorothiazide. Waiver request of in vivo testing: 10 mg/12.5 mg based on (i) acceptable bioequivalence studies on the 20-/12.5-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Fosinopril Sodium Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure: Metabolite fosinoprilat in plasma. Bioequivalence based on (90% CI): Metabolite fosinoprilat. Waiver request of in vivo testing: 10 mg, and 20 mg based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Gabapentin Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way, crossover in vivo; Strength: 800 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way, crossover in vivo; Strength: 800 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Gabapentin in plasma. Bioequivalence based on (90% CI): Gabapentin. Waiver request of in vivo testing: 100 mg, 300 mg, 400 mg, and 600 mg based on (i) acceptable bioequivalence studies on the 800-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Gemifloxacin Mesylate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 320 mg (base equivalent); Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: Females should not be lactating. Subjects should not have a history of prolongation of the QTC interval, or ongoing proarrhythmic conditions such as clinically significant bradycardia or acute myocardial ischemia. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 320 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional Comments: Females should not be lactating. Subjects should not have a history of prolongation of the QTC interval, or ongoing proarrhythmic conditions such as clinically significant bradycardia or acute myocardial ischemia. Analytes to measure (in appropriate biological fluid): Gemifloxacin in plasma. Bioequivalence based on (90% CI): Gemifloxacin. Waiver request of in vivo testing: Not applicable.
- Glimepiride/Rosiglitazone Maleate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 1 mg/4 mg; Subjects: Normal, healthy males and females, general population. Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Additional Comments: Because of the potential for hypoglycemia from BE studies using the 4-mg dose of glimepiride tablets, in vivo BE study of the 1 mg glimepiride/4 mg rosiglitazone maleate tablets is recommended. In addition, each dose in the study should be administered with 240 mL of 20% glucose solution to minimize hypoglycemic effects. After dosing, 60 mL of 20% glucose solution should be given to each subject every 15 minutes for the following 4 hours 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 1 mg/4 mg; Subjects: Normal, healthy males and females, general population. Females must have a negative baseline pregnancy test within 24 hours prior

to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Additional comments: Please see additional comments above. Analytes to measure (in appropriate biological fluid): Glimepiride and Rosiglitazone in plasma. Bioequivalence based on (90% CI): Glimepiride and Rosiglitazone. Waiver request of in vivo testing: 2 mg/4 mg, 4 mg/4 mg, 2 mg/8 mg, and 4 mg/8 mg tablets, based on acceptable (i) bioequivalence studies on the 1-mg/4-mg tablet; (ii) proportional similarity of the formulations; and (iii) acceptable in vitro dissolution testing of all strengths.

- Glimepiride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 1 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Because of the potential for hypoglycemia from using a dose of 4 mg of glimepiride tablets, you should conduct the bioequivalence studies using the 1 mg dose. Each dose in the studies should be administered with 240 mL of 20% glucose solution to minimize hypoglycemic effects. After dosing, 60 mL of 20% glucose solution should be given to each subject every 15 minutes for the following 4 hours. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 1 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please comment above. Analytes to measure: Glimepiride in plasma. Bioequivalence based on (90% CI): Glimepiride. Waiver request of in vivo testing: 2 mg and 4 mg based on (i) acceptable bioequivalence studies on the 1-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Glipizide; Metformin Hydrochloride Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 5 mg/500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Since the drug product causes hypoglycemia, it is recommended that subjects receive 60 mL of 20% glucose solution in water after each dose and every 15 minutes for 4 hours during fasting and fed bioequivalence studies. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 5 mg/500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure: Glipizide and metformin in plasma. Bioequivalence based on (90% CI): Glipizide and metformin. Waiver request of in vivo testing: 2.5 mg/250 mg and 2.5 mg/500 mg based on (i) acceptable bioequivalence studies on the 5-mg/500-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Glyburide; Metformin Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 5 mg/500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: The drug products should be administered with 240 mL of 20% glucose solution in water, followed by 60 mL of the glucose solution administered every 15 minutes for up to 4 hours after dosing. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 5 mg/500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: The drug products should be administered with 240 mL of 20% glucose solution in water, followed by 60 mL of the glucose solution administered every 15 minutes for up to 4 hours after dosing. Analytes to measure: Glyburide and Metformin. Bioequivalence based on (90% CI): Glyburide and Metformin. Waiver request of in vivo testing: 1.25 mg/250 mg and 2.5 mg/500 mg based on (i) acceptable bioequivalence studies on the 5-mg/500-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Granisetron Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 1 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 1 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Granisetron in plasma. Bioequivalence based on (90% CI): Granisetron. Waiver request of in vivo testing: Not applicable.
- Hydrochlorothiazide; Irbesartan Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 25 mg/300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 25 mg/300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure: Hydrochlorothiazide and irbesartan in plasma. Bioequivalence based on (90% CI): Hydrochlorothiazide and irbesartan. Waiver request of in vivo testing: 12.5 mg/150 mg and 12.5 mg/300 mg based on (i) acceptable bioequivalence studies on the 25-mg/300-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Lisinopril; Hydrochlorothiazide Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 25 mg/20 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Female subjects enrolled in the BE studies should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 25 mg/20 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure: Lisinopril and Hydrochlorothiazide in plasma. Bioequivalence based on (90% CI): Lisinopril and Hydrochlorothiazide. Waiver request of in vivo testing: 12.5/10 mg and 12.5 mg/20 mg based on (i) acceptable bioequivalence studies on the 25-mg/20-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Hydrochlorothiazide; Losartan Potassium Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 25 mg/100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 25 mg/100 mg; Subjects: Normal, healthy males and females, general population. Additional

comments: Please see comments above. Analytes to measure: Hydrochlorothiazide, losartan, and its carboxylic metabolite in plasma. For the carboxylic acid metabolite, the following data should be submitted: (1) individual and mean concentration, (2) individual and mean pharmacokinetic parameters, and (3) geometric means and ratios of means for AUC and C_{max}. Bioequivalence based on (90% CI): Hydrochlorothiazide and Losartan. Waiver request of in vivo testing: 12.5 mg/50 mg and 12.5 mg/100 mg based on (i) acceptable bioequivalence studies on the 25-mg/100-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Hydrochlorothiazide; Olmesartan Medoxomil Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 25 mg/40 mg Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: The labeling for this drug contains a black box regarding pregnancy and fetal/neonatal morbidity and mortality. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 25 mg/40 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: Please see comment above. Analytes to measure (in appropriate biological fluid): Hydrochlorothiazide and Olmesartan in plasma. Bioequivalence based on (90% CI): Hydrochlorothiazide and Olmesartan. Waiver request of in vivo testing: 12.5-mg/40-mg and 12.5-mg/20-mg strengths based on (i) acceptable bioequivalence studies on the 25-mg/40-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Hydrochlorothiazide; Valsartan Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Randomized, single-dose, two-treatment, two-period crossover in vivo; Strength: 25 mg/160 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: Randomized, single-dose, two-treatment, two-period crossover in vivo; Strength: 25 mg/160 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure (in appropriate biological fluid): Valsartan and hydrochlorothiazide in plasma. Bioequivalence based on (90% CI): Valsartan and hydrochlorothiazide. Waiver request of in vivo testing: 12.5 mg/80 mg and 12.5 mg/160 mg based on (i) acceptable bioequivalence studies on the 25-mg/160-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Irbesartan Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Female subjects should be excluded from the bioequivalence studies if they are pregnant. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 300 mg; Subjects: Normal, healthy males and females, general population Additional comments: Please see comment above. Analytes to measure: Irbesartan in plasma. Bioequivalence based on (90% CI): Irbesartan. Waiver request of in vivo testing: 75 mg and 150 mg based on (i) acceptable bioequivalence studies on the 300-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Isosorbide Mononitrate Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-way, crossover in vivo; Strength: 120 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Single-dose, two-way, crossover in vivo; Strength: 120 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Isosorbide mononitrate in plasma. Bioequivalence based on (90% CI): Isosorbide mononitrate. Waiver request of in vivo testing: 30 mg and 60 mg based on (i) acceptable bioequivalence studies on the 120-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.
- Isradipine Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-way, crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Single-dose, two-way, crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Isradipine in plasma. Bioequivalence based on (90% CI): Isradipine. Waiver request of in vivo testing: 5 mg based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.
- Lamivudine Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid):

Lamivudine in plasma. Bioequivalence based on (90% CI): Lamivudine. Waiver request of in vivo testing: 150 mg based on (i) acceptable bioequivalence studies on the 300-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Lamivudine Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of Study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Lamivudine in plasma. Bioequivalence based on (90% CI): Lamivudine. Waiver request of in vivo testing: Not applicable.
- Lamivudine; Zidovudine Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 150 mg/300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 150 mg/300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Lamivudine and Zidovudine in plasma. Bioequivalence based on (90% CI): Lamivudine and Zidovudine. Waiver request of in vivo testing: Not applicable. Products at this Web site conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Lamotrigine Chewable Dispersible Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: Single-dose of 50 mg (2 × 25 mg); Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: Single-dose of 50 mg (2 × 25 mg); Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Lamotrigine in plasma. Please utilize a validated analytical method such as LC-MS/MS to reliably measure plasma lamotrigine concentrations. An LLOQ of 10 ng/mL is recommended to adequately characterize the pharmacokinetics at 50 mg study dose. Bioequivalence based on (90% CI): Lamotrigine. Waiver request of in vivo testing: 2 mg and 5 mg based on (i) acceptable bioequivalence studies on the 25-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Products at this Web site conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.
- Lamotrigine Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: Single-dose of 50 mg (2 × 25 mg); Subjects: Normal, healthy males and females, general population. Additional comments: Due to safety concerns, studies on the highest strength are not recommended. 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: Single dose of 50 mg (2 × 25 mg); Subjects: Normal, healthy males and females, general population. Additional comments: See comment above. Analytes to measure (in appropriate biological fluid): Lamotrigine in plasma. Please utilize a validated analytical method such as LC-MS/MS to reliably measure plasma lamotrigine concentrations. An LLOQ of 10 ng/mL is recommended to adequately characterize the pharmacokinetics at 50 mg study dose. Bioequivalence based on (90% CI): Lamotrigine. Waiver request of in vivo testing: 100 mg, 150 mg, and 200 mg based on (i) acceptable bioequivalence studies on the 25-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please find the dissolution information for this product at this Web site and conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Leflunomide Tablets/Oral. Recommended studies: 3 studies. 1. Type of study: Fasting Design: Single-dose, two-way crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fasting Design: Single-dose, two-way crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Only female subjects who are unable to bear children should be included in the study and male subjects wishing to father a child during the study should be excluded from the study. Since the half-life of the metabolite A77 1726 is very long, you may consider bioequivalence studies with parallel designs. 3. Type of study: Fed Design: Single-dose, two-way crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure: Please measure only the leflunomide's metabolite, A77 1726, in plasma. Bioequivalence based on (90% CI): The metabolite of leflunomide, A77 1726. Waiver request of in vivo testing: 10 mg based on (i) acceptable bioequivalence studies on the 20-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Levonorgestrel Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: Single-dose, two-way crossover in vivo; Strength: 0.75 mg; Subjects: Normal, healthy females, general population. Additional comments: Analytes to measure: Levonorgestrel in plasma. Bioequivalence based on (90% CI): Levonorgestrel. Waiver request of in vivo testing: Not applicable.
- Lidocaine Patch/Topical. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, in vivo, using three topical patches; Strength: 5%, 700 mg/patch; Subjects: Normal, healthy males and females, general population. Additional comments: Apply three topical patches (2100 mg total dose) simultaneously over a 12-hour period. You may use a smaller number of patches provided the plasma concentrations of lidocaine are measurable to adequately characterize the pharmacokinetic profile of lidocaine for bioequivalence assessment based on the 90% confidence interval criteria. Please include a 24-hour postdose sampling time in the bioequivalence study. In addition to pharmacokinetic data, please report the "apparent dose" delivered. The apparent dose can be determined by subtracting the remaining amount of lidocaine in each patch (used patch) from the manufactured amount. The amount of adhesive residue from each patch left on the skin should be analyzed and included in the calculation. Analytes to measure: Lidocaine in plasma. Please utilize a validated analytical method such as LC-MS/MS to

reliably measure plasma lidocaine concentrations. An LLOQ of 0.20 ng/mL is recommended to adequately characterize the pharmacokinetics at the 2100 mg study dose. Bioequivalence based on (90% CI): Lidocaine. 2. Type of study: Skin irritation/sensitization study Design: Single-dose, in vivo (preceded by an induction phase and a rest period); Strength: 5%, 700 mg/patch; Subjects: Normal, healthy males and females, general population. Additional comments: Specific recommendations are provided below for the skin irritation/sensitization/adhesion study. General comments: Please note that the name of RLD is designated as lidocaine topical patch, 5%. This designation is based on the concentration of lidocaine in the adhesive, which is 5%. Please formulate your product to contain 5% of lidocaine in the adhesive, to have the same surface area and the same total amount of lidocaine in the patch as the RLD.

- Linezolid Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 600 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 600 mg; Subjects: Normal, healthy males and females, general population. Additional Comments: Analytes to measure (in appropriate biological fluid): Linezolid in plasma. Bioequivalence based on (90% CI): Linezolid. Waiver request of in vivo testing: Not applicable.
- Liothyronine Sodium Tablets/Oral. Recommended studies: 1 study. 1. Type of study: Fasting Design: Single-dose, two-way crossover in vivo; Dose and Strength: 100 μg (2 × 50 μg); Subjects: Normal, healthy males and females, general population. Additional comments: Baseline levels of liothyronine should be measured at 3 predose time points (−30 minutes, −15 minutes, and 0 minute). The mean of the three predose samples should be subtracted from each measured postdose concentration. Analytes to measure (in appropriate biological fluid): Total (free + bound) liothyronine in plasma. Bioequivalence based on (90% CI): Total (free + bound) liothyronine in plasma after baseline correction. Waiver request of in vivo testing: 25 μg and 5 μg based on (i) acceptable bioequivalence studies on the 50 μg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Lisinopril Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Lisinopril in plasma. Bioequivalence based on (90% CI): Lisinopril. Waiver request of in vivo testing: 2.5 mg, 5 mg, 10 mg, 20 mg, and 30 mg, based on acceptable (i) bioequivalence studies on the 40-mg strength, and (ii) proportional similarity of the formulations and (iii) acceptable in vitro dissolution testing of all strengths.
- Lopinavir; Ritonavir Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 200 mg/50 mg (400 mg/100 mg dose); Subjects: Normal, healthy males and females, general population. Additional comments: Pregnant and lactating women should be excluded from participation in studies. Women must have a negative baseline pregnancy test prior to receiving the drug. 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 200 mg/50 mg (400 mg/100 mg dose); Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Lopinavir and ritonavir in plasma. Bioequivalence based on (90% CI): Lopinavir and ritonavir. Waiver request of in vivo testing: Not applicable.
- Loratadine Orally Disintegrating Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Loratadine and the active metabolite, descarboethoxyloratadine, in plasma. Please submit the metabolite data as supportive evidence of the comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Bioequivalence based on (90% CI): Loratadine. Waiver request of in vivo testing: Not applicable.
- Losartan Potassium Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Pregnant women should be excluded from participation in the bioequivalence studies. 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: See comment above. Analytes to measure (in appropriate biological fluid): Losartan and the metabolite carboxylic acid in plasma. Bioequivalence based on (90% CI): Losartan. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the carboxylic acid metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Waiver request of in vivo testing: 25 mg and 50 mg based on (i) acceptable bioequivalence studies on the 100-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Mefloquine Hydrochloride Tablets/Oral. Recommended studies: 1 study. Type of study: Fed Design: Single-dose, parallel design in vivo; Strength: 250 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Mefloquine has been shown to cause esophagitis/gastritis when administered under fasting conditions. A fasting bioequivalence study is not recommended. Analytes to measure: Mefloquine in plasma. Bioequivalence

based on (90% CI): Mefloquine. Waiver request of in vivo testing: Not applicable.

- Meloxicam Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-way, crossover in vivo; Strength: 15 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Single-dose, two-way, crossover in vivo; Strength: 15 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Meloxicam in plasma. Bioequivalence based on (90% CI): Meloxicam. Waiver request of in vivo testing: 7.5 mg based on (i) acceptable bioequivalence studies on the 15-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Products at this Web site conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products. Specifications of the application.
- Memantine Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Females should not be of childbearing potential. 2. Type of study: Fed Design: Single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Females should not be of childbearing potential. Additional comments: Analytes to measure (in appropriate biological fluid): Memantine in plasma. Bioequivalence based on (90% CI): Memantine. Waiver request of in vivo testing: 5 mg, based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) formulation proportionality of 10-mg and 5-mg strengths, and (iii) acceptable dissolution testing on both strengths.
- Mercaptopurine Tablet/Oral. Recommended studies: 1 study. Submission of an investigational new drug application is required prior to the conduct of a bioequivalence study for a cytotoxic drug product such as Mercaptopurine (see 21 CFR § 320.31). Type of study: Steady-state study in patients; Strength: 50 mg; Studies may be conducted at steady state in patients receiving therapeutic doses (usually 100–200 mg/day in the average adult) or maintenance daily doses (usually 50–100 mg/day in the average adult). Patients should be in a stable regimen using the same dosage unit (multiples of the same strength). Additional comments: Patients with inherited deficiency of the enzyme thiopurine methyl transferase must be excluded from these studies. The protocol may exclude concomitant chemotherapy and should exclude prior exposure to doxorubicin. The informed consent should include a description of the known genotoxicity of 6-mercaptopurine in human cells and animal models. Analytes to measure (in appropriate biological fluid): Mercaptopurine in plasma. Bioequivalence based on (90% CI): Mercaptopurine. Waiver request of in vivo testing: Not applicable.
- Mesalamine Enema/Rectal. Recommended studies: 1 study. The following study is recommended to establish bioequivalence of mesalamine rectal enema provided that the test product is qualitatively (Q1) and quantitatively (Q2) the same as the RLD: Type of study: Fasting Design: Single-dose, two-way crossover in vivo or replicate design; Strength: 4 G/60 mL; Subjects: Normal, healthy males and females, general population. Additional comments: The proposed generic and RLD formulations should have comparable particle size. Analytes to measure (in appropriate biological fluid: Mesalamine (5-ASA) in plasma. Bioequivalence based on (90% CI): Mesalamine (5-ASA). Waiver request of in vivo testing: Not applicable. In vitro dissolution testing under the following conditions should be submitted to support documentation of bioequivalence: Please conduct comparative dissolution testing on 12 dosage units of the test and reference products using 900 mL of the following media: 0.1 N HCl, and buffers at pH 4.5, pH 6.8, and pH 7.2 using Apparatus II (paddle) at 25 and 50 rpm. Please ensure that the dissolution method is adequate to distinguish mesalamine dissolved in dissolution media from drug particles. You may modify the filtration method in the dissolution testing, if necessary.
- Mesalamine Suppository/Rectal. Recommended studies: 3 studies. 1. Type of study: Bioequivalence study with clinical end points Design: Parallel design, three arm (test, reference, and placebo) in vivo; Strengths: 500 mg and 1000 mg; Subjects: Patients with ulcerative proctitis. Additional comments: Please submit a protocol to the Clinical Review Team for recommendations on study design. 2. Type of study: Bioequivalence studies with pharmacokinetic end points (fasting) Design: Single-dose, two-way crossover in vivo; Strengths: 500 mg 1000 mg, comparing to the respective strengths of the RLD; Subjects: Normal, healthy males and females, general population. Additional comments: Because the 500-mg and 1000-mg strengths are not proportionally similar, a bioequivalence study with clinical end points and a bioequivalence study with pharmacokinetic end points (fasting) will be needed for each strength product, if you wish to develop each strength. Analytes to measure (pharmacokinetic study): Mesalamine in plasma Bioequivalence (pharmacokinetic study) based on (90% CI): Mesalamine. Waiver request of in vivo testing: Not applicable.
- Metaxalone Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 800 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 800 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Metaxalone in plasma. Bioequivalence based on (90% CI): Metaxalone. Waiver request of in vivo testing: 400 mg based on (i) acceptable bioequivalence studies on the 800-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please note that Metaxalone Tablets, 400 mg, have been discontinued from the market. If you would like to market the 400-mg strength, please submit a Citizen Petition pursuant to 21 CFR 314.122, requesting that the FDA determine whether this strength was discontinued due to safety and/or effectiveness reasons. Please follow the Citizen Petition format outlined in 21 CFR 10.20 and 10.30.
- Metformin Hydrochloride Extended-release Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 750 mg; Subjects: Normal, healthy males and females, general population Additional Comments: The drug products should be administered with 240 mL of a 20% glucose solution in water, followed by 60 mL of the glucose solution administered every 15 minutes for up to 4 hours after dosing. 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 750 mg; Subjects: Normal, healthy males and females, general population Additional comments: Please

see comment above. Analytes to measure (in appropriate biological fluid): Metformin in plasma. Bioequivalence based on (90% CI): Metformin. Waiver request of in vivo testing: 500 mg based on (i) acceptable bioequivalence studies on the 750-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.
- Metformin Hydrochloride; Pioglitazone Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-way crossover in vivo; Strength: 850 mg metformin HCl and 15 mg pioglitazone HCl (as the base); Subjects: Normal, healthy males and females, general population. Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Additional comments: To avoid hypoglycemic episodes in healthy volunteers, the drug products should be administered with 240 mL of a 20% glucose solution in water, followed by 60 mL of the glucose solution administered every 15 minutes for up to 4 hours after dosing. 2. Type of study: Fed Design: Single-dose, two-way crossover in vivo; Strength: 850 mg metformin HCl and 15 mg pioglitazone HCl (as the base); Subjects: Normal, healthy males and females, general population. Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Additional comments: To avoid hypoglycemic episodes in healthy volunteers, the drug products should be administered with 240 mL of a 20% glucose solution in water, followed by 60 mL of the glucose solution administered every 15 minutes for up to 4 hours after dosing." Analytes to measure (in appropriate biological fluid): Metformin, Pioglitazone, and Hydroxypioglitazone (M-IV) in plasma. Bioequivalence based on (90% CI): Metformin and pioglitazone. Waiver request of in vivo testing: (500 mg and 15 mg) Metformin HCl, Pioglitazone HCl tablets, based on (i) acceptable bioequivalence study on the (850 mg and 15 mg) tablet, and (ii) acceptable in vitro dissolution testing of all strengths.
- Metoprolol Succinate Extended Release Tablets/Oral. Recommended studies: 3 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. 3. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 50 mg; Subjects: Normal, healthy males and females, general population. Analytes to measure (in appropriate biological fluid): Metoprolol in plasma. Bioequivalence based on (90% CI): Metoprolol. Waiver request of in vivo testing: 25 mg, 100 mg tablets, based on (i) acceptable bioequivalence studies on the 50-mg and 200-mg strengths, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2 and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Because of concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows: Testing Conditions: 900 mL, 0.1 N HCl, Apparatus II (paddle) at 50 rpm, with and without the alcohol (see below): Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours. Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range, and %CV on both strengths.
- Minocycline Hydrochloride Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-way crossover in vivo; Strength: 135 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: Single-dose, two-way crossover in vivo; Strength: 135 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Analytes to measure (in appropriate biological fluid): Minocycline in plasma. Bioequivalence based on (90% CI): Minocycline. Waiver request of in vivo testing: 45 mg and 90 mg based on (i) acceptable bioequivalence studies on the 135-mg strength, (ii) proportionally similar 45 mg and 90 mg formulations to the 135-mg strength, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.
- Mirtazapine Orally Disintegrating Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting

Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 15 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Due to safety concerns, studies on the lower strength are recommended. 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 15 mg; Subjects: Normal, healthy males and females, general population Additional comments: Please see above comment. Analytes to measure: Mirtazapine in plasma. Bioequivalence based on (90% CI): Mirtazapine. Waiver request of in vivo testing: 30 mg and 45 mg based on (i) acceptable bioequivalence studies on the 15-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Modafinil Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Modafinil using an achiral assay. Bioequivalence based on (90% CI): Modafinil. Waiver request of in vivo testing: 100 mg based on (i) acceptable bioequivalence studies on the 200-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Moexipril Hydrochloride Tablet/Oral. Recommended studies: 1 study. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 15 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Pregnant women should be excluded from participation in the bioequivalence study. Analytes to measure (in appropriate biological fluid): Moexipril in plasma. Bioequivalence based on (90% CI): Moexipril. Waiver request of in vivo testing: 7.5 mg based on (i) acceptable bioequivalence studies on the 15-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Montelukast Sodium Chewable Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Montelukast in plasma. Bioequivalence based on (90% CI): Montelukast. Waiver request of in vivo testing: 4 mg based on (i) acceptable bioequivalence studies on the 5-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Mycophenolate Mofetil Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 500 mg; Subjects: Normal, healthy males and females, general population. Additional Comments: 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Mycophenolate mofetil, and the active metabolite, mycophenolic acid in plasma. Bioequivalence based on (90% CI): Mycophenolate mofetil. If mycophenolate mofetil plasma concentrations can be reliably measured and its pharmacokinetics accurately determined, please analyze the data for the parent compound using the confidence interval approach. The data for the active metabolite can be used as supportive evidence. However, if you can demonstrate that it is not possible to measure mycophenolate mofetil in plasma accurately and reliably, please analyze the metabolite using the confidence interval approach. Waiver request of in vivo testing: Not applicable.
- Nabumetone Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-way crossover in vivo; Strength: 750 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Single-dose, two-way crossover in vivo; Strength: 750 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: 6-methoxy-2-naphthylacetic acid (6-MNA). Bioequivalence based on (90% CI): 6-methoxy-2-naphthyl-acetic acid (6-MNA). Waiver request of in vivo testing: 500 mg based on (i) acceptable bioequivalence studies on the 750-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Nateglinide Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-way crossover in vivo; Strength: 120 mg; Subjects: Normal, healthy males and females, general population. Additional comments: All subjects should fast overnight for at least 10 hours prior to dosing and for 4 hours after dosing. A single oral dose (120 mg) should be administered with 240 mL of 20% glucose solution. Since, multiple plasma concentration peaks were often observed under fasting conditions, please ensure that the same sampling schedule is followed during the study for both test and reference drug administration. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: Single-dose, two-way crossover in vivo; Strength: 120 mg; Subjects: Normal, healthy males and females, general population Additional comments: A single oral dose (120 mg) should be administered with 240 mL of water 30 minutes after start of a standard high-fat FDA breakfast. Subjects should start the recommended meal 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Analytes to measure (in appropriate biological fluid): Nateglinide in plasma. Bioequivalence based on (90% CI): Nateglinide. Waiver request of in vivo testing: 60 mg, based on (i) acceptable bioequivalence studies on the 120-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Nelfinavir Mesylate Tablets/Oral. Recommended studies: 3 studies. 1. Type of study: Fasting Design: Randomized, single-dose, two-treatment, two-period crossover in vivo; Strength: 625 mg; Subjects: Normal, healthy males and females, general population. Additional comments: High pharmacokinetic variability has been observed with

nelfinavir when administered to fasting subjects. Thus, it is the firm's responsibility to enroll an adequate number of subjects to demonstrate bioequivalence. Since nelfinavir appears to be a highly variable drug when administered under fasting conditions, conducting a replicate-design study as an alternative to a two-way crossover study may be considered. A replicate study design has the advantage that fewer subjects can be used than in a two-way crossover study. The FDA recommends that a replicate design bioequivalence study use the following two sequences: ABAB (Test Reference Test Reference) and BABA (Reference Test Reference Test). 2. Type of study: Fasting Design: Randomized, single-dose, two-treatment, two-period crossover in vivo; Strength: 250 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see above. 3. Type of study: Fed Design: Randomized, single-dose, two-treatment, two-period crossover in vivo; Strength: 625 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see above. Analytes to measure (in appropriate biological fluid): Nelfinavir in plasma. Please develop a method of adequate sensitivity to accurately measure nelfinavir concentrations in plasma. If it is not possible to accurately measure nelfinavir plasma concentrations following administration of a single dosage unit, it is acceptable to administer a higher dose. A single dose as high as 1250 mg may be safely administered to healthy, normal subjects. Bioequivalence based on (90% CI): Nelfinavir. Waiver request of in vivo testing: Not applicable.

- Nevirapine Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, randomized, two-treatment, one-period, parallel, open-label in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Due to safety concerns of severe life-threatening skin reactions and hepatotoxicity, single-dose parallel study designs in healthy volunteers are recommended. 2. Type of study: Fed Design: Single-dose, randomized, two-treatment, one-period, parallel, open-label in vivo; Strength: 200 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure (in appropriate biological fluid): Nevirapine in plasma. Bioequivalence based on (90% CI): Nevirapine. Waiver request of in vivo testing: Not applicable.
- Olanzapine Orally Disintegrating Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Due to safety concerns, studies should be conducted using the 5-mg strength. 2. Type of study: Fed Design: Single-dose, two-treatment, two-period crossover in vivo; Strength: 5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see above comment. Analytes to measure: Olanzapine in plasma. Bioequivalence based on (90% CI): Olanzapine. Waiver request of in vivo testing: 10 mg, 15 mg, and 20 mg based on (i) acceptable bioequivalence studies on the 5-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Product at this Web site.
- Olmesartan Medoxomil Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Single-dose, two-way crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: Labeling for this drug contains a black box regarding pregnancy and fetal/neonatal morbidity and mortality. 2. Type of study: Fed Design: Single-dose, two-way crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Olmesartan in plasma. Bioequivalence based on (90% CI): Olmesartan. Waiver request of in vivo testing: 20 mg and 5 mg based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Omeprazole, Sodium Bicarbonate, and Magnesium Hydroxide Chewable Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 40 mg/600 mg/700 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Analytes to measure (in appropriate biological fluid): Omeprazole in plasma. Bioequivalence based on (90% CI): Omeprazole. Waiver request of in vivo testing: 20 mg/600 mg/700 mg based on (i) acceptable bioequivalence studies on the 40-mg/600-mg/700-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Omeprazole Magnesium Delayed-release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Omeprazole in plasma. Bioequivalence based on (90% CI): Omeprazole. Waiver request of in vivo testing: Not applicable.
- Ondansetron Orally Disintegrating Tablet. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 8 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 8 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Ondansetron in plasma. Bioequivalence based on (90% CI): Ondansetron. Waiver request of in vivo testing: 4 mg based on (i) acceptable bioequivalence studies on the 8-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Ondansetron Hydrochloride Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 24 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 24 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Ondansetron in plasma. Bioequivalence based on (90% CI): Ondansetron. Waiver request of in vivo testing: 4 and 8 mg based on (i)

acceptable bioequivalence studies on the 24-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Oxcarbazepine Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 600 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 600 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Oxcarbazepine and active metabolite 10-monohydroxy derivative in plasma using a chiral assay. Bioequivalence based on (90% CI): Oxcarbazepine. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Waiver request of in vivo testing: 150 mg and 300 mg based on (i) acceptable bioequivalence studies on the 600-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Oxymorphone Hydrochloride Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please use a narcotic antagonist such as naltrexone if the study involves healthy subjects. You should consult a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Oxymorphone and its metabolite, 6-OH-oxymorphone in plasma. Bioequivalence based on (90% CI): Oxymorphone. For 6-OH-oxymorphone, please submit individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Waiver request of in vivo testing: 5 mg, 10 mg, and 20 mg based on (i) acceptable bioequivalence studies of the 40-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. For modified release products, dissolution profiles generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 phosphate buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, 4 and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 tablets. Because of concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows: Testing Conditions: 900 mL, 0.1 N HCl, Apparatus I (basket) at 75 rpm, with and without the alcohol (see below): Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours. Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range, and %CV on both strengths.
- Oxymorphone Hydrochloride Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please use a narcotic antagonist such as naltrexone if the study involves healthy subjects. You should consult a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist. Analytes to measure (in appropriate biological fluid): Oxymorphone and its metabolite, 6-OH-oxymorphone in plasma. For 6-OH-oxymorphone, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Bioequivalence based on (90% CI): Oxymorphone. Waiver request of in vivo testing: 5 mg, based on acceptable (i) bioequivalence studies on the 10-mg strength, (ii) proportional similarity of the formulations, and (iii) acceptable in vitro dissolution testing of all strengths.
- Paliperidone Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 6 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 6 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure (in appropriate biological fluid): Paliperidone in plasma. Bioequivalence based on (90% CI): Paliperidone. Waiver request of in vivo testing: 3 mg and 9 mg based on (i) acceptable bioequivalence studies of the 6-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, 6.8 buffer, and water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 tablets.

- Pantoprazole Sodium Delayed Release Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Pantoprazole in plasma. Bioequivalence based on (90% CI): Pantoprazole. Waiver request of in vivo testing: 20 mg based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Perindopril Erbumine Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 8 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Female subjects enrolled in the BE studies should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 8 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Perindopril and the active metabolite, perindoprilat in plasma. Bioequivalence based on (90% CI): Perindopril. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Waiver request of in vivo testing: 2 mg and 4 mg based on (i) acceptable bioequivalence studies on the 8-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Phenytoin Chewable Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 300 mg dose (6 × 50 mg) and use a washout period of at least 14 days; Subjects: Normal, healthy males and females, general population. Additional comments: The tablets should be swallowed whole. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 300-mg dose (6 × 50 mg) and use a washout period of at least 14 days; Subjects: Normal, healthy males and females, general population. Additional Comments: The tablets should be swallowed whole. Analytes to measure (in appropriate biological fluid): Phenytoin in plasma. Bioequivalence based on (90% CI): Phenytoin. Waiver request of in vivo testing: Not applicable.
- Pilocarpine Hydrochloride Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 7.5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 7.5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Pilocarpine and the metabolite, pilocarpic acid in plasma. Pilocarpine has been shown to be unstable in heparinized plasma and convert to pilocarpic acid during storage. Therefore, you should pay attention to the stabilization of pilocarpine and separation of the drug from its metabolites in the assay development and validation. Recent literature states that the use of EDTA as an anticoagulant during blood sampling may be helpful in stabilizing pilocarpine. The stability of pilocarpine in plasma samples and the assay specificity of pilocarpine, especially in relation to its metabolites and plasma endogenous components, should be clearly demonstrated in the assay method validation report submitted to the FDA. Bioequivalence based on (90% CI): Pilocarpine. If pilocarpine can be reliably measured, a confidence interval approach for bioequivalence determination should be used for pilocarpine. If pilocarpine cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for pilocarpic acid. Waiver request of in vivo testing: 5 mg based on (i) acceptable bioequivalence studies on the 7.5-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Pimozide Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 2 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Analytes to measure (in appropriate biological fluid): Pimozide in plasma Pimozide has a long terminal elimination half-life. Please ensure adequate washout periods between treatments in the crossover studies. You may also consider using a parallel study design due to pimozide's long half-life. For long half-life drug products, an AUC truncated to 72 hours may be used in place of AUC0–t or AUC–inf. Please collect sufficient blood samples in the bioequivalence study to adequately characterize the peak concentration (C_{max}) and time to reach peak concentration (t_{max}). Bioequivalence based on (90% CI): Pimozide. Waiver request of in vivo testing: 1 mg based on (i) acceptable bioequivalence studies on the 2-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Pravastatin Sodium Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 80 mg; Subjects: Normal, healthy males and females, general population. Additional Comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 80 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Pravastatin in plasma. Bioequivalence based on (90% CI): Pravastatin. Waiver request of in vivo testing: 10 mg, 20 mg, and 40 mg based on (i) acceptable bioequivalence studies on the 80-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Quetiapine Fumarate Tablet/Oral. Recommended studies: 3 studies. 1. Type of study: Fasting Design: single-dose, in –vivo; Strength: 25 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please include careful safety precautions in your protocols, including adequate monitoring of vital signs and adverse events, stopping criteria in the event of an unacceptable degree of hypotension or tachycardia, and appropriate evaluation and management of adverse events. Please assure

that the investigator(s) will be vigilant in recognizing and managing any unacceptable clinical or laboratory findings. It is recommended that a study protocol be submitted for review before initiating a bioequivalence study for this product. 2. Type of study: Fed Design: single-dose, in vivo; Strength: 25 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. 3. Type of study and design: Steady-state, in vivo; Strength: 300 mg; Subjects: Schizophrenic patients already receiving quetiapine in a stable regimen. Additional comments: Please see comments above. Analytes to measure: Quetiapine in plasma. Bioequivalence based on (90% CI): Quetiapine. Waiver request of in vivo testing: 50 mg, 100 mg, 150 mg, 200 mg, and 400 mg based on (i) acceptable bioequivalence studies on the 25-mg and 300-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products.

- Quinapril Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way, crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Pregnant women should be excluded from participation in bioequivalence studies with ACE inhibitors. 2. Type of study: Fed Design: single-dose, two-way, crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population Additional comments: Pregnant women should be excluded from participation in bioequivalence studies with ACE inhibitors. Analytes to measure: Quinapril and the metabolite, Quinaprilat in plasma. Bioequivalence based on (90% CI): Quinapril. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Waiver request of in vivo testing: 5 mg, 10 mg, and 20 mg based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Raloxifene Hydrochloride Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 60 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 60 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Raloxifene and the metabolites, raloxifene-4′-glucuronide and raloxifene-6′-glucuronide in plasma. Bioequivalence based on (90% CI): Raloxifene. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Waiver request of in vivo testing: Not applicable.
- Ribavirin Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 600 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 600 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Ribavirin in plasma. Bioequivalence based on (90% CI): Ribavirin. Waiver request of in vivo testing: 200 mg, and 400-mg strengths based on (i) acceptable bioequivalence studies on the 600-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Riluzole Tablets/Oral. Recommended studies: 1 study. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 50 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Riluzole in plasma. Bioequivalence based on (90% CI): Riluzole. Waiver request of in vivo testing: Not applicable.
- Risedronate Sodium; Calcium Carbonate Tablets/Oral (co-packaged). Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 35 mg (risedronate sodium tablet); Subjects: Normal, healthy males and females, general population. Additional comments: As an option, due to the relatively long half-life, the firm may wish to conduct this study using a parallel design. As an additional option for either the crossover or parallel design, the firm may wish to truncate the AUC at 72 hours. Analytes to measure (in appropriate biological fluid): Risedronate in plasma. Bioequivalence based on (90% CI): Risedronate. Waiver request of in vivo testing: Not applicable. For calcium carbonate table please conduct comparative dissolution testing on 12 dosage units.
- Risedronate Sodium Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 75 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 35 mg; Subjects: Normal, healthy males and females, general population. Additional comments: As an option, due to the relatively long half-life, the firm may wish to conduct this study using a parallel design. As an additional option for either the crossover or parallel design, the firm may wish to truncate the AUC at 72 hours. Analytes to measure (in appropriate biological fluid): Risedronate in plasma. Bioequivalence based on (90% CI): Risedronate. Waiver request of in vivo testing: 5 mg and 30 mg based on (i) acceptable bioequivalence study on the 35-mg and 75-mg strengths, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Risperidone Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 1 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Due to safety concerns, bioequivalence studies should be conducted using the 1-mg strength. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 1 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure: Risperidone in plasma. Bioequivalence based on (90% CI): Risperidone. Waiver request of in vivo testing: 0.25 mg, 0.5 mg, 2 mg, 3 mg,

and 4 mg based on (i) acceptable bioequivalence studies on the 1-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Rizatriptan Benzoate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Rizatriptan in plasma. Bioequivalence based on (90% CI): Rizatriptan. Waiver request of in vivo testing: 5 mg, based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Rosiglitazone Maleate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 8 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 8 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Rosiglitazone in plasma. Bioequivalence based on (90% CI): Rosiglitazone. Waiver request of in vivo testing: 2 mg and 4 mg, based on (i) acceptable bioequivalence studies on the 8-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Rosuvastatin Calcium Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of Study: Fed Design: single-dose, two-way crossover in vivo; Strength: 40 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Rosuvastatin in plasma. Bioequivalence based on (90% CI): Rosuvastatin. Waiver requests of in vivo testing: 5-mg, 10-mg, and 20-mg strengths based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) proportional similarity across all strengths, and (iii) acceptable dissolution testing of all strengths.
- Saquinavir Mesylate Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Saquinavir in plasma. Bioequivalence based on (90% CI): Saquinavir. Waiver request of in vivo testing: Not applicable.
- Sertraline Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Due to safety concerns, bioequivalence studies should be conducted on the 100-mg strength. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Sertraline in plasma. Bioequivalence based on (90% CI): Sertraline. Waiver request of in vivo testing: 25 mg, 50 mg, 150 mg, and 200 mg based on (i) acceptable bioequivalence studies on the 100-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Sildenafil Citrate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males. Additional comments: Analytes to measure (in appropriate biological fluid): Sildenafil and active metabolite piperazine N-desmethylsildenafil in plasma. Bioequivalence based on (90% CI): Sildenafil. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: Individual and mean concentrations; Individual and mean pharmacokinetic parameters and Geometric means and ratios of means for AUC and C_{max}. Waiver request of in vivo testing: 25 mg and 50 mg based on (i) acceptable bioequivalence studies on the 100-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Simvastatin Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 80 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 80 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Simvastatin and its β-hydroxyacid metabolite in plasma. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the β-hydroxy metabolite of simvastatin, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Bioequivalence based on (90% CI): Simvastatin. Waiver request of in vivo testing: 5 mg, 10 mg, 20 mg, and 40 mg based on (i) acceptable bioequivalence studies on the 80-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the method specified in the USP method.
- Sirolimus Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 2 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 2 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Sirolimus in plasma. Bioequivalence based on (90% CI): Sirolimus. Waiver request of in vivo testing: 1 mg based on (i) acceptable bioequivalence studies on the 2-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Solifenacin Succinate Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, parallel in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Note: As an option, you may conduct this study using a single-dose, two-way crossover design. As an additional option for either the crossover or parallel design, you may truncate the AUC at 72 hours, provided the drug demonstrates low intrasubject variability in distribution and clearance. 2. Type of Study: Fed Design: single-dose, parallel in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Solifenacin in plasma. Bioequivalence based on (90% CI): Solifenacin. Waiver request of in vivo testing: 5 mg based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Sumatriptan Succinate Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Sumatriptan in plasma. Bioequivalence based on (90% CI): Sumatriptan. Waiver request of in vivo testing: 25 mg and 50 mg, based on (i) acceptable bioequivalence studies on the 100-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Tadalafil Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males, general population. Additional comments: 2. Type of Study: Fed Design: single-dose, two-way crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Tadalafil in plasma. Bioequivalence based on (90% CI): Tadalafil. Waiver request of in vivo testing: 5 mg and 10 mg based on (i) acceptable bioequivalence studies on the 20-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Telithromycin Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 400 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: The study design should include a screen for signs and symptoms of possible hepatotoxicity prior to administering each subsequent dose of telithromycin in a crossover or replicate crossover design. In order to minimize the risk of hepatotoxicity, please do not exceed a 400-mg dose in the BE study. Subjects who consume alcohol should be excluded from BE studies of telithromycin. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 400 mg; Subjects: Normal, healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Telithromycin in plasma. Bioequivalence based on (90% CI): Telithromycin. Waiver request of in vivo testing: 300 mg based on (i) acceptable bioequivalence studies on the 400-mg strength, (ii) proportionally similar across both strengths, and (iii) acceptable in vitro dissolution testing of both strengths.
- Telmisartan Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 80 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 80 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure (in appropriate biological fluid): Telmisartan in plasma. Bioequivalence based on (90% CI): Telmisartan. Waiver request of in vivo testing: 20 mg and 40 mg, based on (i) acceptable bioequivalence studies on the 80-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Tenofovir Disoproxil Fumarate Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Tenofovir in serum. Bioequivalence based on (90% CI): Tenofovir. Waiver request of in vivo testing: Not applicable.
- Terbinafine Hydrochloride Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Randomized, single-dose, two-treatment, two-period crossover in vivo; Strength: 250 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Randomized, single-dose, two-treatment, two-period crossover in vivo; Strength: 250 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Terbinafine in plasma. Bioequivalence based on (90% CI): Terbinafine. Waiver request of in vivo testing: Not applicable.
- Testosterone Extended Release Tablets/Buccal. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 30 mg; Subjects: Testosterone-deficient (hypogonadal) males. Additional comments: Subjects should not currently be receiving any treatment for their hypogonadism. The inclusion criterion for testosterone-deficient (hypogonadal) males is serum testosterone levels below 2.5 ng/mL. At least three predose levels will serve as baseline. A "fed" BE study is not recommended because the product is a buccal adhesive, not to be ingested. This obviates the need for oral dose dumping assessment due to food. 2. Type of study: In vitro adhesion comparative performance testing study Design: A tensiometry study is recommended to compare the peak detachment force for test and reference products. Water is recommended between the buccal tablets and the base plate of the tensiometer. The loading weight and length

of time the loading weight is applied to press the buccal tablet into contact with the base plate should be specified. Following removal of the weight, the rate at which the buccal tablet is pulled away from the base plate should be specified. The peak detachment force should be measured as the force required to detach the buccal tablet from the base plate. The comparative adhesion test should be conducted using 12 individual units of the test and reference products. Prior to conducting studies for submission to the ANDA, the firm should determine appropriate loading weight, length of time the loading weight is applied to press the buccal tablet into contact with the base plate of the tensiometer, and the rate at which the buccal tablet is pulled away from the base plate. These studies should be conducted to assure the appropriateness of the test conditions to the test and reference products. Analytes to measure (in appropriate biological fluid): Total testosterone in plasma. Bioequivalence based on (90% CI): Baseline-adjusted testosterone. Waiver request of in vivo testing: Not applicable.

- Ticlopidine Hydrochloride Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 250 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 250 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Ticlopidine in plasma. Bioequivalence based on (90% CI): Ticlopidine. Waiver request of in vivo testing: Not applicable.
- Tinidazole Tablet/Oral. Recommended studies: 1 study. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 500 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Tinidazole in plasma. Bioequivalence based on (90% CI): Tinidazole. Waiver request of in vivo testing: 250 mg based on (i) acceptable bioequivalence studies of the 40-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Dissolution testing to document bioequivalence: Apparatus: USP Apparatus I (basket) Rotation speed: 100 rpm Medium: 0.1 N HCl (or 0.1 N HCl with NaCl) at pH 1.2, pH 4.5 acetate buffer, pH 6.8 phosphate buffer, and water Volume: 900 mL Temperature: 37°C Sample times: 5, 10, 15, 20, 25, 30, and 40 minutes or as needed for profile comparisons. Additional comments: All raw data (test and reference products) should be submitted with means at each sampling point, the range (minimum and maximum values), the percentage of coefficient of variation (%CV), and f2 value tabulated (if appropriate). The dissolution testing should be conducted on 12 units from the same lot numbers that are used in the in vivo bioequivalence study.
- Tolterodine Tartrate Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: Randomized, single-dose, two-treatment, two-period, two-sequenced crossover in vivo; Strength: 2 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: Randomized, single-dose, two-treatment, two-period, two-sequenced crossover in vivo; Strength: 2 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Tolterodine and the active metabolite, 5-hydroxymethyltolterodine (5-OHM) in plasma. Bioequivalence based on (90% CI): Tolterodine. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Waiver request of in vivo testing: 1 mg based on (i) acceptable bioequivalence studies on the 2-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Topiramate Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 25 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Due to safety concerns, studies should be conducted on the 25-mg strength. Animal studies with topiramate have demonstrated selective developmental toxicity, including teratogenicity. Although no studies have been conducted in pregnant women taking topiramate, in postmarketing experience, cases of hypospadias have been reported in male infants exposed in utero to topiramate, with or without other anticonvulsants; however, a causal relationship with topiramate has not been established. Therefore, the following precautions are recommended for the bioequivalence study: Pregnant women should be excluded from the study, and a negative pregnancy test should be required within 24 hours before dosing for all women of childbearing potential. Women of childbearing potential should be enrolled only if using an effective method of contraception. Written informed consent must include the finding of birth defects in animal studies and the unknown risk to a human fetus if exposed to this drug. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 25 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Topiramate in plasma. Bioequivalence based on (90% CI): Topiramate. Waiver request of in vivo testing: 50 mg, 100 mg, and 200 mg based on (i) acceptable bioequivalence studies on the 25-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Torsemide Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Due to safety concerns associated with administering Torsemide Tablets, 100 mg, to healthy subjects, in vivo bioequivalence studies should be conducted on the 20-mg strength. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure (in appropriate biological fluid): Torsemide in plasma. Bioequivalence based on (90% CI): Torsemide. Waiver request of in vivo testing: 5 mg, 10 mg, and 100 mg, based on (i) acceptable bioequivalence studies on the 20-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Tramadol Hydrochloride; Acetaminophen Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting

Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 37.5 mg/325 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 37.5 mg/325 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Tramadol using an achiral assay and acetaminophen. Bioequivalence based on (90% CI): Tramadol and acetaminophen. Waiver request of in vivo testing: Not applicable.

- Tramadol Extended Release Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 100 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Tramadol in plasma by achiral assay (nonstereospecific method). Bioequivalence based on (90% CI): Tramadol. Waiver request of in vivo testing: 200 mg and 300 mg based on (i) acceptable bioequivalence studies on the 100-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Because of concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows: Testing conditions: 900 mL, 0.1 N HCl, Apparatus I (basket) at 75 rpm, with and without the alcohol (see below): Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours. Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range, and %CV on both strengths.
- Tramadol Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 50 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 50 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Tramadol in plasma using an achiral assay. Bioequivalence based on (90% CI): Tramadol. Waiver request of in vivo testing: Not applicable.
- Trandolapril Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 4 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 4 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure: Trandolapril and its active metabolite, trandolaprilat in plasma. Bioequivalence based on (90% CI): Trandolapril. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and C_{max}. Waiver request of in vivo testing: 1 mg and 2 mg based on (i) acceptable bioequivalence studies on the 4-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Trospium Chloride Tablet/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Analytes to measure (in appropriate biological fluid): Trospium in plasma. Bioequivalence based on (90% CI): Trospium. Waiver request of in vivo testing: Not applicable.
- Valacyclovir Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 1000 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 1000 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Valacyclovir and its metabolite, acyclovir, in both studies. If valacyclovir plasma concentrations can be reliably measured and its pharmacokinetic parameters accurately determined, you should analyze the valacyclovir data using the confidence interval approach. The acyclovir data can be used to provide supportive evidence of comparable therapeutic outcome. Bioequivalence based on (90% CI): Valacyclovir. If valacyclovir cannot be reliably measured, you should analyze the acyclovir data obtained from these studies using the confidence interval approach. Waiver request of in vivo testing: 500 mg based on (i) acceptable bioequivalence studies on the 1000-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Valsartan Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 320 mg; Subjects: Normal, healthy males and females, general population. Additional comments: A dose of 320 mg can be

safely administered to healthy subjects. Please include provisions for appropriate monitoring and intervention in the case of possible drug-related adverse events (e.g., subjects complaining of dizziness/lightheadedness should have blood pressure/heart rate assessed). Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 320 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure (in appropriate biological fluid): Valsartan in plasma. Bioequivalence based on (90% CI): Valsartan. Waiver request of in vivo testing: 40 mg, 80 mg, and 160 mg based on (i) acceptable bioequivalence studies on the 320-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

- Vardenafil Hydrochloride Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males, general population. Additional comments: 2. Type of Study: Fed Design: single-dose, two-way crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Vardenafil in plasma. Bioequivalence based on (90% CI): Vardenafil. Waiver request of in vivo testing: 2.5 mg, 5 mg, and 10 mg, based on (i) acceptable bioequivalence studies on the 20-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Varenicline Tartrate Tablet/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 1.0 mg; Subjects: Normal, healthy males and females, general population, smokers, and nonsmokers may be used. Additional comments: Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 1.0 mg; Subjects: Normal, healthy males and females, general population, smokers, and nonsmokers may be used. Additional comments: Please see comments above. Analytes to measure (in appropriate biological fluid): Varenicline in plasma. Bioequivalence based on (90% CI): Varenicline. Waiver request of in vivo testing: 0.5 mg, based on (i) acceptable bioequivalence studies of the 1-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Zafirlukast Tablets/Oral. Recommended studies: 1 study. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 20 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Zafirlukast in plasma. Bioequivalence based on (90% CI): Zafirlukast. Waiver request of in vivo testing: 10 mg based on acceptable (i) bioequivalence studies on the 20-mg tablet, and (ii) proportional similarity of the formulations and (iii) acceptable in vitro dissolution testing of all strengths.
- Zalcitabine Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 0.75 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 0.75 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Zalcitabine in plasma. Bioequivalence based on (90% CI): Zalcitabine. Waiver request of in vivo testing: 0.375 mg based on (i) acceptable bioequivalence studies on the 0.75-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Zaleplon Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Patients should be advised not to drive if they are experiencing drowsiness and/or dizziness at the end of the study. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Zaleplon in plasma. Bioequivalence based on (90% CI): Zaleplon. Waiver request of in vivo testing: 5 mg based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
- Zidovudine Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 300 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Zidovudine in plasma. Bioequivalence based on (90% CI): Zidovudine. Waiver request of in vivo testing: Not applicable. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.
- Zileuton Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 600 mg; Subjects: Normal, healthy males and females, general population. Additional comments: 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 600 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure (in appropriate biological fluid): Zileuton in plasma. Bioequivalence based on (90% CI): Zileuton. Waiver request of in vivo testing: Not applicable.
- Zolmitriptan Orally Disintegrating Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: The whole tablet should be placed on the tongue and allowed to disintegrate for 30 seconds. After 30 seconds, all subjects should consume 240 mL of water. 2. Type of study: Fed Design: single-dose, two-treatment, two-period crossover in vivo; Strength: 5 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Please see comment above. Analytes to measure (in appropriate biological fluid): Zolmitriptan in plasma. Bioequivalence based on (90% CI): Zolmitriptan. Waiver request of in vivo

testing: 2.5 mg based on acceptable (i) bioequivalence studies on the 5-mg strength, and (ii) proportional similarity of the formulations and (iii) acceptable in vitro dissolution testing of all strengths.

- Zolpidem Tablets/Oral. Recommended studies: 2 studies. 1. Type of study: Fasting Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Patients should be advised not to drive if they are experiencing drowsiness and/or dizziness at the end of the study. 2. Type of study: Fed Design: single-dose, two-way crossover in vivo; Strength: 10 mg; Subjects: Normal, healthy males and females, general population. Additional comments: Analytes to measure: Zolpidem in plasma. Bioequivalence based on (90% CI): Zolpidem. Waiver request of in vivo testing: 5 mg based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

GMP Audit Template, EU Guidelines (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm)

		Compliance 1 2 3[a]	Remarks	EU-Guide
1	**PERSONNEL**			
1.1	Qualified personnel available?	☐ ☐ ☐		2.1
1.2	Organization charts available?	☐ ☐ ☐		2.2
1.3	Job descriptions available?	☐ ☐ ☐		2.2
1.4	Responsibilities clearly defined?	☐ ☐ ☐		2.2
	Key personnel			
	Responsible persons designated for:			
1.5	• Production?	☐ ☐ ☐		2.5
1.6	• Quality control?	☐ ☐ ☐		2.6
1.7	Are they independent from each other?	☐ ☐ ☐		2.3
1.8	Are joint functions clearly defined?	☐ ☐ ☐		2.7
1.9	Are the responsible persons working full time?	☐ ☐ ☐		2.3
1.10	Have the responsible persons the appropriate formation, knowledge, and experience?	☐ ☐ ☐		2.1/2.2
1.11	Have the relevant departments enough personnel?	☐ ☐ ☐		2.1
	Training			
1.12	Continuous training programs for the production and QC staff?	☐ ☐ ☐		2.8
1.13	Initial job training for all employees?	☐ ☐ ☐		2.9
1.14	Teaching aids (videos, slides, brochures) available?	☐ ☐ ☐		2.9
1.15	External training courses for the staff?	☐ ☐ ☐		2.9
1.16	Training records?	☐ ☐ ☐		2.9
1.17	Special training in sensitive areas? (sterile prod., toxic subs.)	☐ ☐ ☐		2.10
1.18	Information for visitors to the manufacturing area?	☐ ☐ ☐		2.11
2	**HYGIENE**			
	Personnel hygiene			
	Detailed written hygiene programs for:			
2.1	• clothing?	☐ ☐ ☐		2.13
2.2	• use of washrooms?	☐ ☐ ☐		2.13
2.3	• behaviour in production areas?	☐ ☐ ☐		2.13
2.4	Precautions against sick or personnel with open wounds in production?	☐ ☐ ☐		2.14
	Medical examination			
2.5	• on recruitment?	☐ ☐ ☐		2.15
2.6	• regular reexaminations?	☐ ☐ ☐		2.15

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Duty of notification after:			
2.7	• trips to tropical countries?	☐ ☐ ☐		2.15
2.8	• cases of contagious illness in the family?	☐ ☐ ☐		2.15
2.9	Instructions for appropriate working clothes?	☐ ☐ ☐		2.16
2.10	Absence of food and drinks (chewing gum) in the working area?	☐ ☐ ☐		2.17
2.11	Measures against contact with open product (gloves, etc.)?	☐ ☐ ☐		2.18
2.12	Instructions for hand washing in production?	☐ ☐ ☐		2.19
2.13	Change of clothes when entering and leaving the production area?	☐ ☐ ☐		5.19
2.14	Change rooms and toilets easily within reach?	☐ ☐ ☐		3.31
2.15	Toilets and restrooms sufficiently separated from production areas?	☐ ☐ ☐		3.30/3.31
2.16	Workshops separate from production areas?	☐ ☐ ☐		3.32
2.17	Laboratory animal rooms totally segregated from production rooms?	☐ ☐ ☐		3.33
3	**WAREHOUSE**			
	Rooms, general:			
3.1	Suitable for the intended use?	☐ ☐ ☐		3
3.2	• adequate size?	☐ ☐ ☐		3
3.3	• clean?	☐ ☐ ☐		3
3.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
3.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
3.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
3.7	Appropriate lighting and air conditioning?	☐ ☐ ☐		3.3
3.8	Recording of temperature and humidity?	☐ ☐ ☐		
3.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
3.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
	Type of warehousing:			
3.11	Separation of goods sufficient?	☐ ☐ ☐		3.18
3.12	Provision for different storage temperatures?	☐ ☐ ☐		3.19
3.13	Goods receiving zone weather protected?	☐ ☐ ☐		3.20
3.14	Cleaning zone for incoming goods?	☐ ☐ ☐		3.20
3.15	Separate quarantine area with controlled access?	☐ ☐ ☐		3.21
3.16	Separate, protected sampling area?	☐ ☐ ☐		3.22
	Separate and safe storage of:			
3.17	• returned goods?	☐ ☐ ☐		3.23
3.18	• rejected goods?	☐ ☐ ☐		3.23
3.19	Separate and safe storage of highly active, toxic, or dangerous substances?	☐ ☐ ☐		3.24
3.20	Safe storage of narcotics?	☐ ☐ ☐		3.24
3.21	Safe storage of printed packaging materials?	☐ ☐ ☐		3.25
3.22	Security measurements against theft?	☐ ☐ ☐		3.25

		Compliance 1 2 3	Remarks	EU-Guide
3.23	Smoke detectors?	☐ ☐ ☐		3.25
3.24	Fire extinguishing system?	☐ ☐ ☐		3.25
	Operations:			
3.25	Reception, sampling, and labeling according to written procedures?	☐ ☐ ☐		5.2
3.26	Is a sampling plan available?	☐ ☐ ☐		Suppl. 4
3.27	Cleaning of incoming containers?	☐ ☐ ☐		5.3
3.28	Investigation and recording of damaged deliveries?	☐ ☐ ☐		5.4
3.29	FIFO principle?	☐ ☐ ☐		5.7
3.30	Inventory system?	☐ ☐ ☐		5.8
3.31	The location of materials can be detected at all times?	☐ ☐ ☐		
3.32	Incoming goods: containers and seals intact?	☐ ☐ ☐		5.27
3.33	Incoming goods: conformity with bill of delivery?	☐ ☐ ☐		5.27
	Labeling of incoming containers with:			
3.34	• internal name and code?	☐ ☐ ☐		5.29
3.35	• allocated batch number?	☐ ☐ ☐		5.29
3.36	• quarantine status?	☐ ☐ ☐		5.29
3.37	• expiry date or reanalysis date?	☐ ☐ ☐		5.29
3.38	Identity test for each incoming container?	☐ ☐ ☐		5.29
3.39	Are the sampled containers marked?	☐ ☐ ☐		5.30
3.40	Are reference samples taken?	☐ ☐ ☐		5.30
3.41	Safe storage of printed packaging materials?	☐ ☐ ☐		5.41
3.42	Lot tracing of all packaging materials possible?	☐ ☐ ☐		5.42
3.43	Are excessive packaging materials destroyed?	☐ ☐ ☐		5.43
	Release of starting materials by:			
	Physical/inventory checks on raw materials, packaging materials, and finished goods:			

	Item:	Stocks: Physical:	Stocks: Inventory:	Storage conditions:	

4	**DISPENSING/ASSEMBLING**			
	Rooms, general:			
4.1	Suitable for the intended use?	☐ ☐ ☐		3
4.2	• adequate size?	☐ ☐ ☐		3
4.3	• clean?	☐ ☐ ☐		3
4.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
4.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2

		Compliance 1 2 3[a]	Remarks	EU-Guide
4.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
4.7	Appropriate lighting and air conditioning?	☐ ☐ ☐		3.3
4.8	Recording of temperature and humidity?	☐ ☐ ☐		
4.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
4.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements:			
4.11	Segregated from production and warehouse?	☐ ☐ ☐		3.13
4.12	Separate weighing cabins?	☐ ☐ ☐		3.13
4.13	Separate AHU for each cabin?	☐ ☐ ☐		3.12
	Air pressure gradient from weighing cabin → corridor:			3.3
4.14	Dust extraction systems available?	☐ ☐ ☐		5.11
	Operations:			
4.15	Balances regularly calibrated?	☐ ☐ ☐		3.41
4.16	Only pharmaceutical raw materials in this area?	☐ ☐ ☐		5.17
4.17	Check on remains from previous materials before entering of new materials into a weighing cabin?	☐ ☐ ☐		5.9/5.35
4.18	Only one material in one cabin?	☐ ☐ ☐		5.9
4.19	Are dispensed materials correct labeled?	☐ ☐ ☐		5.29
4.20	Only released products in the dispensing?	☐ ☐ ☐		5.31
4.21	Cleaning SOPs for the dispensing?	☐ ☐ ☐		4.28
4.22	Previously dispensed material recorded on weighing protocol?	☐ ☐ ☐		4.8
4.23	Safety measures against mix-ups during assembling (e.g., cage pallets)?	☐ ☐ ☐		5.32/5.34
5	**SOLIDS MANUFACTURING**			
	Field of activity:			
	• Granulation	☐		
	• Compression	☐		
	• Encapsulation	☐		
	• Film and sugar coating	☐		
	• Visual inspection (capsules, tablets, etc.)	☐		
	• Premix (human)	☐		
	Rooms, general:			
5.1	Suitable for the intended use?	☐ ☐ ☐		3
5.2	• adequate size?	☐ ☐ ☐		3
5.3	• clean?	☐ ☐ ☐		3
5.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
5.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
5.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
5.7	Appropriate lighting and air conditioning?	☐ ☐ ☐		3.3
5.8	Recording of temperature and humidity?	☐ ☐ ☐		
5.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
5.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Rooms, special requirements:			
5.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6
5.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
5.13	Logical flow of materials?	☐ ☐ ☐		3.7
5.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
5.15	Easy cleaning possible?	☐ ☐ ☐		3.10
5.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
5.17	Appropriate air handling system?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
5.18	Appropriate dust extraction system?	☐ ☐ ☐		3.14
5.19	Appropriate lighting?	☐ ☐ ☐		3.16
5.20	Separate rest rooms?	☐ ☐ ☐		3.30
5.21	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
5.22	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
5.23	Suitable for the intended use?	☐ ☐ ☐		3.34
5.24	Well maintained?	☐ ☐ ☐		3.34
5.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
5.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
5.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
5.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
5.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
5.30	Calibration records available?	☐ ☐ ☐		3.41
5.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
5.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
5.33	Not functioning equipment in the production area (if yes: clearly marked)?	**Y N** ☐ ☐ ☐		3.44
5.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
5.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
5.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
5.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
5.38	Check of each single container of the starting materials (contents, weight, identity)?	☐ ☐ ☐		5.3
5.39	Limits for yields?	☐ ☐ ☐		5.8
5.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
5.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
5.42	Appropriate measures against generation of dust (e.g., closed systems)?	☐ ☐ ☐		5.11

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Correct labeling of containers, materials, equipment, and rooms with:			5.12
5.43	• product name and batch no.	☐ ☐ ☐		5.12
5.44	• quarantine status?	☐ ☐ ☐		5.12
5.45	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐		5.14
5.46	Special procedures for the production of antibiotics, hormones, etc.?	☐ ☐ ☐		5.19
5.47	• Campaign production?	☐ ☐ ☐		5.19
5.48	• Special monitoring?	☐ ☐ ☐		5.19
5.49	• Validated decontamination procedure?	☐ ☐ ☐		5.19
5.50	Double check on weight?	☐ ☐ ☐		5.34
5.51	Line clearance before start of production?	☐ ☐ ☐		5.35
5.52	Investigation of deviations in yields?	☐ ☐ ☐		5.39
5.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐		5.62
5.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐		5.63
5.55	Special release procedure (QA) for those batches?	☐ ☐ ☐		5.64
5.56	Use of protective clothing (hair cover, shoes, masks, gloves)?	☐ ☐ ☐		2.16
5.57	Clothing regulation for visitors?	☐ ☐ ☐		2.11
	IPC			5.38
	Who performs IPC?			
5.58	Are IPC methods approved by QC?	☐ ☐ ☐		6.18
	Performance of IPCs:	*During Start-up?* **Yes No**	*Frequency*	*Automatic data recording?* **Yes No**
	Tablets/Kernels			
5.59	Individual weights	☐ ☐		☐ ☐
5.60	Disintegration	☐ ☐		☐ ☐
5.61	Thickness	☐ ☐		☐ ☐
5.62	Hardness	☐ ☐		☐ ☐
5.63	Friability/Abrasion	☐ ☐		☐ ☐
	Sugar/Film coated tablets			
5.64	Weights	☐ ☐		☐ ☐
5.65	Disintegration	☐ ☐		☐ ☐
5.66	Residual absolute humidity (IR or)	☐ ☐		☐ ☐
	Capsules			
5.67	Individual weights	☐ ☐		☐ ☐
5.68	Disintegration	☐ ☐		☐ ☐
	Validation			
5.69	Validation according to fixed procedures?	☐ ☐ ☐		5.21
5.70	New procedures released only after validation?	☐ ☐ ☐		5.22
	Validation of changes of			
5.71	• processes?	☐ ☐ ☐		5.23
5.72	• starting materials?	☐ ☐ ☐		5.23
5.73	• equipment?	☐ ☐ ☐		5.23

		Compliance 1 2 3[a]	Remarks	EU-Guide
5.74	Revalidation in fixed intervals?	☐ ☐ ☐		5.24
5.75	Procedures for the retrospective validation of old procedures?	☐ ☐ ☐		
6	**LIQUIDS MANUFACTURING**			
	Operations carried out:			
	• Dispensing (if different from solid)	☐ ☐ ☐		
	• Syrups and suspensions	☐ ☐ ☐		
	• Drops	☐ ☐ ☐		
	• Ointment manufacture	☐ ☐ ☐		
	• Ointment filling	☐ ☐ ☐		
	• Ampoule solution manufacture	☐ ☐ ☐		
	• Sterile or aseptic ampoule filling	☐ ☐ ☐		
	• Sterile freeze drying	☐ ☐ ☐		
	• Sterile powder filling	☐ ☐ ☐		
	Rooms, general:			
6.1	Suitable for the intended use?	☐ ☐ ☐		3
6.2	• adequate size?	☐ ☐ ☐		3
6.3	• clean?	☐ ☐ ☐		3
6.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
6.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
6.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
6.7	Appropriate lighting and air conditioning?	☐ ☐ ☐		3.3
6.8	Recording of temperature and humidity?	☐ ☐ ☐		
6.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
6.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements:			
6.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6
6.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
6.13	Logical flow of materials?	☐ ☐ ☐		3.7
6.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
6.15	Easy cleaning possible?	☐ ☐ ☐		3.10
6.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
6.17	Appropriate air handling system with filtered air where open products are exposed to the environment?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
6.18	Appropriate lighting?	☐ ☐ ☐		3.16
6.19	Separate rest rooms?	☐ ☐ ☐		3.30
6.20	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
6.21	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
6.22	Suitable for the intended use?	☐ ☐ ☐		3.34
6.23	Well maintained?	☐ ☐ ☐		3.34

		Compliance 1 2 3[a]	Remarks	EU-Guide
6.24	Tanks, containers, pipework, and pumps designed for easy cleaning and sanitation (dead legs)?	☐ ☐ ☐		Suppl. 2
6.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
6.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
6.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
6.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
6.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
6.30	Calibration records available?	☐ ☐ ☐		3.41
6.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
6.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
6.33	Not functioning equipment in the production area (if yes: clearly marked)?	Y N ☐ ☐ ☐		3.44
6.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
6.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
6.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
6.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
6.38	Check of each single container of the starting materials (contents, weight, identity)?	☐ ☐ ☐		5.3
6.39	Limits for yields?	☐ ☐ ☐		5.8
6.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
6.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
	Correct labeling of containers, materials, equipment, and rooms with:			5.12
6.42	• product name and batch no.	☐ ☐ ☐		5.12
6.43	• quarantine status?	☐ ☐ ☐		5.12
6.44	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐		5.14
6.45	Special procedures for the production of antibiotics, hormones, etc.?	☐ ☐ ☐		5.19
6.46	• Campaign production?	☐ ☐ ☐		5.19
6.47	• Special monitoring?	☐ ☐ ☐		5.19
6.48	• Validated decontamination procedure?	☐ ☐ ☐		5.19
6.49	Double check on weight?	☐ ☐ ☐		5.34
6.50	Line clearance before start of production?	☐ ☐ ☐		5.35
6.51	Investigation of deviations in yields?	☐ ☐ ☐		5.39
6.52	Specification of max. storage time and storage conditions if products are not immediately filled or packaged?	☐ ☐ ☐		Suppl. 9
6.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐		5.62
6.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐		5.63
6.55	Special release procedure (QA) for those batches?	☐ ☐ ☐		5.64
6.56	Use of protective clothing (hair cover, shoes, masks, gloves)?	☐ ☐ ☐		2.16
6.57	Clothing regulation for visitors?	☐ ☐ ☐		2.11

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Water			
6.58	Loop system for purified water?	☐ ☐ ☐		Suppl. 4
6.59	Antimicrobial treatment of purified water?	☐ ☐ ☐		Suppl. 4
6.60	Loop system for water for injection?	☐ ☐ ☐		Suppl. 4
	Storage temperature of water for injection:			Suppl. 4
6.61	Loop system constructed to avoid deadlegs?	☐ ☐ ☐		Suppl. 4
6.62	Regular microbiological monitoring?	☐ ☐ ☐		Suppl. 4
6.63	Regular endotoxin control?	☐ ☐ ☐		Suppl. 4
	Special requirements for sterile and aseptic products			Suppl.
	Rooms and equipment			
6.64	Access of staff and materials to clean areas *only* through airlocks?	☐ ☐ ☐		1
6.66	Rooms classified according to the EC-Guide?	☐ ☐ ☐		3
	Classification for products to be sterilized:			
6.67	• Solution preparation (EC: class C, with special precautions class D):	Class:		5
6.68	• Filling (EC: under LF in class C):	Class:		5
	Classification for aseptic products:			
6.69	• Handling of starting materials that can be sterile filtered (EC: class C):	Class:		6
6.70	• Handling of starting materials that cannot be sterile filtered (EC: class A in class B):	Class:		6
6.71	Handling and filling of bulk (EC: class A in Class B):	Class:		6
6.72	All rooms easy to clean disinfect?	☐ ☐ ☐		17
6.73	Doors, windows, frames, lighting, etc. without edges?	☐ ☐ ☐		18
6.74	Suspended ceilings (if yes: sealed?)?	☐ ☐ ☐		19
6.75	Traps constructed to avoid microb. contamination?	☐ ☐ ☐		21
6.76	Appropriate constructed changing rooms?	☐ ☐ ☐		22
6.77	Measures against opening of both doors of airlocks?	☐ ☐ ☐		23
6.78	Overpressure gradient from cleanest areas to others?	☐ ☐ ☐		24
6.79	AHU validated and regularly revalidated?	☐ ☐ ☐		25
6.80	Control instruments for pressure gradient?	☐ ☐ ☐		26
6.81	Warning system for errors in air supply?	☐ ☐ ☐		26
6.82	Recording of pressure gradients?	☐ ☐ ☐		26
6.83	Do conveyor belts leave sterile areas?	☐ ☐ ☐		28
6.84	Maintenance works outside from clean areas possible?	☐ ☐ ☐		28
6.85	Cleaning and disinfection procedure after maintenance works?	☐ ☐ ☐		29
6.86	Regular revalidation of all equipment and systems?	☐ ☐ ☐		30
6.87	Water prepared, circulated, and stored to exclude microb. contamination?	☐ ☐ ☐		31
6.88	Cleaning and disinfection of rooms according to validated SOPs rooms?	☐ ☐ ☐		32
	• Disinfection methods?			
6.89	Microb. monitoring of cleaning and disinfection agents?	☐ ☐ ☐		33

		Compliance 1 2 3[a]	Remarks	EU-Guide
6.90	Microb. monitoring program of production areas?	☐ ☐ ☐		35
6.91	Results recorded and considered for the release?	☐ ☐ ☐		35
	Personnel and Hygiene			
6.92	Minimal no. of personnel in clean areas?	☐ ☐ ☐		7
6.93	Special and regular training?	☐ ☐ ☐		8
6.94	Regular medical examinations?	☐ ☐ ☐		10
6.95	Appropriate clean room clothes (material, design)?	☐ ☐ ☐		12
6.96	Protective clothes worn correctly?	☐ ☐ ☐		12
6.97	Prohibition of cosmetics, jewelry and watches?	☐ ☐ ☐		13
6.98	New clean room clothes for each working cycle?	☐ ☐ ☐		15
6.99	Appropriate washing and sterilization of clothes?	☐ ☐ ☐		16
	Operations			
6.100	Validation (media filling) in regular intervals?	☐ ☐ ☐		38
	Monitoring of water preparation system, frequency:			
6.101	• microbiological:			40
6.102	• chemical:			40
6.103	• particles:			40
6.104	• endotoxins:			40
6.105	Microbiological monitoring of starting materials?	☐ ☐ ☐		42
6.106	Max. storage times defined for sterilized equipment?	☐ ☐ ☐		45
6.107	Max. storage time defined between solution preparation and filtration?	☐ ☐ ☐		46
6.108	Material transfer to clean areas through double door autoclaves?	☐ ☐ ☐		48
	Sterilization processes			
6.109	All processes validated?	☐ ☐ ☐		50
6.110	Sterilized and not sterilized materials clearly separated?	☐ ☐ ☐		54
	Trays and boxes clearly labeled with			
6.111	• Product name and code	☐ ☐ ☐		54
6.112	• Batch no.	☐ ☐ ☐		54
6.113	• Status: sterilized or not sterilized	☐ ☐ ☐		54
	Sterilizers:			
6.114	• Recording of temp., pressure, and time?	☐ ☐ ☐		55
6.115	• Coldest point determined?	☐ ☐ ☐		55
6.116	• Independent counter check probe?	☐ ☐ ☐		55
6.117	• Heat-up time for each product determined?	☐ ☐ ☐		56
6.118	• Sterile cooling media?	☐ ☐ ☐		57
6.119	• Tightness tests for vacuum autoclaves?	☐ ☐ ☐		58
6.120	• Clean steam for steam autoclaves?	☐ ☐ ☐		58
6.121	• Circulated air with overpressure?	☐ ☐ ☐		61
6.122	• Recirculated air: sterile filtered?	☐ ☐ ☐		61
6.123	• Ethylene oxide autoclaves: humidity, temp., and time recorded?	☐ ☐ ☐		69
6.124	• Ethylene oxide autoclaves: use of bioindicators?	☐ ☐ ☐		70

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Filtration			
6.125	Double filtration?	☐ ☐ ☐		75
6.126	Integrity testing of filters immediately after use?	☐ ☐ ☐		77
6.127	Are results part of the batch protocol?	☐ ☐ ☐		77
6.128	Optical control of each single container of ampoules, vials, and infusions?	☐ ☐ ☐		82
	IPC			
6.129	Written IPC procedures and SOPs?	☐ ☐ ☐		
	Particle testing of			
6.130	• Rooms	☐ ☐ ☐		
6.131	• Primary packaging materials	☐ ☐ ☐		
6.132	• System of warning and action limits?	☐ ☐ ☐		
	Microbiological monitoring of			
6.133	• Rooms			
6.134	• Personnel			
6.135	• Euipment			
6.136	Residual O_2 of ampoules, infusions, and syrups?	☐ ☐ ☐		
6.137	Endotoxin testing of water and packaging materials?	☐ ☐ ☐		
6.138	Calibration of equipment?	☐ ☐ ☐		
6.139	Regular revalidation of equipment?	☐ ☐ ☐		
7	**PACKAGING**			
	Operations carried out • Blistering • Foil-packaging • Filling into tablet glasses • Effervescent Packaging • Powder filling • Syrup/drops filling • Ointment filling	 ☐ ☐ ☐ ☐ ☐ ☐ ☐		
	Rooms			
7.1	Suitable for the intended use?	☐ ☐ ☐		3
7.2	• adequate size?	☐ ☐ ☐		3
7.3	• clean?	☐ ☐ ☐		3
7.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
7.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
7.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
7.7	Appropriate lighting and air conditioning?	☐ ☐ ☐		3.3
7.8	Recording of temperature and humidity?	☐ ☐ ☐		
7.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
7.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
7.11	Adequate separation of the packaging lines?	☐ ☐ ☐		3.15
	Operations			
7.12	Only *one* product per line?	☐ ☐ ☐		5.44

		Compliance 1 2 3[a]	Remarks	EU-Guide
7.13	Check list for clearance before processing a new product/new batch?	☐ ☐ ☐		5.45
7.14	Adequate labeling of the lines (product name and code)?	☐ ☐ ☐		5.46
7.15	Check of all materials delivered to the line (quantity, identity, conformity with order)?	☐ ☐ ☐		5.47
7.16	Cleaning of primary packaging materials?	☐ ☐ ☐		5.48
7.17	Immediate labeling after filling?	☐ ☐ ☐		5.49
7.18	Careful check of all printing processes (code, expiry date)?	☐ ☐ ☐		5.50
7.19	Special safety measures for off-line printing?	☐ ☐ ☐		5.51
7.20	Regular checks of all control devices (code reader, counter, etc.)?	☐ ☐ ☐		5.52
7.21	Printings clear and durable?	☐ ☐ ☐		5.53
7.22	Balancing of printed packaging materials and bulk?	☐ ☐ ☐		5.56
7.23	Destruction of excessive coded packaging material after completion of an order?	☐ ☐ ☐		5.57
7.24	Are the finished products kept in quarantine until final release?	☐ ☐ ☐		5.58
7.25	Appropriate storage after release?	☐ ☐ ☐		5.60
	IPC			
7.26	Checks on identity of bulk and packaging materials?	☐ ☐ ☐		5.47
	Regular line checks on:			
7.27	• Aspect of the packages	☐ ☐ ☐		5.54a
7.28	• Completeness	☐ ☐ ☐		5.54b
7.29	• Conformity of quantity and quality of materials with packaging order	☐ ☐ ☐		5.54c
7.30	• Correct imprint	☐ ☐ ☐		5.54d
7.31	• Correct function of control devices	☐ ☐ ☐		5.54d
	Are the following IPC checks performed?			
7.32	• Leaking	☐ ☐ ☐		
7.33	• Release torque of screw caps	☐ ☐ ☐		
7.34	• pH, density, drop weight, viscosity, sedimentation	☐ ☐ ☐		
8	**DOCUMENTATION**			
	Specifications			
8.1	Specifications for raw/packaging materials available?	☐ ☐ ☐		4.10
	Do they include:			
8.2	• internal name and code	☐ ☐ ☐		4.11
8.3	• name of supplier and/or manufacturer?	☐ ☐ ☐		4.11
8.4	• reference sample (printed pack. mat.)?	☐ ☐ ☐		4.11
8.5	• sampling procedure?	☐ ☐ ☐		4.11
8.6	• qualitative/quantitative specifications with limits?	☐ ☐ ☐		4.11
8.7	• storage conditions?	☐ ☐ ☐		4.11
8.8	• maximum storage period?	☐ ☐ ☐		4.11
	Goods receiving?			
8.9	Written procedures for the reception of deliveries?	☐ ☐ ☐		4.19

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Do records receipt include:			
8.10	• product name on labels and delivery note?	☐ ☐ ☐		4.20
8.11	• internal name and code?	☐ ☐ ☐		4.20
8.12	• receiving date?	☐ ☐ ☐		4.20
8.13	• name of supplier and/or manufacturer?	☐ ☐ ☐		4.20
8.14	• batch number of supplier?	☐ ☐ ☐		4.20
8.15	• total quantity and number of containers?	☐ ☐ ☐		4.20
8.16	• allocated internal batch number?	☐ ☐ ☐		4.20
8.17	SOPs for labeling, quarantine, and storage conditions of all incoming goods available?	☐ ☐ ☐		4.21
	Sampling procedures (SOPs) include:			
8.18	• authorized sampling personnel?	☐ ☐ ☐		4.22
8.19	• methods, equipment, and quantities?	☐ ☐ ☐		4.22
8.20	• safety measures?	☐ ☐ ☐		4.22
	Master formulae			
8.21	Are master formulae for each product and batch size available?	☐ ☐ ☐		4.3
8.22	Is the master formula approved and signed by the authorized persons?	☐ ☐ ☐		4.3
	The master formula includes:			
8.23	• product name and code?	☐ ☐ ☐		4.14a
8.24	• description of galenical form, dosage, and batch size?	☐ ☐ ☐		4.14b
8.25	• all active ingredients with name, code, and weight?	☐ ☐ ☐		4.14c
8.26	• all excipients used during manufacture with name, code, and weight?	☐ ☐ ☐		4.14c
8.27	• yields with limits?	☐ ☐ ☐		4.14d
	Does the working procedure include:			
8.28	• the production line?	☐ ☐ ☐		4.15a
8.29	• equipment to be used?	☐ ☐ ☐		4.15a
8.30	• reference to methods for cleaning, assembling, and calibration of machines?	☐ ☐ ☐		4.15b
8.31	• detailed stepwise manufacturing prescription?	☐ ☐ ☐		4.15c
8.32	• IPCs to be performed with limits?	☐ ☐ ☐		4.15d
8.33	• precautions to be followed?	☐ ☐ ☐		4.15e
8.34	Are batch records kept for each batch processed?	☐ ☐ ☐		4.17
	Do batch records include:			
8.35	• Protocol of line clearance?	☐ ☐ ☐		4.17
8.36	• Name of the product and batch no.?	☐ ☐ ☐		4.17a
8.37	• Date and time of start and end of production?	☐ ☐ ☐		4.17b
8.38	• Name and initials of responsible workers for each step?	☐ ☐ ☐		4.17c,d
8.39	• Batch and analytical no. and actual weight of all starting materials?	☐ ☐ ☐		4.17e
8.40	• Equipment used?	☐ ☐ ☐		4.17f
8.41	• Results of IPCs with initials of person who carries them out?	☐ ☐ ☐		4.17g
8.42	• Yields of the relevant manufacturing steps?	☐ ☐ ☐		4.17h
8.43	• Detailed notes on problems and process deviations?	☐ ☐ ☐		4.17i

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8.44	Records on reprocessing of batches?	☐ ☐ ☐		
	Packaging instructions:			
8.45	Packaging instructions for each product, package size, and presentation?	☐ ☐ ☐		4.16
	Do they include:			
8.46	• Product name?	☐ ☐ ☐		4.16a
8.47	• Description of galenical form and strength?	☐ ☐ ☐		4.16b
8.48	• Package size?	☐ ☐ ☐		4.17c
8.49	• List of all packaging materials with code for a standard batch size?	☐ ☐ ☐		4.17d
8.50	• Samples of printed packaging materials?	☐ ☐ ☐		4.17e
8.51	• Special precautions?	☐ ☐ ☐		4.17f
8.52	• Description of the process and equipment?	☐ ☐ ☐		4.17g
8.53	• IPCs to be performed with sampling instruction?	☐ ☐ ☐		4.17h
8.54	Are packaging batch records kept for each batch or part batch?	☐ ☐ ☐		4.18
	Do the packaging batch records include:			
8.55	• Protocol of line clearance?	☐ ☐ ☐		4.18
8.56	• Name of the product?	☐ ☐ ☐		4.18a
8.57	• Date and time when operations have been performed?	☐ ☐ ☐		4.18b
8.58	• Name of the responsible person?	☐ ☐ ☐		4.18c
8.59	• Initials of workers carrying out operations?	☐ ☐ ☐		4.18d
8.60	• Notes on identity checks and conformity with packaging instructions?	☐ ☐ ☐		4.18e
8.61	• Results of IPCs	☐ ☐ ☐		4.18e
8.62	• Details of operations and equipment used?	☐ ☐ ☐		4.18f
8.63	• Samples of printed packaging materials with codes (MFD, EXP, Batch no., etc.)?	☐ ☐ ☐		4.18g
8.64	• Record of problems and process deviations?	☐ ☐ ☐		4.18h
8.65	• Quantities of packaging materials delivered, used, destroyed, or returned?	☐ ☐ ☐		4.18i
8.66	• No. of packs consumed?	☐ ☐ ☐		4.18j
	Testing			
	Do the written testing procedures include:			
8.67	• Test methods?	☐ ☐ ☐		4.23
8.68	• Equipment for testing?	☐ ☐ ☐		4.23
8.69	Tests documented?	☐ ☐ ☐		4.23
	Others			
8.70	Procedures for release and rejection of materials and finished products?	☐ ☐ ☐		4.24
8.71	Final release by authorized person?	☐ ☐ ☐		4.24
8.72	Records about distribution of each batch?	☐ ☐ ☐		4.25
	Procedures and protocols about			
8.73	• Validation?	☐ ☐ ☐		4.26
8.74	• Set up and calibration of equipment?	☐ ☐ ☐		4.26
8.75	• Maintenance, cleaning, and disinfection?	☐ ☐ ☐		4.26

		Compliance 1 2 3[a]	Remarks	EU-Guide
8.76	• Training records?	☐ ☐ ☐		4.26
8.77	• Environmental monitoring of production areas?	☐ ☐ ☐		4.26
8.78	• Pest control?	☐ ☐ ☐		4.26
8.79	• Complaints?	☐ ☐ ☐		4.26
8.80	• Rrecalls?	☐ ☐ ☐		4.26
8.81	• Returned goods?	☐ ☐ ☐		4.26
8.82	Instructions for use of manufacturing and testing equipment?	☐ ☐ ☐		4.27
	Log books for major equipment incl. date and name of persons who performed:			
8.83	• Validation?	☐ ☐ ☐		4.28
8.84	• Calibration?	☐ ☐ ☐		4.28
8.85	• Maintenance, cleaning, and repair works?	☐ ☐ ☐		4.28
8.86	Chronological records of use of major equipment and manufacturing areas?	☐ ☐ ☐		4.29
9	**QUALITY CONTROL**			**6**
	General requirements			
9.1	Independent QC department available?	☐ ☐ ☐		6.1
9.2	Head of QC well qualified and sufficiently experienced?	☐ ☐ ☐		6.1
9.3	Qualified personnel available?	☐ ☐ ☐		2.1
9.4	Organization charts available?	☐ ☐ ☐		2.2
9.5	Job descriptions available?	☐ ☐ ☐		2.2
9.6	Responsibilities clearly defined?	☐ ☐ ☐		2.2
9.7	Continuous training programs for QC staff?	☐ ☐ ☐		2.2
9.8	Initial job training for all employees?	☐ ☐ ☐		2.9
9.9	Training records?	☐ ☐ ☐		
9.10	QC personnel admitted to the production rooms for sampling, etc.?	☐ ☐ ☐		
	QC Laboratories			
9.11	Suitable for the intended use?	☐ ☐ ☐		3.26
9.12	Laboratories of adequate size?	☐ ☐ ☐		3.26
9.13	Appropriate level of maintenance?	☐ ☐ ☐		3.1
9.14	Adequate separation from the production area?	☐ ☐ ☐		3.26
9.15	Controlled access of authorized personnel only?	☐ ☐ ☐		3.5
9.16	Special laboratory to handle biological samples available?	☐ ☐ ☐		3.29
9.17	Special laboratory to handle radioactive material available?	☐ ☐ ☐		3.29
9.18	Separate recreation rooms for the personnel available?	☐ ☐ ☐		3.30
9.19	Animal laboratories present?	☐ ☐ ☐		3.33
9.20	Animal laboratories separated from other areas?	☐ ☐ ☐		3.33
9.21	Animal laboratories equipped with a separate air handling system?	☐ ☐ ☐		3.33
	QC Documentation			
9.22	Do procedures exist for self-inspection? release or rejection of products or raw material? product complaints? product recalls?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		

		Compliance 1 2 3[a]	Remarks	EU-Guide
	local stability testing?	☐ ☐ ☐		
	storage of reference samples?	☐ ☐ ☐		
	validation of analytical procedures?	☐ ☐ ☐		
9.23	Specifications available for			6.7
	raw materials?	☐ ☐ ☐		
	bulk products?	☐ ☐ ☐		
	packaging materials?	☐ ☐ ☐		
9.24	Analytical procedures for every product?	☐ ☐ ☐		
9.25	Are Basel methods followed?	☐ ☐ ☐		
9.26	Validation of locally developed test methods?	☐ ☐ ☐		
9.27	Sampling procedures available for			6.7
	raw materials?	☐ ☐ ☐		
	bulk products?	☐ ☐ ☐		
	packaging materials?	☐ ☐ ☐		
9.28	Suppliers certificates available?	☐ ☐ ☐		6.7
9.29	Calibration program for analytical instruments installed?	☐ ☐ ☐		6.7
9.30	Maintenance program for analytical instruments?	☐ ☐ ☐		6.7
9.31	Retention system for QC records?	☐ ☐ ☐		6.8
9.32	Batch documents stored for expiry + 1 year or 5 years (EEC 75/319, article 22) minimum?	☐ ☐ ☐		6.8
9.33	Are original data-like notebooks stored in addition to the batch documents?	☐ ☐ ☐		6.10
9.34	Can the original data be traced back easily and quickly from the analytical report number or batch number?	☐ ☐ ☐		6.10
9.35	Are trend analyses being performed for			6.9
	analytical results?	☐ ☐ ☐		
	yields?	☐ ☐ ☐		
	environmental monitoring data?	☐ ☐ ☐		
	Sampling			
9.36	Written procedures for taking samples?	☐ ☐ ☐		6.11
9.37	Do procedures define			
	method of sampling?	☐ ☐ ☐		
	necessary equipment?	☐ ☐ ☐		
	quantity of the sample?	☐ ☐ ☐		
	subdivision of the sample?	☐ ☐ ☐		
	sample container?	☐ ☐ ☐		
	labeling of samples?	☐ ☐ ☐		
	storage conditions?	☐ ☐ ☐		
	cleaning and storage of sampling equipment?	☐ ☐ ☐		
	identification of containers sampled	☐ ☐ ☐		
9.38	Are samples representative for the batch they are taken from? (sampling plan)	☐ ☐ ☐		6.12
9.39	Are critical steps being surveilled and validated by additional sampling (for example beginning or end of a process).	☐ ☐ ☐		6.12
9.40	Sample containers labeled with			6.13
	name of the content	☐ ☐ ☐		
	batch number	☐ ☐ ☐		
	date of sampling	☐ ☐ ☐		
	batch containers sampled	☐ ☐ ☐		
9.41	Are samples taken by QC/QA?	☐ ☐ ☐		

		Compliance 1 2 3[a]	Remarks	EU-Guide
9.42	Reference samples retained for validity plus 1 year?	☐ ☐ ☐		6.14
9.43	Storage of reference samples under the recommended storage conditions?	☐ ☐ ☐		6.14
9.44	Finished products stored in the final packaging?	☐ ☐ ☐		6.14
9.45	Quantity of the reference sample makes 1 (better 2) complete reanalysis possible?	☐ ☐ ☐		6.14
9.46	Sample room secure?	☐ ☐ ☐		
9.47	Sample room neatly organized and not overcrowded?	☐ ☐ ☐		
	Testing			
9.48	Are the applied analytical methods validated?	☐ ☐ ☐		6.15
9.49	Analytical methods in compliance with the registration?	☐ ☐ ☐		6.16
9.50	Are all results recorded and checked for correctness?	☐ ☐ ☐		6.16
9.51	Are all calculations checked?	☐ ☐ ☐		6.16
9.52	Do the testing protocols contain			6.17
	name and galenical form of material?	☐ ☐ ☐		
	batch number?	☐ ☐ ☐		
	supplier if applicable?	☐ ☐ ☐		
	specification reference?	☐ ☐ ☐		
	method reference?	☐ ☐ ☐		
	analytical results?	☐ ☐ ☐		
	reference to analytical certificates?	☐ ☐ ☐		
	date of the analysis?	☐ ☐ ☐		
	name of the analyst?	☐ ☐ ☐		
	name of the person verifying the data?	☐ ☐ ☐		
	statement of release or rejection?	☐ ☐ ☐		
	date and signature of the release person?	☐ ☐ ☐		
9.53	Are all IPC methods in production approved by QC?	☐ ☐ ☐		6.18
9.54	Are written methods available for the preparation of reagents and volumetric solutions?	☐ ☐ ☐		6.19
9.55	Is a record maintained of standardization of volumetric solutions?	☐ ☐ ☐		6.2
9.56	Are reagents for prolonged use labeled with			6.20
	date of the preparation?	☐ ☐ ☐		
	sign of the preparator?	☐ ☐ ☐		
9.57	Are unstable reagents labeled with			6.20
	expiry date?	☐ ☐ ☐		
	storage conditions?	☐ ☐ ☐		
9.58	Are volumetric solutions labeled with			6.20
	the last date of standardization?	☐ ☐ ☐		
	last current factor?	☐ ☐ ☐		
9.59	Are reference standards labeled with			6.21
	name and potency	☐ ☐ ☐		
	suppliers reference	☐ ☐ ☐		
	date of receipt	☐ ☐ ☐		
	date of expiry	☐ ☐ ☐		
9.60	Are reference standards stored properly and under the control of a designated person?	☐ ☐ ☐		
9.61	Are animals used for testing of components, materials, or products			
	quarantined before use?	☐ ☐ ☐		
	checked for suitability?	☐ ☐ ☐		
	Are records maintained showing the history of their use?	☐ ☐ ☐		

		Compliance 1 2 3[a]	Remarks	EU-Guide
10	**COMPLAINTS AND PRODUCT RECALLS**			**8**
	Complaints			8.1
10.1	Does a written complaint procedure exist?	☐ ☐ ☐		8.2
10.2	Are product complaints carefully reviewed?	☐ ☐ ☐		8.1
10.3	Is a person designated to handle complaints and to decide on measures to be taken?	☐ ☐ ☐		8.1
10.4	Is each complaint concerning a product recorded with all original details?	☐ ☐ ☐		8.3
10.5	Are product complaints thoroughly investigated?	☐ ☐ ☐		8.3
10.6	Is a responsible person of QC involved in the study?	☐ ☐ ☐		8.3
10.7	Is it considered that other batches might be concerned as well?	☐ ☐ ☐		8.4
10.8	Are decisions and measures as a result recorded?	☐ ☐ ☐		8.5
10.9	Is this record added to the corresponding batch documents?	☐ ☐ ☐		8.5
10.10	Are the complaint records regularly revised with respect to specific or recurring problems?	☐ ☐ ☐		8.6
10.11	Are the authorities informed of serious quality problems with a product?	☐ ☐ ☐		8.7
	Recalls			8.8
10.12	Does a written recall procedure exist?	☐ ☐ ☐		8.9
10.13	Is a person nominated responsible for the execution and coordination of a recall?	☐ ☐ ☐		8.8
10.14	Responsible person independent of the marketing and sales organization?	☐ ☐ ☐		8.8
10.15	Are the competent authorities informed of an imminent recall?	☐ ☐ ☐		8.11
10.16	Does the person responsible for a recall have access to the distribution records?	☐ ☐ ☐		8.12
10.17	Do the distribution records contain sufficient information on customers with addresses? phone numbers inside or outside working hours? batches and amounts delivered? medical samples?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		8.12
10.18	Are recalled products stored separately in a secure area?	☐ ☐ ☐		8.13
10.19	Is a final record made including a reconciliation between the delivered and recovered quantities?	☐ ☐ ☐		8.14
10.20	Is the effectiveness of the arrangements for recalls checked critically from time to time?	☐ ☐ ☐		8.15
11	**SELF-INSPECTION**			**9**
11.1	Does a self-inspection procedure exist, which defines frequency and program?	☐ ☐ ☐		9.1
11.2	Are self-inspections carried out to check compliance with GMP rules?	☐ ☐ ☐		9.1
11.3	Are self-inspections conducted in an independent and detailed way? by designated competent persons from the company or external experts?	 ☐ ☐ ☐ ☐ ☐ ☐		9.2
11.4	Are self-inspections recorded?	☐ ☐ ☐		9.3

		Compliance 1 2 3[a]	Remarks	EU-Guide
11.5	Do reports contain the observations made during a self-inspection? proposals for corrective measures?	 ☐ ☐ ☐ ☐ ☐ ☐		9.3
11.6	Are actions subsequently taken recorded?	☐ ☐ ☐		9.3
12	**CONTRACT MANUFACTURE AND ANALYSIS**			**7**
12.1	Written contract between contract giver and contract acceptor available?	☐ ☐ ☐		7.1
12.2	Are responsibilities and duties clearly defined?	☐ ☐ ☐		7
12.3	All arrangements in accordance with the marketing authorization of the product concerned?	☐ ☐ ☐		7.2
	The contract giver			
12.4	Competence of the acceptor to carry out the work successful and according to GMP assessed?	☐ ☐ ☐		7.3
12.5	Acceptor provided with all the informations necessary to carry out the contract work?	☐ ☐ ☐		7.4
12.6	Acceptor informed of safety aspects?	☐ ☐ ☐		7.4
12.7	Conformance of products supplied by the acceptor ensured?	☐ ☐ ☐		7.5
12.8	Product released by a qualified person on the acceptor's side?	☐ ☐ ☐		7.5
	The contract acceptor			
12.9	Does the acceptor have adequate premises and equipment? knowledge and experience? competent personnel? a manufacturing authorization?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.6
12.10	Does the acceptor ensure that all products or materials delivered to him are suitable?	☐ ☐ ☐		7.7
12.11	There must be no work passed to a third party without the permission of the giver.	☐ ☐ ☐		7.8
12.12	If a third party is involved it must have the necessary manufacturing and analytical information.	☐ ☐ ☐		7.8
	The contract			
12.13	Does the written contract specify the responsibilities?	☐ ☐ ☐		7.10
12.14	Have technical aspects been drawn up by competent persons?	☐ ☐ ☐		7.10
12.15	Release of material and check for compliance with the marketing authorization defined?	☐ ☐ ☐		7.11
12.16	Is defined who is responsible for purchasing of materials? IPC controls testing and release of materials? manufacturing and quality control? sampling? storage of batch documentation?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.12
12.17	Are manufacturing, analytical, and distribution records available to the contract giver?	☐ ☐ ☐		7.13
12.18	Contract permits the giver to visit the facilities of the acceptor?	☐ ☐ ☐		7.14
12.19	In the case of contract analysis: Does the contract acceptor understand that he is subject to inspection by the competent authorities?	☐ ☐ ☐		7.15

		Compliance 1 2 3[a]	Remarks	EU-Guide
13	**AUDIT OF SUPPLIERS**			**2.7**
13.1	Supplier audits performed for			
	excipients?	☐ ☐ ☐		
	active substances?	☐ ☐ ☐		
	packaging material?	☐ ☐ ☐		

[a] 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

GLOSSARY

Acceptance criteria—Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active pharmaceutical ingredient (API) *(or drug substance)*—Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Airlock—An enclosed space with two or more doors, which is interposed between two or more rooms, for example, of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for use either by people or for goods and/or equipment.

API starting material—A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials are normally of defined chemical properties and structure.

Authorized person—The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested, and approved for release in compliance with the laws and regulations in force in that country.

Batch (or Lot)—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Batch Number (or Lot Number)—A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

Batch records—All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bioburden—The level and type (e.g., objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates, or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Bulk product—Any product that has completed all processing stages up to, but not including, final packaging.

Calibration—The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Clean area—An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Computer system—A group of hardware components and associated software designed and assembled to perform a specific function or group of functions. A process or operation integrated with a computer system.

Consignment (or delivery)—The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Contamination—The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage, or transport.

Contract manufacturer—A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical—Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Critical operation—An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Cross-contamination—Contamination of a material or product with another material or product. Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Deviation—Departure from an approved instruction or established standard.

Drug (medicinal) product—The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug substance—See Active pharmaceutical ingredient

Expiry date (or expiration date)—The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Finished product—A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.

Impurity—Any component present in the intermediate or API that is not the desired entity.

Impurity profile—A description of the identified and unidentified impurities present in an API.

In-process control—Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate—A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Large-volume parenterals—Sterile solutions intended for parenteral application with a volume of 100 mL or more in one container of the finished dosage form.

Lot—See Batch

Lot number—See Batch number

Manufacture—All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Manufacturer—A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of pharmaceuticals.

Marketing authorization (product license, registration certificate)—A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling, and shelf life.

Master formula—A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master record—A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Material—A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother liquor—The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It may be used for further processing.

Packaging—All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

Packaging material—Any material intended to protect an intermediate or API during storage and transport. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical product—Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is, subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Procedure—A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process aids—Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon, etc.).

Process control—See In-process control

Production—All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labeling and relabeling, to completion of the finished product.

Qualification—Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality assurance (QA)—The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality control (QC)—Checking or testing that specifications are met.

Quality unit(s)—An organizational unit independent of production which fulfills both quality assurance and quality control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine—The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Raw material—A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reconciliation—A comparison between the theoretical quantity and the actual quantity.

Recovery—The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

Reference standard, primary—A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity.

Reference standard, secondary—A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing—Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate), or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and preapproved as part of the marketing authorization.

Retest date—The date when a material should be reexamined to ensure that it is still suitable for use.

Reworking—Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not preapproved as part of the marketing authorization.

Self-contained area—Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well-established procedures, controls, and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

Signature (signed)—See definition for signed

Signed (signature)—The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent—An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification—A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Standard operating procedure (SOP)—An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g., equipment operation, maintenance, and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting material—Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Validation—A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity, or system actually leads to the expected results (see also qualification).

Validation protocol—A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, expected—The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, theoretical—The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

4

Guidance on Formulating Compressed Solids

The manufacturing of compressed solids is a complex process, requiring several steps to render powders compressible, yet easily dispersed, and with the active ingredient dissolved when placed at the site of administration. As a result, the formulations that deliver the drugs to the site of action, while maintaining an appropriate stability profile, are valuable. However, a formulation, as described in this volume, requires an understanding of the manufacturing environment conducive to manufacturing a compliant dosage form. The sections in this chapter highlight some of these considerations that would benefit formulators. The topics of interest are presented in alphabetical order for quick reference.

I. ABBREVIATED DIRECTIONS

Abbreviated directions are necessary, particularly where a direct compression involved is provided. However, these directions can be expanded based on examples given elsewhere. General working steps, such as sifting the material, the timing for blending lubricants, the use of stainless steel vessels, etc., are common to all.

II. ACTIVE PHARMACEUTICAL INGREDIENT

The active pharmaceutical ingredient (API) ultimately controls the quality of a product. The generic manufacturer faces a serious problem when procuring supplies of APIs coming off patent. Whereas Title 35 USC, Section 112, Paragraph 1 for patentability of invention requires that the inventor fully disclose the invention, the fact is that "full disclosure" does not necessarily mean disclosing steps that do not appear material in the production of the raw material. For example, it is routine practice (though questionable) for inventors of new chemical entities not to describe every step needed to remove impurities, to obtain the correct crystal structure (of a polymorph), or to obtain the correct particle size in the manufacturing process. As a result, generic manufacturers face serious situations when trying to reproduce and replicate a branded product. The issue of impurities is serious, and the regulatory authorities are getting tougher. In most instances, an unidentified peak can result in the rejection of an application. If the manufacturer of an API is unable to control the impurity profile, serious problems can arise in the manufacturing of the products.

III. BIO VS. PRODUCTION BATCHES

It is important that the manufacturer compare the drug substance used to manufacture the stability batch, bioequivalence batch, or clinical batch and the drug substance used for commercial batches. Therefore, the specifications, analytical methods, and test results for the lots of the drug substance used to manufacture these batches should be written precisely. Because the safety of the drug may be based upon the types and levels of impurities, and different physical characteristics may affect dissolution or content uniformity, these data must be developed.

IV. CLEANING VALIDATION

Solid drug powders can reach into deep cavities of the equipment, making the equipment difficult to clean. It is of utmost GMP importance that all equipment be entirely disassembled and thoroughly cleaned prior to switching to the manufacture of another drug. Appropriate standards of practice (SOP) validating cleanliness of equipment are required to assure compliance with the GMP. Problems arise in the use of highly potent, water-insoluble drugs, which are difficult to remove.

V. COATINGS

Tablets may be coated for a variety of reasons, including protection of the ingredients from air, moisture, or light; masking of unpleasant tastes and odors; improvement of appearance; and control of the site of drug release in the gastrointestinal tract. Classically, tablets were coated with sugar applied from aqueous suspensions containing insoluble powders, such as starch, calcium carbonate, talc, or titanium dioxide, suspended by means of acacia or gelatin. For purposes of identification and aesthetic value, the outside coatings may be colored. The finished coated tablets are polished by applying dilute solutions of wax in solvents, such as chloroform or powdered mix. Water-protective coatings consisting of substances, such as shellac or cellulose acetate phthalate are often applied out of nonaqueous solvents before the application of sugar coats. Excessive quantities should be avoided. The drawbacks of sugar coatings include a lengthy time necessary for application, the need for waterproofing, which adversely affects dissolution, and the increased bulk of the finished tablet.

These factors resulted in increased acceptance of film coatings. Film coatings consist of water-soluble or dispersible materials, such as hydroxypropyl methylcellulose, methylcellulose, hydroxypropylcellulose, carboxymethylcellulose sodium, and mixtures of cellulose acetate phthalate and polyethylene glycols (PEGs) applied out of nonaqueous or aqueous solvents. The evaporation of the solvents leaves a thin film that adheres directly to the tablet and allows it to retain the original shape, including grooves or identification codes. Where the drug may be destroyed or inactivated by the gastric juice or where it may irritate the gastric mucosa, the use of "enteric" coatings is indicated. Such coatings are intended to delay the release of the medication until the tablet passes through the stomach.

VI. COMPLIANCE WITH REGULATORY REQUIREMENTS

Compliance with the current good manufacturing practices (cGMP) in the manufacturing of solid dosage forms comprises three phases of the validation process: product development, design of the validation protocol, and demonstration runs (validation) of the equipment and process in the manufacture of full-scale commercial production batches. In all preapproval and postapproval inspections, the primary purpose is to assure compliance with validated processes.

The U.S. FDA issued specific guidelines that define process validation as establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product, while meeting its predetermined specifications and quality attributes. The three components of this definition include documented evidence, consistency, and predetermined specifications. Documented evidence includes the experiments, data, and analytical results that support the master formula, the in-process and finished product specifications, and the filed manufacturing process. With regard to consistency, several batches would have to be manufactured, using the full-scale batch size, to demonstrate that a process meets the consistency test. At least three batches are needed to demonstrate consistency.

VII. COMPRESSION PROCESS CONTROL

Compressed solids are subject to dissolution problems. As a result, compression parameters, such as hardness of tablets, are important. Generally, harder tablets are often difficult to eject and take longer to disintegrate. However, control of friability may require harder tablets. Newer compression equipment has built-in online monitoring of compressed culls. Where such systems are not available, continuous monitoring of compression is required to assure that the batch does not have highly diversified properties, including friability and hardness.

VIII. CONTENT UNIFORMITY

Control of the physical characteristics of the excipient is important because variations in such characteristics may also affect the performance of the dosage form. Changes in particle size of some excipient, for example, may affect content uniformity. Therefore, there is a need to test physical characteristics (particle size) for each batch of excipient. For many single-source excipients, particle size is a supplier specification and is usually tightly controlled. Having established a specification and not testing each lot of excipient upon receipt may be satisfactory in such cases. However, for some multisource excipients and where the dosage formulator expects to shift sources of supply, there may be differences in physical characteristics (particle size) that may affect dose uniformity and dissolution.

IX. CROSS-CONTAMINATION

Environmental controls for cross-contamination and protection of operators must be considered when creating an appropriate environment. Of prime importance are pressure differentials, relative humidity (often, total grains of moisture are measured), temperature, and air changes. The regulatory requirements for segregation of penicillin and cephalosporin are well established. Similar situations arise when hormones and oncolytics are manufactured. Highly active drugs pose another set of problems, wherein a low level of contamination can seriously affect the health of the operators and also create a cross-contamination situation. Remember, highly potent drugs can contaminate other products easily because there is always a threshold for preventing contamination. Generally, it is a good idea to manufacture potent drugs in separate areas.

X. DESEGREGATION OF POWDERS

Differences in particle sizes, particle shapes, hydrophilicities of powder surfaces, strengths of crystal lattice, polymorphic structures, environmental humidities, powder surface electrostatic charges, and the force and the nature of force applied all make a difference in how powders mix and demix. Segregation is a typical characteristic known from the example of separating chafe from hay by shaking the hay. The same process applies to mixing pharmaceutical ingredients in a mixer. The aim of mixing is to desegregate different powders, and it may require the use of some surfactants or other excipients to enhance the mixing or desegregation process. Overmixing, which increases electrostatic charges, can lead to segregation particularly after lubricants are added. Lubricants, by nature, are often hydrophobic (such as magnesium stearate) and readily develop electrostatic charge. The validation process develops a rationale for mixing times at all stages, from the initial mixing to mixing with binding solutions to blending with lubricants. To reduce charges, lubricants are not sifted through finer meshes. Segregation may also occur in a tablet machine hopper, causing serious problems of content uniformity.

XI. DISINTEGRATION TEST

A disintegration test is provided to determine compliance with the limits on disintegration stated in the individual monographs, except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed as modified-release dosage forms. Determine the type of units under testing from the labeling and from observation, and apply the appropriate procedure to six or more dosage units. Disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

The apparatus consists of a basket-rack assembly, a 1000 mL, low-form beaker, 138 to 155 mm in height, with an inside diameter of 97 to 110 mm for the immersion fluid; a thermostatic arrangement for heating the fluid between 35°C and 39°C; and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 5.3 cm and not more than 5.7 cm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke, the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom of the vessel on the downward stroke. The time

required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

A. Uncoated Tablets

Place one tablet in each of the six tubes of the basket, and operate the apparatus, using water maintained at $37 \pm 2^{\circ}C$ as the immersion fluid, unless otherwise specified in the individual monograph. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets: all the tablets disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

B. Plain Coated Tablets

Apply the test for uncoated tablets, operating the apparatus for the time specified in the individual monograph.

C. Delayed-Release (Enteric-Coated) Tablets

Place one tablet in each of the six tubes of the basket, and if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at $37 \pm 2^{\circ}C$ as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at $37 \pm 2^{\circ}C$ as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

D. Buccal Tablets

Apply the test for uncoated tablets. After 4 hours, lift the basket from the fluid and observe the tablets: all the tablets disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

E. Sublingual Tablets

Apply the test for uncoated tablets. Observe the tablets within the time limit specified in the individual monograph: all the tablets disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

XII. DISSOLUTION

This test is provided to determine compliance with the dissolution requirements, where stated in the individual monograph, for a tablet or capsule dosage form. Of the types of apparatus described herein, use the one specified in the individual monograph. Where the label states that an article is enteric coated, and a dissolution or disintegration test does not specifically state that it is to be applied to enteric-coated articles, the individual monograph should include how to handle it. For gelatin-coated tablets that do not conform to the dissolution specification, repeat the test as follows. Where water or a medium with a pH of less than 6.8 is specified as the medium in the individual monograph, the same medium specified may be used with the addition of purified pepsin that results in an activity of 750,000 units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP units of protease activity per 1000 mL.

XIII. DISINTEGRATION AND DISSOLUTION

Disintegration is an essential attribute of tablets intended for administration by mouth, except for those intended to be chewed before swallowing and for some types of extended-release tablets. A disintegration test is provided, and limits on the times in which disintegration is to take place, appropriate for the types of tablets concerned, are given in the individual monographs. For drugs of limited water solubility, dissolution may be a more meaningful quality attribute than disintegration. A dissolution test is required in a number of monographs on tablets. In many cases, it is possible to correlate dissolution rates with biological availability of the active ingredient. However, such tests are useful mainly as a means of screening preliminary formulations and as a routine quality-control procedure.

XIV. DRUG SUBSTANCE CHARACTERIZATION

Characterization of the chemical and physical properties of a drug substance is one of the most important steps in the development of a solid dosage form. The identification of chemical properties, especially impurities, is very important. In addition, the physical properties of the API, such as solubility, polymorphism, hygroscopicity, particle size, density, etc., must be addressed. The literature and actual experience demonstrate that the physical quality (e.g., particle size of raw materials) can sometimes produce a significant impact on the availability and clinical effect of a dosage form drug. Therefore, it is appropriate that the physical characteristics of a drug substance be characterized, the impact of the physical characteristics be determined, and a specification for the bulk drug product be established, if necessary.

XV. DRYING PROCESS

Manufacturing formulas clearly specify how granules are to be dried. The temperature and length of drying are important, not only for losing a certain amount of moisture but also for achieving a specific granular structure. The end point of granulation is often described in terms of loss on drying (LOD), which is often characterized in terms of the Ohaus or Brabender index (e.g., LOD at 105°C for 1 hour) or an equivalent. Fluid-bed dryers and the newer granulator-vacuum dryers offer different rates of moisture loss and may form granules of different characteristics. The scale-up process should validate any changes in the equipment used and the technique used to dry granules. The validation should include compression tests and stability evaluations.

XVI. DYES IN FORMULATIONS

Manufacturers choose to include dyes in formulations for several reasons: for aesthetics, for identification, and for hiding inevitable mottling. Dyes can be included in the cores or in coating solutions when used. The Appendix to this book includes several formulations for coating solutions. Certifiable color additives (FD&C Certified) are available for use in foods or pharmaceuticals as either "dyes" or "lakes." Dyes dissolve in water and are manufactured as powders, granules, liquids, or other special-purpose forms. Lakes are the water-insoluble forms of dyes. Lakes are more stable than dyes and are ideal for coloring products containing fats and oils or items lacking sufficient moisture to dissolve dyes. Typical uses include coated tablets, cake and doughnut mixes, hard candies, and chewing gums. It is imperative that the manufacturer seek clarification of the status of a particular dye or lake before using it, particularly if the product has to be shipped to other countries. Labeling requirements include identification of all color additives. (The PDR is a good source to use to learn which colors are used in a particular product. For generic manufacturers, this is a good starting point.)

XVII. EQUIPMENT

The formulations provided do not specify equipment, and the manufacturer is supposed to select appropriate equipment for the batch size required. The selection of equipment must be based on full knowledge of the limitations of the equipment. The following sections (A–D) briefly describe some issues associated with equipment.

A. Blenders

Many solid oral dosage forms are made by direct compression. Two types of mixers are generally used: low energy and high energy. The low-energy mixers represent the classic type of slow mixers, such as ribbon blenders, tumblers, and the planetary pony pan. The high-energy mixers include some basic features of the low-energy mixer, but also contain some type of high-speed blade, commonly termed an intensifier bar or chopper.

1. Pony Pan

This mixer has historically been used for the manufacture of wet granulations. Because of its open pan or pot, granulating agents, such as starch paste, could be added while mixing. Because it is usually open at the top to allow the mixing blades to penetrate the powder, mixing operations are usually dusty and can lead to potential cross-contamination problems. The usefulness of these mixers is limited to wet granulating. With this type of mixer, there is good horizontal (side-to-side) blending. However, vertical (top-to-bottom) mixing does not occur. Powder placed in the mixer first will be poorly mixed. Segregation or demixing is also a recognized problem. To minimize this problem, some manufacturers empty the pan contents halfway through the mixing cycle in an attempt to turn the powder over at the bottom of the mixer. To alleviate the problem of the lack of mixing along the sides or walls of the pan, manufacturers often utilize a handheld steel paddle at various times during mixing. This type of mixing is difficult to control and reproduce. Thus, it would be difficult to validate.

The potential for segregation and poor mixing along the sides and particularly the bottom of the pony blender makes this type of blender less desirable for the dry blending of granulations of drug products. Consequently, whenever such dry blending is encountered, the manufacturer should be alert to potential problems with blending validation and content uniformity. Whenever in-process samples of the granulation are collected as part of an investigation or inspection, the formula card along with the weight of the dosage unit to be manufactured are needed for calculations.

2. Ribbon

In the ribbon blender, powder is mixed horizontally and vertically. Loading operations can be dusty. However, during the actual blending, it is enclosed, thereby limiting the amount of dust generated to the environment.

The major and potentially the most serious problem with the ribbon blender is that there is a "dead-spot" or zone at the discharge valve in some of these blenders. To compensate for this dead-spot, manufacturers recycle the powder from this area at some point during the mixing process. Obviously, there should be adequate and specific directions and procedures for assuring that this critical step is performed. Another concern with this mixer is poor mixing at the ends of the center horizontal mixing bar and at the shell wall because of blade clearance. The level of powder placed in this mixer is normally at the top of the outer ribbon blade, and as with other mixers, care must be taken not to overfill the mixer.

Cleaning problems, particularly at the ends of the ribbon blender where the horizontal bar enters the blender, have been identified. If manufacturers do not disassemble and clean the seals and packing between batches, they should have data to demonstrate the absence of foreign contaminants between batches of different products processed in the blender.

3. Tumbler

Common mixers of this type include the twin-shell and double cone. These mixers exert a gentle mixing action. Because of this mild action, lumps of powder will not be broken up and mixed. Powders may also clump due to static charges, and segregation can occur. Low humidity can contribute to this problem. Blending under very dry conditions was found to lead to charge buildup and segregation, while blending of some products under humid conditions led to lumping. More so than with other mixers, powder charge levels should not exceed 60% to 65% of the total volume of the mixer.

Fabricators of tumbler-type blenders identify the volume as the actual working capacity and not the actual volume of the blender. It is important to correlate the bulk density of the granulation with the working capacity of the blender.

4. High Shear (High Energy)

There are several fabricators of these mixers, including GRAL, Diosna, and Lodige or Littleford. These mixers are highly efficient and ideally suited for wet granulations. The end point of wet granulations can be determined by measurement on a gauge of the work needed to agitate the blend. The mixing vessel is enclosed, and dust only enters the environment when loading.

One of the problems associated with these mixers is the transfer or conversion of products blended in the older types of mixers to these blenders. Mixing times are going to be different, and the physical characteristics of the blend may also be different.

These mixers are efficient. For wet granulations, it is important to control the rate and amount of addition of the solvent. Because of their efficiency, drug substances may

partially dissolve and recrystallize upon drying as a different physical form.

An intensifier bar in the center of the blender, which rotates at very high speeds, breaks down smaller and harder agglomerates. A major disadvantage of this type of blender is that the extremely high speed of the intensifier bar generates considerable heat that can sometimes result in the charring of some sugar-base granulations. It should be pointed out that these same comments are applicable to other high-energy mixers, which also rely on high-speed choppers to disperse powders. Also, between-product cleaning of the blender requires disassembly of the intensifier bar.

5. Plastic Bag

Any discussion of mixers would not be complete without addressing the plastic bag. Manufacturers resorted to the blending or manufacture of a trituration in a plastic bag. Obviously, it is difficult to reproduce such a process, and there is the potential for loss of powder as a result of breakage or handling. When the plastic bag has been used, directions are usually not specific, and one would not know by reading the directions that a plastic bag was employed. The use of a plastic bag cannot be justified in the manufacture of a pharmaceutical product. In fact, it continues to be a popular method, as often mentioned in the formulations described in this treatise.

B. Dryers

Two basic types of dryers are used. One is the oven dryer, where the wet granulation is spread on trays and dried in an oven. The second dryer is the fluid-bed dryer, in which the wet granulation is "fluidized" or suspended in air. A third type recently introduced involves drying of granulations in vacuo while being mixed and processed. Generally, the fluid-bed dryer yields a more uniform granulation with spherical particles. However, this may result in compression problems that may require additional compression force to remedy these problems. It is not unusual to see manufacturers change from an oven dryer to a fluid-bed dryer. However, such a change should be validated for equivalency with conducted in vitro esting, such as hardness, disintegration, and comparative dissolution, and stability testing. Major changes in process details will require demonstration of bioequivalence.

Other issues of concern with drying include moisture uniformity and cross-contamination. Tray dryers present more moisture uniformity problems than fluid-bed dryers. Obviously, a dryer should be qualified for heat uniformity and a program developed to assure moisture uniformity in granulations at the end point of drying. With respect to fluid-bed dryers, moisture problems can occur if the granulation is not completely fluidized.

Regarding cross-contamination, oven dryers, particularly those in which air is recirculated, present cross-contamination problems because air recirculates through a common filter and duct. For fluid-bed dryers, the bag filters present cross-contamination problems. To minimize problems, manufacturers should use product-dedicated bags.

C. Tablet Compression Equipment

Another important variable in the manufacturing process is the tablet press or encapsulating machine. The newer dosage form equipment requires granulations with good flow characteristics and good uniformity. The newer tablet presses control weight variation by compression force and require uniform granulation to function correctly. Setup of the microprocessor-controlled tablet press usually includes some type of challenge to the system. For example, a short punch is sometimes placed among the other punches. If the press is operating correctly, it will sound an alarm when a lower- or higher-weight tablet is compressed.

Different tablet compression equipment can cause dose uniformity, weight uniformity, and hardness problems. For example, vibrations during tablet compression can cause segregation of the granulation in the feed hopper. The speed of the machine can affect fill of the die and tablet weight. Therefore, as previously discussed, it is important to have specific operating directions.

Many unit operations now provide for blending in totes, with discharge of the tote directly into tablet compression equipment. Because of segregation problems at the end of discharge, tablets from the end of compression should be tested for content uniformity. The use of inserts in totes was shown to minimize segregation.

With regard to the newer computer-controlled tablet compression equipment, buckets of tablets are often rejected because of potential weight variation problems. The disposition of these tablets, as well as the granulation and tablets used to set up the press, should be in accordance with written methods. Reworking processes for culls must be validated.

With regard to encapsulation operations, the hygroscopic nature of gelatin capsules and some of the granulations requires humidity controls for storage of the empty capsules and their subsequent filling. Scale-up of capsule products also presented some problems because of the different types of encapsulation equipment. Older equipment that operated on gravity fill, such as the Lilly and Parke-Davis machines, was commonly used for manufacturing capsules in clinical manufacturing areas. When formulations were scaled up to high-speed encapsulation equipment, flow problems and poor weight variation resulted. Additionally, some of the newer equipment provides for the formation of a slug, which could impact dissolution.

D. Coating Equipment

Many tablets are now coated with an aqueous film coat that is usually very soluble. Current technology provides for fixed sprays of the coating solution. The volume of coating solution, rate, and temperature can be controlled by some of the more highly automated operations. However, for many sugar-coated, enteric-coated, and delayed-release products, some portions of the coating process are not highly soluble and are performed manually. Generally, the shellac undercoat used for sugar-coated tablets presented disintegration and dissolution problems, particularly in aged samples.

With respect to poor disintegration, ferrous sulfate tablets probably represent the classical example. Over the years, there have been many recalls from many different manufacturers for poor disintegration of coated ferrous sulfate tablets. Likewise, there have been many problems with poor dissolution attributed to the coating process. Again, the shellac undercoat hardens, and even sometimes cracks, resulting in poor dissolution.

The numbers of applications of coats, volume of coating solution in a specific application, and temperature of the solution during applications are parameters that need to be addressed. For example, the temperature of the application and even heat during drying can cause dissolution failures in aged tablets. Another problem associated with the coating process concerns the heat applied to products that are sensitive to heat. For example, it was shown that estrogen tablets are heat sensitive and exhibited stability problems. Thus, it is important to control this phase of the process.

There are a few products, such as some of the antihistamine tablets, in which the drug substance is applied during the coating process. Other products require the active drug substance to be applied as a dust on tacky tablets as part of the coating process. For these products, it is particularly important to apply the drug in the coating solution in many controlled applications.

Again, it is important as part of the validation of these processes to demonstrate dose uniformity and dissolution and control the parameters of the coating process.

XVIII. EXCIPIENTS

Excipients are well defined in the official pharmacopoeia. No specific pharmaceutical grades are specified in this book, except where there is a specific reason to do so. However, it is known that different pharmacopoeia may have different specifications, such as particle size, impurities, moisture, etc. The harmonization of excipients, a global effort that is underway, would go a long way in making the choice of excipients. The manufacturer is referred to http://www.ipecamericas.org/index.html and the *Handbook of Pharmaceutical Excipients* for further advice. A large number of proprietary excipients are widely used, such as Ac-Di-Sol®, Explotab®, Aerosil®, Ludipress®, Avicel®, etc., and many of these are now part of pharmacopoeias. There is a significant advantage, though the cost is high, in using these ingredients because they offer additional benefits, often reducing processing time. Additionally, the suppliers of these ingredients are always willing to provide formulation support and have large databases, particularly pertaining to stability of drugs, that may be of great value to manufacturers. The following sections (A–F) list the most commonly used excipients in compressed solids.

A. Coating Agent

Carboxymethylcellulose, sodium cellacefate (formerly cellulose acetate phthalate), cellulose acetate, cellulose acetate phthalate (see cellacefate), ethylcellulose, ethylcellulose aqueous dispersion gelatin glaze, pharmaceutical hydroxypropyl, cellulose hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate (see hypromellose phthalate), hypromellose phthalate (formerly hydroxypropyl methylcellulose phthalate), methacrylic acid copolymer, methacrylic acid copolymer dispersion, methylcellulose PEG, polyvinyl acetate, phthalate shellac sucrose, titanium dioxide wax, carnauba wax, microcrystalline zein.

B. Glidant

Calcium silicate, magnesium silicate, silicon dioxide, colloidal talc.

C. Tablet Binder

Acacia alginic acid carboxymethylcellulose, sodium cellulose, microcrystalline dextrin ethylcellulose gelatin glucose, liquid guar gum hydroxypropyl methylcellulose, methylcellulose polyethylene oxide povidone starch, pregelatinized syrup.

D. Diluent

Calcium carbonate, calcium phosphate, dibasic calcium phosphate, tribasic calcium sulfate cellulose, microcrystalline cellulose, powdered dextrates, dextrin, dextrose, excipient, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, pregelatinized sucrose, sugar, compressible sugar, confectioner's sugar.

E. Disintegrant

Alginic acid cellulose, microcrystalline croscarmellose sodium, crospovidone polacrilin, potassium, sodium starch, glycolate starch, starch, pregelatinized.

F. Lubricant

Calcium stearate, glyceryl behenate, magnesium stearate, mineral oil, light PEG, sodium stearyl fumarate stearic acid, stearic acid, purified talc, vegetable oil, hydrogenated type I zinc stearate.

The choice of excipients is made based on three distinct considerations:

- Compatability with the active drug—Many excipients have active functional groups that can interact with the active drug and enhance its degradation. Even the water of hydration or moisture in the excipients can create difficulties in solid-state degradation of the active drug; so, it is not only the selection of the ingredient but also the grade (such as anhydrous or hydrous) that is important.
- Effect on efficacy—Excipients are known to alter the release patterns (e.g., a strong binder would delay break up of the tablet) and often bind the drug molecules in the gastrointestinal tract. The evaluation should be made in the full composition of ingredients because the presence of two ingredients may change their individual characteristics.
- Cost of formulation—Even though excipients contribute a small cost of the total formulation, the declining cost of APIs makes the selection of excipients based on cost an important consideration. This is particularly true when generic manufacturers are filing ANDAs knowing well that they will compete on a price basis. However, the total cost of formulation should not only be calculated on the basis of excipients. Often, the use of expensive excipients reduces process time, eliminates certain process steps, and even allows for the use of a cheaper packaging material. The manufacturer must, therefore, calculate the overall manufacturing cost. This aspect of formulation creates unique considerations by the multinational companies doing business worldwide; they are often forced to develop alternate formulations depending on the availability of excipients, manpower cost, and local environmental considerations.

The rule of thumb in the selection of excipients remains—keep it simple and at the bare minimum. The goal of excipients selection should be clearly defined—the dosage form yielding to a solution form at a predetermined rate (not necessarily the fastest in all instances).

The formulations described in this volume provide a quantitative listing of excipients recommended. An astute formulator would know the need to alter their quantity based on the type of equipment used to process them, the size of the batch processed at one time, and the quality of compressed product obtained. Therefore, all quantitative listings of excipients must be considered the best starting point, which can be adjusted and optimized, if necessary. In many instances, a range of excipients is allowed, such as in the case of a binder solution, to yield a suitable mass (as it is often described in the formulation of wet massing).

Where exact quantities of excipients are not available, but the excipients are identified for an innovator's product, this is still a better starting point than establishing the choice of excipients. Knowledge of the physicochemical

characteristics of the API takes a more pivotal role when the information available is limited. Obviously, one can readily identify the role of the identified, but not quantified, excipients. Some experimentation is required. However, as provided throughout this volume, significant knowledge can be gained by benchmarking the formulation. Other similar drugs or excipients should provide a good clue of the starting quantities. It is noteworthy that in obtaining the copies of competitor NDAs, through the Freedom of Information Act, some quantities are often redacted, leaving the formulator to guess. However, this should not be a difficult step, as long as the quantities of excipients chosen provide a similar weight, thickness, and disintegration and dissolution characteristics.

A common practice by innovator companies, as the NCE gets closer to the patent term expiry, is to patent a variety of formulations; for example, in the case of Aug-mentin®, the innovator chose to patent a different combination of amoxicillin and clavulanic acid and developed a composition for pediatric therapy. The purpose of this exercise is to keep generic competition out; the generic product in some cases may be the same, but not exact. The patent-end changes may also include changes in specification, choice of solvent systems used, or other cosmetic changes. However, a generic manufacturer would do well by just following the original formulation (for obvious reasons of regulatory compliance) because this has withstood the test of time. The author recommends that no changes should be made to an otherwise working formula, albeit this may improve processing, until such a time that the generic manufacturer has sufficient experience with the product. Most unusual things can happen when unsuspecting changes, appearing benign at the surface, are made to proven formulas. Given the cost of bioequivalence study requirements for compressed solids, changes in formulation should not be made unless essential and, even then, only for compliance purposes.

XIX. DIRECT COMPRESSION

The technology involved in direct compression assumes great importance in the tablet formulations, because it is often the cheapest means, particularly in the production of generics, that the active substance permits. The limiting factors are the physical properties of the active substance and its concentration in the tablets. Even substances such as ascorbic acid that are hardly suitable for direct compression, owing to the friability of their crystals, can normally be directly pressed into tablets at concentrations of 30% to 40%. However, this technique is not as suitable if the content of ascorbic acid is higher. This limit may be shifted upward by special direct compression auxiliaries, for example Ludipress. Two important alternatives, viz. Ludipress grades and Kollidon VA 64, can be found in the BASF line of pharmaceutical excipients for direct compression.

Ludipress is a speciality derived from lactose, Kollidon 30, and Kollidon CL. It thus combines the properties of a filler, binder, disintegrant, and flow agent and also often acts as a release accelerator. By virtue of its versatility, formulations containing it are usually very simple. It can also be combined with almost all active substances with the exception of those that enter into a chemical interaction with lactose (Maillard reaction).

Active substances, for example many analgetics, behave very differently with Ludipress when the dosage is extremely high. Acetylsalicylic acid and metamizole can be pressed when little Ludipress has been added; ibuprofen requires a larger amount; and the fraction of Ludipress required in the tablets is too large for paracetamol (= acetaminophen).

An alternative to the Ludipress grades is the outstanding dry binder Kollidon VA 64 together with excipients, for example calcium phosphate, microcrystalline cellulose, lactose, or starch, and a disintegrant, for example Kollidon CL. This combination even allows 500 mg of paracetamol to be pressed into good tablets with a weight of 700 mg.

No other dry binder has a binding power and plasticity comparable to those of Kollidon VA 64. Plasticity, in particular, is an important parameter in direct compression. This property of Kollidon VA 64 is not adversely effected by increasing the pressure. The beneficial properties of Kollidon VA 64 can also be exploited for the production of concentrated active substance that is subsequently used for direct tabletting. Kollidon VA 64 and Ludipress can also be combined with one another.

XX. FILL WEIGHTS

Fill weights are provided in all formulations. These may not coincide with scale for many reasons, as described elsewhere: differences in the salt forms, hydrates, or overages added in manufacturing and also to provide the extra margin of variation in filling during fast compression operations.

XXI. FINAL PACKAGING

A formulation design does not end with assuring that good tablets are formed; it must allow for handling during packaging, such as sliding into blister sheets or dropping into bottles. Actual fill runs must be conducted, and then the finished product must be subjected to simulated, and finally, the actual rigors of shipping before finalizing a formulation. Know that during shipping, the product may be exposed to diverse and often harsh weather conditions. Silica gel is often placed in the finished packs, or cotton is inserted, mainly to provide moisture or absorb odor (in the case of cotton).

XXII. FINAL TESTING

Finished product testing, particularly assay, content uniformity, and dissolution, is required. In the review of dissolution test results, it is important to eventually see results close to 100% dissolution. In some cases, manufacturers profile the dissolution results only to the specification. However, if lower but still acceptable results are obtained (such as 85%), it is important to continue the test. This can be performed by increasing the speed of the apparatus. If a product completely dissolves, yet only results in a value of 85%, it may indicate some problem with the test. Likewise, high dissolution results (115%) also indicate some problem with the test. Obviously, unusual or atypical results should be explained in the validation report.

XXIII. FINES

Solids, when grinded to small particle sizes (as when passing through sieves or crushing granules), yield a distribution of various particle sizes. A certain amount of very fine particles,

such as those passing #100 mesh, is required to fill in the gaps in a good compaction process; however, a large proportion of fines (as they are called) can create a problem in the flow or compaction of material. As a result, many master formulas require the reworking of fines back to granules. Any such recommendation should be carried out considering the type of processing and equipment used. These are mere suggestions; if a product compacts well, then it has the right proportion of fines.

XXIV. FORMULA EXCESSES

The difference between the scale and the quantity used for manufacturing is a result of either adjustment for the chemical form used (such as salt form for labeled base), hydrate forms (to compensate for additional water), potency variations (such as for antibiotics and biologicals), manufacturing excesses (for losses of drug during manufacturing), stability excesses (to compensate for loss during the shelf life; this is most important for vitamin products), and solvent/hydration loss (such as during manufacturing).

XXV. GEOMETRIC DILUTION

In all instances where low-dose drugs are manufactured, the mixing of ingredients should be done in a geometric dilution process; for example, a tablet containing 100 mg per tablet will first require mixing the active drug with a smaller quantity of excipient and then building up the volume to make sure the API is properly distributed. Further consistency to the product is imparted during the mixing of the granulated mixture.

XXVI. GRANULATION/MIX ANALYSIS

A critical step in the manufacture of an oral solid dosage form is the blending of the final granulation. If uniformity is not achieved at this stage, then one could assume that some dosage units would not comply with uniformity requirements. The major advantage of blend analysis (from a uniformity perspective) is that specific areas of the blender that have the greatest potential to be nonuniform can be sampled. This is particularly true of the ribbon-type blender and planetary or pony-type mixers.

In some cases, such as for large or tumbler-type blenders, it is impractical to sample from the blender directly. In such cases, granulations or blends could be sampled at the time of blender discharge or directly from drums. If sampling from drums, samples from the top, middle, and bottom of each drum should be collected.

In most cases, sampling thieves are readily available for sampling the small quantities that need to be taken from key areas of the blender or the drums. If samples larger than one dosage unit must be collected, however, adequate provisions must be made to prevent excessive handling manipulation between the time of sampling and the time of analysis.

Good science and logic would seem to dictate that sample sizes of the approximate equivalent weight of the dosage unit should be sampled in order to test for uniformity. Many industrial pharmacy and engineering texts confirm this approach. Large granulation sample sizes, such as 1 oz, will provide little information with respect to uniformity. Generally, further mixing after sampling and prior to analysis can yield misleading results.

The acceptance criteria for granulation dose uniformity testing needs to be continuously evaluated. Although many manufacturers evaluate dose uniformity using the compendia dose uniformity specifications (85–115% with an RSD of 6–7.8), such specifications should be tighter where supported by the firm's historical data on the level of blend uniformity with its equipment for a given product. In many cases, compendia assay limits for the finished product (90–110% of label claim) are broad enough for this purpose, and most manufacturers should be able to demonstrate blend assay results well within these limits. If larger sample sizes are taken for assay to evaluate total composite assay, then the specific USP or filed criteria for assay should be used.

In addition to the analysis of blends for dose uniformity and potency, blends are tested for physical characteristics.

A major physical parameter used to demonstrate equivalence between batches is the particle size profile. This is particularly important for comparison of the biobatch with production batches and should be repeated when processes are modified or changed. The particle size profile will provide useful information for demonstrating comparability.

Particle size profiles are particularly important for the tablet made by a wet granulation process. The size and even the type of granule can affect the pore size in a tablet as well as its dissolution. For example, dissolution failure may be attributed to a change in the milling screen size, yielding a granulation with larger granules. When coated, larger pores permit increased penetration into the tablet by the coating solution, resulting in slower dissolution.

Another test typically performed on the granulation, particularly when the wet granulation process is used, is loss on drying (LOD) and moisture content. If organic solvents are employed, then residual solvent residues are also tested. In the validation of a drying process, LOD levels are determined before, during, and after drying in order to demonstrate times and levels. As with processing variables, levels (specifications) are established in the development phase, with the validation phase used to confirm the adequacy of the process.

XXVII. INGREDIENT WARNING

Whereas many organic solvents are removed, traces may remain, and these may cause reactions, particularly in children; additionally, appropriate consideration should be given to the choice of using lactose for its intolerance in some of the use of sulfites or preservatives to which patients may be allergic.

XXVIII. IN-PROCESS TESTING

In-process testing is the testing performed on dosage forms during their compression/encapsulation stages to assure consistency throughout these operations. For tablets, individual tablet weights, moisture, hardness (compression force), and disintegration are performed. Because hardness and disintegration specifications are established during development and biobatch production, testing is performed to demonstrate equivalency (comparability) and consistency.

Specifications required to control the manufacturing process must be established and justified. This will require

granulation studies that would include blend uniformity, sieve analysis, and moisture. In the formulations provided in this book, the in-process milestones are not generally identified; the manufacturer is supposed to know this. Critical in-process testing stages for compressed solids are

- assuring cleanliness of equipment;
- checking and recording temperature where specified for dissolving or mixing ingredients, such as in the making of binder solutions or slurries;
- testing of granules for content uniformity, flow rate, tap density, moisture content (LOD), or other specific testing, as required;
- testing of tablets during compression for weight, thickness, friability, and disintegration;
- final testing of weight, friability, content uniformity, disintegration, and dissolution; and
- assay and finished product release.

With regard to moisture, some tablets set up (harden) upon aging as a result of poor moisture control and inadequate specifications. For example, this was shown to be a major problem with carbamazepine tablets.

XXIX. LOSS ON DRYING

This procedure determines the amount of volatile matter of any kind that is driven off under the conditions specified. Mix and accurately weigh the substance to be tested, and, unless otherwise directed in the individual monograph, conduct the determination on 1 to 2 g. If the test specimen is in the form of large crystals, reduce the particle size to about 2 mm by quickly crushing. Take a glass-stoppered, shallow weighing bottle that has been dried for 30 minutes under the same conditions to be employed in the determination. Put the test specimen in the bottle, replace the cover, and accurately weigh the bottle and the contents. By gentle, side-wise shaking distribute the test specimen as evenly as practicable to a depth of about 5 mm and not more than 10 mm in the case of bulky materials. Place the loaded bottle in the drying chamber, remove the stopper, and leave it in the chamber. Dry the test specimen at the temperature and for the time specified in the monograph. (*Note:* The temperature specified in the monograph is to be regarded as being within the range of $\pm 2^{\circ}C$ of the stated Figure.) Upon opening the chamber, close the bottle promptly, and allow it to come to room temperature in a desiccator before weighing.

If the substance melts at a lower temperature than that specified for the determination of LOD, maintain the bottle with its contents for 1 to 2 hours at a temperature $5^{\circ}C$ to $10^{\circ}C$ below the melting temperature, then dry at the specified temperature. Where the specimen under test is a tablet, use powder from not less than four tablets ground to a fine powder. Where the individual monograph directs that the LOD should be determined by thermogravimetric analysis, a sensitive electrobalance must be used. Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus must be used. When drying in a desiccator is specified, exercise particular care to ensure that the desiccant is kept fully effective by frequently replacing. Where drying in a capillary-stoppered bottle in vacuum is directed in the individual monograph, use a bottle or tube fitted with a stopper having a 225 ± 25 mm diameter capillary, and maintain the heating chamber at a pressure of 5 mm or less of mercury. At the end of the heating period, admit dry air to the heating chamber, remove the bottle, and with the capillary stopper still in place, allow it to cool in a desiccator before weighing.

Many pharmacopoeial articles are hydrates or contain water in adsorbed form. As a result, the determination of the water content is important in demonstrating compliance with the pharmacopoeial standards. Generally, one of the methods given next is called for in the individual monograph, depending upon the nature of the article. In rare cases, a choice is allowed between two methods. When the article contains water of hydration, method I (titrimetric), method II (azeotropic), or method III (gravimetric) is employed, as directed in the individual monograph.

XXX. MANUFACTURING YIELDS

The formulas provided here include scale as well as quantities for 1000 tablets; often in a scale-up, yields must be calculated to extrapolate exact quantities needed for a specific batch size; yields vary because of differences in the tablet weight (within the specified range), losses in equipment, and losses to the environment. The exhaust or vacuum can carry with it a lot of product at times.

XXXI. MASTER FORMULA

This document must include specific manufacturing directions for the full-scale commercial process, including in-process and finished product specifications. The cGMP-compliant master formula will have room for direct entry onto the documents of all critical parameters, such as temperature, mixing times, LOD, etc., beside signatures of the persons responsible for complying with the specifications. No specific guidelines are provided for the formatting of this document. However, those skilled in assuring compliance with the GMP know the art of capturing most eventualities that may arise in the manufacturing of the product. The key is to assure that no individual discretions are allowed.

XXXII. MULTIPLE-ITEM ENTRIES

In the formulations provided in this book, an ingredient may appear in multiple places; this is necessary so as to identify the different quantities used at different stages and at different times for different purposes. For example, the dry form of starch may be mixed with the drug and then used in the making of a paste for granulation. Similarly, solvents are often listed in many places.

XXXIII. MULTIPLE STRENGTHS OF FORMULATIONS

The formulations disclosed in this book handle multiple strengths in two ways: one to adjust the fill weight of tablets and the other to provide a different formulation. There are specific reasons for this. Where the quantity of API is high, a simple doubling of fill weight might not work, and an adjustment to the excipients will be required. On the other hand are products where the API is less than 1% of the total weight, in which case, the formulation remains the same, with one of the

major components, such as lactose or dicalcium phosphate, providing compensation for the additional weight. Then, the tablet can be compressed at the same weight.

XXXIV. NOVEL DRUG DELIVERY SYSTEMS

From osmotically driven release of the API to wax matrices to plastic "ghosts" (e.g., Gradumet®), the compressed solid dosage forms offer a variety of possibilities for incorporating novel drug delivery systems. It should be noted that the compression force required to manufacture the dosage form can deform a structured component; on the other hand, the high compression force and the resultant rise in temperature that is inevitable can be used to create unique dosage form designs. One such example is the use of PEG 6000 or 8000 in direct compression formulations. The compression pressures in a typical tabletting machine or in a roller compactor are generally high enough to produce sufficient heat to melt the PEGs and then congeal to provide adequate binding without the need for wet massing. The author used this technique to formulate a myriad of drugs, particularly those subject to stability problems, such as vitamins. PEGs are compatible with most drugs, are cheap, and dissolve rapidly to release the drug. The author highly recommends using this technique to formulate directly compressible formulations instead of using the direct-compression-grade raw materials that are very expensive. Another technique that lends itself appropriately to solid compression is the use of solid solutions. Many drugs, when melted with water-soluble compounds, such as succinic acid, PEG, etc., congeal in a molecular dispersion, which, when placed in the gastrointestinal environment, releases the drug rapidly—it is already in a solution state. Wax embedding is another process (such as used for diltiazem) for moderating the release of drugs.

Briefly, the formulator has many tools available with which to formulate novel drug delivery systems with compression of solids. These techniques have, however, not been exploited as widely as their potential offers. The young formulators not yet biased by the need to follow a traditional route of formulating are encouraged to experiment with a myriad of possibilities, using components that have well proven their utility but in a different role. Remember, a temperature rise during the compression process is a source of energy that can be put to use.

XXXV. PARTICLE COATING

Even though solid-state compression excludes moisture, which is the primary starting point in chemical degradation, these dosage forms are not impervious to atmosphere; this protection is generally provided by coating the final compressed dosage form, such as by sealing with waxes. However, there are instances where it may be necessary to coat the particles of the drug before incorporating them into formulations. There can be several reasons for doing this, besides imparting greater stability. It is done to mask the taste, for example, in chewable tablets, to improve flow in tablets comprising a larger proportion of the active drug, to impart specific release characteristics, or to protect the gastrointestinal mucosa (such as in the case of particle-coated iron tablets). Coated particles should be treated as a specialized form of excipient, which must be properly tested for its specifications prior to incorporating in the final dosage form. Most of the particle-coating methods involve a fluid-bed system or coating on a nonpareil bead.

XXXVI. PRESERVATIVES IN COMPRESSED SOLID DOSAGE FORMULATIONS

As a rule of thumb, good formulations include only essential components. Because compressed solids have low moisture content, microbiological stability generally does not pose a problem, with few exceptions. However, in the wet granulation process, slurries or pastes are made that are water-based and are often kept for a few hours before being used, requiring the use of preservatives, particularly when gelatin is also used with starch. Generally, a standard combination of propylparabens and methylparabens would do. Preservatives are also included in compressed solids, where the compositions may be highly hygroscopic, resulting in localized liquefaction of powders that might promote microbial growth.

XXXVII. PUNCH SIZE AND SHAPE

The choice of punch size is dependent on the amount of API, the quantity of excipients needed to make it compressible, and what can be reasonably administered. Tablets ranging in weight from less than 100 mg to over 1 g are compressed in 6- to 15-mm-diameter punches. The size is also important because a proportion between thickness and diameter must be maintained. Thick tablets are difficult to eject from dyes, such as a long cylindrical product. Experienced machine operators know how well a tabletting mix compresses on one punch size and shape, and it becomes difficult to compress using other shapes and sizes. Whereas round tablets are the easiest to compress (from a technical viewpoint of design of punches to ejection), manufacturers use all different shapes, from bugs bunny-shaped vitamins to diamond-shaped Viagra® tablets.

The formulations provided in this book may have to be altered to meet the compaction requirements of different punch shapes and sizes other than those recommended here. Concave punches (giving convex tablets) are made to reduce the contact of compressed material with the wall of the die. This makes ejection of a tablet easier. However, because of the shape, there may be more picking of tablets. In several formulations described here, biplanar flat, round punches are recommended. The identification marks or logos on the tablets create additional problems in the picking of tablets. The polishing of punches remains an essential part of good tablet compressing. Often, punches wear out fast depending on the type of compression material used.

Regardless of what the supplier of a punch recommends, a punch must be replaced once it fails to provide the surface quality needed. Punches should ideally be replaced in groups and not individually (except to replace broken items).

XXXVIII. REWORKING CULLS

During the setup of machines and through rejection, especially in automated rejection systems, there may be a substantial amount of culls available. In most instances, it would be prudent to just discard them; however, for expensive APIs, reworking can be done. An internal SOP should clearly define

the proportion of rework allowed and how the calculations will be made to the BOM.

XXXIX. SCALE-UP

Whereas the formulations given in this book are robust enough to be scaled-up to most sizes, manufacturers may find the need to modify these to comply with scaled-up performance. For example, the quantity of lubricants, the amount of moisture, the size of the granules, etc., are all pertinent.

XL. SEGREGATION

Particulate solids, once mixed, have a tendency to segregate by virtue of differences in the shape, size, and density (other variables are also important) of the particles of which they are composed. This process of separation occurs during mixing as well as during subsequent handling of the completed mix. Generally, large differences in particle size, density, or shape within the mixture result in instability in the mixture. The segregation process normally requires energy input and can be reduced following mixing by careful handling. One of the most common reasons for postblending (after adding lubricants) segregation is overblending. Lubricants develop electric charge very quickly, making compression difficult and altering the dissolution profile. A critical specification in the manufacturing method is the length of blending. Follow this strictly.

XLI. SIFTING INGREDIENTS AND GRANULES

Whereas the specifications of starting materials are specified, the powders often form aggregates during storage; a point-of-use check of aggregation is needed. It is a good idea to sift all ingredients through specified sieves before adding them to mixing or blending vessels. For most raw materials, sifting through a #60 sieve (250 mm) is desired. Know that passing materials through finer sieves can generate electrostatic charges. Wet mass is passed through a #8 (2.38 mm) sieve, and dried granules are passed through a #16 (1.19 mm) mesh sieve. Lubricants should be sieved through a #60 mesh, except for magnesium stearate, which should not be shifted through an opening smaller than that of a #35 mesh. This is necessary to avoid building up electrical charges. A conversion chart for sieve sizes from U.S. Mesh to inches and microns (or millimeters) follows:

U.S. Mesh	Inches	Microns	Millimeters
3	0.2650	6730	6.730
4	0.1870	4760	4.760
5	0.1570	4000	4.000
6	0.1320	3360	3.360
7	0.1110	2830	2.830
8	0.0937	2380	2.380
10	0.0787	2000	2.000
12	0.0661	1680	1.680
14	0.0555	1410	1.410
16	0.0469	1190	1.190
18	0.0394	1000	1.000
20	0.0331	841	0.841
25	0.0280	707	0.707
	0.0232	595	0.595
	0.0197	500	0.500
	0.0165	400	0.400
	0.0138	354	0.354
	0.0117	297	0.297
	0.0098	250	0.250
	0.0083	210	0.210
	0.0070	177	0.177
	0.0059	149	0.149
	0.0049	125	0.125
	0.0041	105	0.105
	0.0035	88	0.088
	0.0029	74	0.074
	0.0024	63	0.063
	0.0021	53	0.053
	0.0017	44	0.044
	0.0015	37	0.037

XLII. SPECIFICATIONS

The development of a product and its manufacturing process and specifications, the design of the validation protocol, and the demonstration (validation) runs of the full-scale manufacturing process require scientific judgment based on good scientific data. The in-process control and product specifications are established during the product development process, with the test batch serving as the critical batch used for the establishment of specifications. Specifications, such as hardness and particle size, should be established before validation of the process; these specifications should be included in the validation protocol. The use of product development runs of the process to establish specifications and demonstrate that the system is validated often causes problems.

XLIII. STABILITY TESTING

Even though compressed solids offer a major advantage over other dosage forms in being the most stable, both chemically and physically, complete stability profiles must be developed every time any change, albeit minor, is made in the formulation, the processing conditions, the equipment used, or even the manufacturing site used. This applies not just to drugs with known stability problems, but even to highly stable drugs, such as erythromycin. Subtle alternations in formulation can bring such major unsuspected changes as prolonged disintegration and dissolution. The stability profiles are developed over a span of time to establish not only the chemical stability (providing the labeled quantity), but also the in vitro release characteristics. Stability testing is also required to be conducted in the specific temperature zone areas as dictated by compendia. This creates a significant problem for multinational companies selling products around the world, where different zone temperature stability requirements come into play. A universal formula is often difficult to design for this reason. Generic manufacturers must, therefore, take this aspect into consideration and mimic the formulations used by innovators in the world regions where these products are to be sold. Unfortunately, it is not as easy to obtain this information for formulations sold outside of the United States. Some reverse engineering may be in order to accomplish this.

XLIV. STORAGE OF IN-PROCESS MATERIAL

At several stages during the manufacturing, the bulk material would have to be kept in quarantine, awaiting QC results, such as LOD measurement, content uniformity of tabletting mix, etc. The master formula should specify the conditions of storage and the length of a validated storage period. In some instances, silica gel is to be kept in the drums storing the product. Follow these instructions carefully. In most instances, the bulk should receive a final blending turnover before filling the compression hoppers; this is necessary in order to avoid any segregation of powders during storage or during transportation to and from the storage facility.

XLV. TABLET FRIABILITY

This friability determination of compressed, uncoated tablets is generally applicable to most compressed tablets. Measurement of tablet friability supplements other physical strength measurements, such as tablet crushing strength. For tablets with a unit mass equal to or less than 650 mg, take a sample of whole tablets corresponding to 6.5 g. For tablets with a unit mass of more than 650 mg, take a sample of 10 whole tablets. The tablets should be carefully dusted prior to testing. Accurately weigh the tablet sample, and place the tablets in the drum. Rotate the drum 100 times, and remove the tablets. Remove any loose dust from the tablets, as before, and accurately weigh. If tablet size or shape causes irregular tumbling, adjust the drum base so that the base forms an angle of about 10 degrees with the benchtop, and the tablets no longer bind together when lying next to each other, which prevents them from falling freely.

Effervescent tablets and chewable tablets may have different specifications as far as friability is concerned, and these tablets normally require special packaging. In the case of hygroscopic tablets, a humidity-controlled environment (relative humidity less than 40%) is required for testing.

XLVI. TABLET MANUFACTURING

Tablets are prepared by three general methods: wet granulation, dry granulation (roll compaction or slugging), and direct compression. The purpose of wet and dry granulation is to improve flow of the mixture and to enhance its compressibility. Dry granulation (slugging) involves the compaction of powders at high pressures into large, often poorly formed tablet compacts. These compacts are then milled and screened to form a granulation of the desired particle size. The advantage of dry granulation is the elimination of heat and moisture in the processing. Dry granulations can be produced by extruding powders between hydraulically operated rollers to produce thin cakes that are subsequently screened or milled to give the desired granule size.

Excipients are available that allow production of tablets at high speeds without prior granulation steps. These directly compressible excipients consist of special physical forms of substances, such as lactose, sucrose, dextrose, or cellulose, which possess the desirable properties of fluidity and compressibility. The most widely used direct-compaction fillers are microcrystalline cellulose, anhydrous lactose, spray-dried lactose, compressible sucrose, and some forms of modified starches. Direct compression avoids many of the problems associated with wet and dry granulations. However, the inherent physical properties of the individual filler materials are highly critical, and minor variations can alter flow and compression characteristics so as to make them unsuitable for direct compression.

XLVII. TABLETS

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They may be classed, according to the method of manufacture, as compressed tablets or molded tablets. The vast majority of all tablets manufactured are made by compression, and compressed tablets are the most widely used dosage form in the United States. Compressed tablets are prepared by the application of high pressures, utilizing steel punches and dies, to powders or granulations. Tablets can be produced in a wide variety of sizes, shapes, and surface markings, depending upon the design of the punches and dies. Capsule-shaped tablets are commonly referred to as caplets. Boluses are large tablets intended for veterinary use, usually for large animals. Molded tablets are prepared by forcing dampened powders under low pressure into die cavities. Solidification depends upon crystal bridges built up during the subsequent drying process and not upon the compaction force. Tablet triturates are small, usually cylindrical, molded, or compressed tablets. Tablet triturates were traditionally used as dispensing tablets in order to provide a convenient, measured quantity of a potent drug for compounding purposes. Such tablets are rarely used today. Hypodermic tablets are molded tablets made from completely and readily water-soluble ingredients and formerly were intended for use in making preparations for hypodermic injection. They are employed orally, or where rapid drug availability is required, such as in the case of nitroglycerin tablets, sublingually. Buccal tablets are intended to be inserted in the Buccal pouch, and sublingual tablets are intended to be inserted beneath the tongue, where the active ingredient is absorbed directly through the oral mucosa. Few drugs are readily absorbed in this way, but for those that are (such as nitroglycerin and certain steroid hormones), there are a number of advantages. Soluble, effervescent tablets are prepared by compression and contain, in addition to active ingredients, mixtures of acids (citric acid, tartaric acid) and sodium bicarbonate, which release carbon dioxide when dissolved in water. They are intended to be dissolved or dispersed in water before administration. Effervescent tablets should be stored in tightly closed containers or moisture-proof packs and should be labeled to indicate that they are not to be swallowed directly.

Chewable tablets are formulated and manufactured so that they may be chewed, producing a pleasant-tasting residue in the oral cavity that is easily swallowed and does not leave a bitter or unpleasant aftertaste. These tablets have been used in tablet formulations for children, especially in multivitamin formulations, and for the administration of antacids and selected antibiotics. Chewable tablets are prepared by compression, usually utilizing mannitol, sorbitol, or sucrose as binders and fillers, and containing colors and flavors to enhance their appearance and taste.

Most compressed tablets consist of the active ingredient and a diluent (filler), binder, disintegrating agent, and lubricant. Approved FD&C and D&C dyes or lakes (dyes adsorbed onto insoluble aluminum hydroxide), flavors, and sweetening agents may also be present. Diluents are added where the quantity of active ingredient is small or difficult to compress.

Common tablet fillers include lactose, starch, dibasic calcium phosphate, and microcrystalline cellulose. Chewable tablets often contain sucrose, mannitol, or sorbitol as fillers. Where the amount of active ingredient is small, the overall tableting properties are, in large measure, determined by the filler. Because of problems encountered with the bioavailability of hydrophobic drugs of low water solubility, water-soluble diluents are used as fillers for these tablets. Binders give adhesiveness to the powder during the preliminary granulation and to the compressed tablet. They add to the cohesive strength already available in the diluent. While binders may be added dry, they are more effective when added out of solution. Common binders include acacia, gelatin, sucrose, povidone, methylcellulose, carboxymethylcellulose, and hydrolyzed starch pastes. The most effective dry binder is microcrystalline cellulose, which is commonly used for this purpose in tablets prepared by direct compression. A disintegrating agent serves to assist in the fragmentation of the tablet after administration. The most widely used tablet disintegrating agent is starch. Chemically modified starches and cellulose, alginic acid, microcrystalline cellulose, and crosslinked povidone are also used for this purpose. Effervescent mixtures are used in soluble tablet systems as disintegrating agents. The concentration of the disintegrating agent, method of addition, and degree of compaction play roles in effectiveness. Lubricants reduce friction during the compression and ejection cycles. In addition, they aid in preventing adherence of tablet material to the dies and punches. Metallic stearates, stearic acid, hydrogenated vegetable oils, and talc are used as lubricants. Because of the nature of this function, most lubricants are hydrophobic, and as such, tend to reduce the rates of tablet disintegration and dissolution. Consequently, excessive concentrations of lubricant should be avoided. PEGs and some lauryl sulfate salts have been used as soluble lubricants, but such agents generally do not possess optimal lubricating properties, and comparatively high concentrations are usually required. Glidants are agents that improve powder fluidity, and they are commonly employed in direct compression where no granulation step is involved. The most effective glidants are the colloidal pyrogenic silicas. Colorants are often added to tablet formulations for aesthetic value or for product identification. Both D&C and FD&C dyes and lakes are used. Most dyes are photosensitive, and they fade when exposed to light. The U.S. FDA regulates the colorants employed in drugs.

XLVIII. WATER-PURIFIED USP

As a general practice, the water used in wet granulation processes should be of at least the water-purified USP grade. Other grades are acceptable, provided their use can be validated, mainly for the reasons of microbiological quality and the presence of other dissolved solids.

XLIX. WEIGHT VARIATION AND CONTENT UNIFORMITY

Tablets are required to meet a weight variation test, where the active ingredient comprises a major portion of the tablet and where control of weight may be presumed to be an adequate control of drug content uniformity. Weight variation is not an adequate indication of content uniformity, where the drug substance comprises a relatively minor portion of the tablet, or where the tablet is sugar coated. Thus, the pharmacopoeia generally requires that coated tablets and tablets containing 50 mg or less of active ingredient, comprising less than 50% by weight of the dosage-form unit, pass a content uniformity test, wherein individual tablets are assayed for actual drug content.

L. WET GRANULATION VS. DRY GRANULATION OR DIRECT COMPRESSION

Drug powders are often not easily compressible. Even if they are compressible, the small quantity that needs to be dispensed requires the adding of excipients for bulking the product; however, the addition of these compatible bulking agents may render the mixture less compressible. Books were written on the physics of powder compression. In a nutshell, the compression of powders involves the breaking of a crystal lattice and the rebonding of lattices to yield a unit structure. Binders provide the bridging gap between and among the ingredients that would rather stay away (to put it simply). With compression machines, the requirement that powders fill the compression cavities as they are compressed no longer holds. The conundrum with powders is that they must flow easily to fill the cavities, but as the particle size gets smaller, the specific surface area increases, along with interparticulate friction that keeps the powder from flowing (angle of repose), subject to the individual characteristics of the chemical. Therefore, for the powders to easily flow into compression cavities, they must be present in granular form, rather than in the form of fine powder. Powders can be converted to granular form by wetting them and drying to form the bonds between particles, particularly in the presence of binding agents (the most popular being starch). The wet granulation process, therefore, involves mixing the powders with a paste of starch (generally approximately 30%) or using polyvinylpyrrolidone (PVP) in an organic solvent to make a wet mass. In most instances, the characteristic of the wet mass is judged by how well it forms a mass as tested. The wet mass is then passed through a coarse mesh, spread on trays, and dried at 50°C to 60°C or directly placed in a fluid-bed dryer. The test of drying is that the LOD ranges from 1% to 3%. This is referred to as wet granulation. Dry granulation is a process where the active drug is mixed with ingredients that are inherently granular and compressible or are made by modifications through wet granulation, to impart good flow ability and compressibility to the mix. Several APIs are also available in direct compressible grades, often coated to impart an additional element of chemical stability. Directly compressible aspirin or ascorbic acid are good examples. The cost of APIs rendered compressible is obviously higher; however, in the long run, it is cheaper to use directly compressible powders.

LI. MULTIVARIATE METHODS IN TABLET FORMULATION

The discussion presented demonstrates that a large number of formulation variables inevitably come into play when formulating a solid dosage form; whereas, each dosage form has its own focus on overcoming inherent difficulties, the release from solid dosage forms and their desirability makes them most widely studied. Drugs are mostly administered in formulated forms and tablets account for more than 80% of all pharmaceutical dosage forms administered. The need to prepare an easily administered dose by mouth or other body cavities in a stable form and one that releases the drug on a

timely basis has been the longest challenge for the pharmaceutical industry. As a result, tablets contain a large number of excipients including fillers or diluents, binders or adhesives, disintegrants, lubricants and glidants, colors, flavors and sweeteners; it might also be necessary to add miscellaneous components such as buffers, depending on the application. What constitutes an ideal combination of these ingredients is of great value to the formulators since not only they have to prepare an effective and stable formulation but this must be done at the lowest possible cost. This evaluation is best made by using such statistical techniques as multivariate methods.

Multivariate techniques make use of statistical experimental design, especially designs that deal with optimization, where much effort is spent on obtaining detailed knowledge about the investigated domain which may include the multivariate characterization of the excipients, in terms of both physical and spectral properties, together with principal component analysis (PCA), statistical experimental design in principal properties (PPs), and partial least squares projections to latent structures (PLS) analysis.

Component analysis: An $N \times K$ data matrix consists of N rows and K columns. The samples or objects in the rows are described by measured or calculated variables given in the columns. In a graphical illustration of a data matrix, the objects are a swarm of N points in a coordinate system of K variables. In cases where a number of objects are described by many variables, the variables tend to be correlated to some extent. This is especially true for spectral variables, where a high absorbance at one wavelength is usually accompanied by similar absorbance values at neighboring wavelengths. PCA uses this correlation to describe the variation in the data with a minimum number of orthogonal components. PCA corresponds to the least squares fitting of a straight line ($A = 1$) or an A-dimensional hyperplane to the data in the K-dimensional variable space. Objects are projected onto a subspace of lower dimension and receive new identities, t-values, often referred to as PPs or scores. The variation of the objects is summarized in the ($N \times A$) matrix, which includes a score vector for each component. Score values from two principal components (PCs), together span a mathematical plane, often referred to as a score plot. Objects are projected onto the plane to form a two-dimensional model of the data. This facilitates the detection of groupings, trends, and outliers (deviating objects) in data sets. The process of detecting and diagnosing outliers is important both when fitting and interpreting the model. An outlier may be an object that does not fit very well into the model, that is, one for which the distance to the model in X is too large to be accepted. Examining the residuals of that particular object will reveal the cause of the deviation. An outlier may, alternatively, be an object that lies far away from other objects in the score plot. Since PCA is a least squares technique such an outlier may cause one of the PCs to run through it or very close to it, resulting in a skewed model. Such outliers should be removed upon identification. PCA models can be calculated using the nonlinear iterative partial least squares (NIPALS) algorithm. The first component explains as much as possible of the variance, the second component is orthogonal to the first and explains as much as possible of the residual variance, and so on. The diversity of PCA applications makes it a very powerful tool in many situations. PCA can be used as a means to discover trends, groupings, and outliers in many types of data, to classify objects, as well as to reduce the number of dimensions and descriptive variables. The features of the PCA model of most interest in any particular study will depend on the systems being investigated and the purposes of the study.

MSC and SNV: multiplicative scatter correction (MSC) is a method for linearization and scatter correction of NIR. It is assumed that the factors affecting physical light scattering of a particular wavelength differ from the chemical factors affecting light absorption. Hence, a corrected spectrum should include only chemical information. In order to normalize the scatter level an "ideal" sample, often the average of the data set is used to correct data for each of the samples. The sample spectrum is regressed onto the average in order to calculate the additive offset and the multiplicative constant. MSC should be used carefully, as all of the samples influence the correction terms, so a deviating sample could have adverse effects on the corrections. The standard normal variate transformation (SNV) as a method for removing unwanted variation from NIR spectra. In contrast to MSC, the correction is performed on an individual sample basis, thus eliminating the possible negative effects of a deviating sample. One of the drawbacks of using SNV, as well as MSC, is that potentially interesting information regarding the particle size is lost. In cases where a response matrix exists there are other methods for removing noise from spectra. The concept of orthogonal signal correction (OSC), a method for removing information in spectra that is not related to the response prior to investigation.

Missing data can be handled by NIPALS. As a rule of thumb, in order to use this approach, there should be five times as many observations in any row or column as the number of dimensions (A) being calculated. The missing values should also be randomly distributed.

Ultravariate characterization is the basis for multivariate design. Descriptive variables that are used to characterize the excipients (for example) may be either physical properties or other variables. Usually, a homogenous group of constituents are put in the same group and characterized by the same variables, where the class of excipients commonly used as lubricants are described using literature data on relevant physical properties. By applying PCA to the descriptive data, the important information is extracted in a few PCs. The PCs are often referred to as latent variables or the PPs of the data set. Each excipient is assigned a score value in each PC. Thus, the excipients are compared and related to on a continuous scale of PPs, which are assumed to reflect real differences in excipient properties and greater distances between excipients along the PCs reflect greater differences in behavior.

LII. PHYSICAL PROPERTIES

Physical properties of the excipients influence the properties of the tablet, for example particle size and bulk volume. Determining physical properties of excipients demands a systematic approach and may consume substantial resources. To establish an optimal choice of excipients, screening experiments are conducted to gain knowledge about parameters that influence the measured results. The traditional approaches to experimental design are difficult to implement when choosing factors to use in a screening study investigating more excipients than can possibly be managed in a mixture design. One alternative is to use physical properties as factors,for example viscosity or some measure of particle size, for each class of excipients. Only a limited number of descriptive variables can be used for each excipient class for a manageable number of experiments. Orthogonal factors can

also be difficult to acquire,for example, it would be difficult to find an excipient with both a large mean particle diameter (a high setting in an imaginary design) and high density (also a high setting in such a design). These factors, together with factors for example LOD and particle shape, can clearly make the task of finding excipients representing extreme settings difficult or impossible. Use of a D-optimal selection from a candidate set described in a few variables could be a feasible option. This alternative has not been investigated by the author or reported in the literature. Another alternative is to use qualitative variables. The drawback of this approach is that only a few excipients, that is, levels in the design, can be included before the number of experiments becomes unfeasibly high. Using PPs and multivariate design instead of qualitative factors is a viable alternative if many excipients are to be included in a screening study. In many cases, of course, the resulting model will be less detailed compared to a model derived from a set of experiments where physical properties of one or a few excipients are studied. Nevertheless, it should at least give a good indication of areas in the multivariate domain that should be further explored, which may be sufficient in some cases.

LIII. PARTICLE SIZE STUDIES

The particle size of new drug substance is a critical parameter as it affects every phase of formulation and its effectiveness. Appropriate particle size is required to achieve optimal dissolution rate in solid dosage forms, control sedimentation and flocculation in suspensions, small particle size (2−5 μm) is required for inhalation therapy, content uniformity, and compressibility is governed by particle size. As a result, the preformulation studies must develop a specification of particle size as early as possible in the course of studies and develop specifications that need to be adhered to throughout the studies.

Conventional methods of grinding in mortar or ball milling (where sample quantity is sufficient; generally it is not and limited to about 25–100 mg) or micronization techniques are used to reduce the particle size. The method used can have significant effect on the crystallinity, polymorphic structures (often to amorphous forms) and drug substance stability that can range from discoloration to significant chemical degradation. Changes in polymorphic forms can be determined by performing XRPD before and after milling.

Micronization where possible allows increase in the surface area to the maximum which can impact on the solubility, dissolution and as a result, bioavailability. Since the aim of most preformulation studies is to determine if a solid dosage form can be administered, knowing that reduction of particle size where it changes dissolution rates can be pivotal in decision making for the selection of dosage forms. In the process of micronization, the drug substance is fed into a confined circular chamber where it is suspended in a high velocity stream of air. Interparticulate collisions result in a size reduction. Smaller particles are removed from the chamber by the escaping air stream towards the center of the mill where they are discharged and collected. Larger particles recirculate until their particle size is reduced. Micronized particles are typically less than 10 μm in diameter. In some instances, micronization can prove counterproductive, where it results in increased aggregation (leading to reduced surface area) or alteration of crystallinity, which must be studied using such methods as microcalorimetry, dynamic vapor sorption or inverse gas chromatography.

The introduction of dynamic vapor sorption (DVS) in 1994 revolutionized the world of gravimetric moisture sorption measurement, bringing outdated, time, and labor intensive desiccator use into the modern world of cutting-edge instrumentation and overnight vapor sorption isotherms. With a resolution down to 0.1 μg, a 1% change in mass of a 10 mg sample on exposure to the humidity controlled gas flow is both easily discernable and reproducible. DVS is a valued tool for studies related to polymorphism, compound stability, bulk and surface adsorption effects of water and organic vapors. The dynamic vapor sorption studies would typically show percent mass increases but often a hysterisis loop relationship is observed where there is crystallization of compound that results in the expelling of excess moisture. This effect can be important in some formulations, such as dry powder inhaler devices, since it can cause agglomeration of the powders and variable flow properties. The DVS is useful study when amorphous forms are involved upon size reduction; in many cases, a low level of amorphous character cannot be detected by techniques such as XRPD; microcalorimetry can detect <10% amorphous content (the limit of detection is 1% or less). The amorphous content of a micronized drug can be determined by measuring the heat output caused by the water vapor inducing crystallization of the amorphous regions.

Excellent instrumentation support and advice is available through Surface Measurement Systems, http://www.smsuk.co.uk/index.php, manufacturer of DVS-Advantage and DVS-1000 and 2000 series of equipment for dynamic vapor interaction studies. The DVS-HT represents the first new generation in gravimetric vapor sorption analyzers for more than a decade by Surface Measurement Systems (5 Wharfside, Rosemont Road, Alperton, Middlesex. HA0 4PE United Kingdom).

A. Particle Size Distribution

Particle size reduction particularly mandates study of particle size distribution studies using such techniques as sieving, optical microscopy in conjunction with image analysis, electron microscopy, the coulter counter and laser diffractometers depending on the anticipated size of the particles. Whereas the size characterization is simple for spherical particles, study of irregular particles required specialized methods. The Malvern Mastersizer Series (http://www.malvern.co.uk/home/index.htm) is an example of an instrument that measures particle size by laser diffraction. The use of this technique is based on light scattered through various angles, which is directly related to the diameter of the particle. Thus, by measuring the angles and intensity of scattered light from the particles, a particle size distribution can be deduced. It should be noted that the particle diameters reported are the same as those that spherical particles would produce under similar conditions. In the former, each particle is treated as spherical and essentially opaque to the impinging laser light.

Two different light scattering methodologies can be used to characterize particles. The classical, also known as "static" or "Rayleigh" scattering or MALLS provides a direct measure of mass.

The dynamic light scattering (DLS), which is also known as "photon correlation spectroscopy" (PCS) or "quasi-elastic light scattering" (QELS), uses the scattered light to measure the rate of diffusion of the particles. This

motion data is conventionally processed to derive a size distribution for the sample, where the size is given by the "Stokes radius" or "hydrodynamic radius" of the protein particle. This hydrodynamic size depends on both mass and shape (conformation). Dynamic scattering is particularly good at sensing the presence of very small amounts of aggregated particles and studying samples containing a very large range of masses. It can be quite valuable for comparing stability of different formulations, including real-time monitoring of changes at elevated temperatures. For submicron materials, particularly colloidal particles, quasi-elastic light scattering is the preferred technique. Two theories dominate the theory of light scattering; the Fraunhofer and Mie. According to Fraunhofer theory, the particles are spherical, nonporous, and opaque; diameter greater than wavelength, particles are distant enough from each other, random motion, and all the particles diffract the light with the same efficiency, regardless of size and shape. The Mie theory takes into account the differences in refractive indices between the particles and the suspending medium. If the diameter of the particles is above 10 μm, then the size produced by utilizing each theory is essentially the same. However, discrepancies may occur when the diameter of the particles approaches that of the wavelength of the laser source.

Although laser light diffraction is a rapid and highly repeatable method in determining the particle size distributions of pharmaceutical powders, the results obtained can be affected by particle shape. The laser light scattering generally reports broader size distribution compared to image analysis. In addition, the refractive index of the particles can introduce an error of 10% under most circumstances and should be accounted for. Another laser-based instrument, relying on light scattering, is the Aerosizer (http://www.erc.ufl.edu/facility/equipment.asp?n=20). Aerosizer measures particles one at a time in the range of 0.20 to 700 microns. The particles may be in the form of a dry powder or may be sprayed from a liquid suspension as an aerosol. The particles are blown through the system and dispersed in air to a preset count rate. The Aerosizer operates on the principle of aerodynamic time of flight. The particles are accelerated by a constant, known force due to airflow and are forced through a nozzle at nearly sonic velocity. Smaller particles are accelerated at a greater rate than large particles due to a greater force-to-mass ratio. Two laser beams measure the time of flight through the measurement region by detecting the light scattered by the particles. Statistical methods are used to correlate the start and stop times of each particle in a particular size range (channel) through the measurement zone. The time of flight is used in conjunction with the density of the particles and calibration curves established to determine the size distribution of the sample.

LIV. SURFACE AREA

Since the surface area exposed to the site of administration determines how fast a particle dissolves in accordance with the Noyes–Whitney equation, these determinations are important. Also in those instances where the particle size is difficult to measure, a gross estimation of surface area is the second best parameter to have to characterize the drug. The most common methods of surface area measurement including gas adsorption (nitrogen or krypton) based on what is most commonly described as the Braunauer, Emmet and Teller, or BET, method applied either as a multipoint or single point determination.

Adsorption is defined as the concentration of gas molecules near the surface of a solid material. The adsorbed gas is called *adsorbate* and the solid where adsorption takes place is known as the *adsorbent*. Adsorption is a physical phenomenon (usually called physisorption) that occurs at any environmental condition (pressure and temperature) but only at very low temperature, it becomes measurable. Thus physisorption experiments are performed at very low temperature, usually at the boiling temperature of liquid nitrogen at atmospheric pressure. Adsorption takes place because of the presence of an intrinsic surface energy. When a material is exposed to a gas, an attractive force acts between the exposed surface of the solid and the gas molecules. The result of these forces is characterized as physical (or Van der Waals) adsorption, in contrast to the stronger chemical attractions associated with chemisorption. The surface area of a solid includes both the external surface and the internal surface of the pores.

Because of the weak bonds involved between gas molecules and the surface (less than 15 KJ/mole), adsorption is a reversible phenomenon. Gas physisorption is considered nonselective, thus filling the surface step-by-step (or layer by layer) depending on the available solid surface and the relative pressure. Filling the first layer enables the measurement of the surface area of the material, because the amount of gas adsorbed when the monolayer is saturated is proportional to the entire surface area of the sample. The complete adsorption/desorption analysis is called an adsorption isotherm.

Once the isotherm is obtained, a number of calculation models can be applied to different regions of the adsorption isotherm to evaluate the specific surface area (i.e., BET, Dubinin, Langmuir, etc.) or the micro- and mesopore volume and size distributions (i.e., BJH, DH, H&K, S&F, etc.).

The surface area of a solid material is the total surface of the sample that is in contact with the external environment. It is expressed as square meters per gram of dry sample. This parameter is strongly related to the pore size and the pore volume that is, the larger the pore volume, the larger the surface area and the smaller the pore size, the higher the surface area. The surface area results from the contribution of the internal surface area of the pores plus the external surface area of the solid or the particles (in case of powders). Whenever a significant porosity is present, the fraction of the external surface area to the total surface area is small.

LV. POROSITY

Most solid powders contain a certain void volume of empty space. This is distributed within the solid mass in the form of pores, cavities, and cracks of various shapes and sizes. The total sum of the void volume is called the porosity. Porosity strongly determines important physical properties of materials such as durability, mechanical strength, permeability, adsorption properties, etc. The knowledge of pore structure is an important step in characterizing materials, predicting their behavior.

There are two main and important typologies of pores: closed and open pores. Closed pores are completely isolated from the external surface, not allowing the access of external fluids in neither liquid nor gaseous phase. Closed pores influence parameters like density, mechanical and thermal

properties. Open pores are connected to the external surface and are therefore accessible to fluids, depending on the pore nature/size and the nature of fluid. Open pores can be further divided in dead-end or interconnected pores. Further classification is related to the pore shape, whenever is possible to determine it. The characterization of solids in terms of porosity consists in determining the following parameters:

- **Pore size:** Pore dimensions cover a very wide range. Pores are classified according to three main groups depending on the access size.
  - Micropores: less than 2 nm diameter
  - Mesopores: between 2 and 50 nm diameter
  - Macropores: larger than 50 nm diameter
- **Specific pore volume and porosity:** The internal void space in a porous material can be measured. It is generally expressed as a void volume (in cm^3 or mL) divided by a mass unit (g).
- **Pore size distribution:** It is generally represented as the relative abundance of the pore volume (as a percentage or a derivative) as a function of the pore size.
- **Bulk density:** Bulk density (or envelope density) is calculated by the ratio between the dry sample mass and the external sample volume.
- **Percentage porosity:** The percentage porosity is represented by ratio between the total pore volume and the external (envelope) sample volume multiplied by 100.
- **Surface area:** See above for discussion.

LVI. TRUE DENSITY

Density is the ratio of the mass of an object to its volume, and for solids this term describes the arrangement of molecules. The study of compaction of powders is described by the Heckel equation. The densities of molecular crystals can be increased by compression. Information about the true density of a powder can be used to predict whether a compound will cream or sediment in a suspension such as metered dose inhaler (MDI) formulation. Therefore, suspensions of compounds that have a true density less than these figures will cream (rise to the surface), and those that are denser will sediment. It should be noted, however, that the physical stability of a suspension is not merely a function of the true density of the material. The true density is thus a property of the material and is independent of the method of determination. In this respect, the determination of the true density can be determined using three methods: displacement of a liquid, displacement of a gas (pycnometry), or floatation in a liquid. The liquid displacement is tedious and tends to underestimate the true density; displacement of a gas is more accurate but needs relatively expensive instrumentation. As an alternative, the floatation method is simple to use and inexpensive.

Gas pycnometry is probably the most commonly used method in the pharmaceutical industry for measuring true density. Gas pycnometers rely on the measurement of pressure changes, as a reference volume of gas, typically helium, added to, or deleted from, the test cell.

LVII. FLOW AND COMPACTION OF POWDERS

The flow properties of a powder will determine the nature and quantity of excipients needed to prepare a compressed or powder dosage form. This refers mainly to factors such as ability to process the powder through machines. To make a quick evaluation, the compound is compressed using an infrared (IR) press and die under 10 tons of pressure with variable dwell times, and the resulting tablets are tested with regard to their crushing strength after storing the tablets for about 24 hours. If longer dwell times result in higher crushing strength then the material is likely plastic; elastic material will show capping at low dwell times; the brittle material will not show any effect of dwell times. It is recommended that the compressed tablets be subject to XPRD to record any changes in the polymorphic forms.

There appears to be a relationship between indentation hardness and the molecular structure of organic materials. However, a prerequisite for predicting indentation hardness is knowledge of the crystal structure. As a result, highly sophisticated, computational methods and extensive crystallography libraries have recently become available to study the. For example, the Pfizer Research relies on the The Cambridge Structural Database (http://www.ccdc.cam.ac.uk/), the world repository of small molecule crystal structures. The Cambridge Structural Database (CSD) is the principal product of the CCDC. It is the central focus of the CSD System, which also comprises software for database access, structure visualization and data analysis, and structural knowledge bases derived from the CSD. The CSD records bibliographic, chemical, and crystallographic information for organic molecules and metal-organic compounds whose 3D structures have been determined using X-ray diffraction or neutron diffraction. The CSD records results of single crystal studies and powder diffraction studies which yield 3D atomic coordinate data for at least all non-H atoms. In some cases, the CCDC is unable to obtain coordinates, and incomplete entries are archived to the CSD. The CSD is distributed as part of the CSD System, which includes software for search and information retrieval (ConQuest), structure visualization (Mercury), numerical analysis (Vista), database creation (PreQuest). The CSD System also incorporates IsoStar, a knowledge base of intermolecular interactions, contains data derived from both the CSD and the PDB. Some software listed above are available for free use.

X-ray microtomography such as available from Skyscan (http://www.skyscan.be/next/home.htm) is used to analyze the effect of compaction on powder particles. It allows for the noninvasive 3D analysis of resulting structures, and has shown that the structure may be controlled by choice of pyrogen and the method of solvent removal. Simple seeding of the substrate surface with drug crystals can be used initially with a view to incorporating more sophisticated substrate polymorph approaches. The Skyscan-1172 represents a new generation in desk-top X-ray micro-CT scan systems. A novel architecture in which both the sample stage and the x-ray camera are moveable allows an unprecedented combination of image resolution, sample size accommodation, scan speed, and sample throughput. This innovative flexible scanner geometry of the Skyscan-1172 is particularly advantageous over intermediate resolution levels, where scans are around 10 times faster (to obtain the same or better image quality) compared to previous scanners with a fixed source-detector design. The Skyscan-1172 features two X-ray camera options: the high-performance 10 megapixel option, and the economy 1.3 megapixel option. The former, 10 megapixel camera allows the maximum scanning versatility, with an image field width of 68 mm (in dual image camera shift mode) or 35 mm (in standard single camera image mode). A nominal resolution (pixel size) of lower than 1 μm is attainable. A scannable height of around 70 mm allows for

either large samples or automatic batch scanning of a column of smaller samples. The system obtains multiple X-ray "shadow" transmission images of the object from different angular views, as the object rotates on a high-precision stage. From these shadow images, cross-section images of the object are reconstructed by a modified Feldkamp cone-beam algorithm, creating a complete 3D representation of internal microstructure and density over a selected range of heights in the transmission images. The best micro-CT scan images are obtained from objects in which microstructure coincides with contrast in X-ray absorption of the sample's constituent materials.

LVIII. COLOR

The color of a powder sample is used to indicate presence of solvents, distribution of particle size, and other possible differences in different lots of a new lead compound. In some instances, degradation of drug can be correlated with color changes to such degree that accurate color measurements can be used as a tool to provide product specification. The compendia often describe color of substances but mostly in subjective terms. Historically, the color evaluation has been a subjective measurement; however, newer quantitative measurement systems make this a more objective process. There are two basic methods for measuring the colors of surfaces.

- The first is to imitate the analysis made by the eye in terms of responses to three stimuli. This technique, known as "tristimulus colorimetry," sets out to measure X, Y, and Z directly.
- The second method is to determine reflectance (R) for each wavelength band across the range of the spectrum to which the eye is sensitive, and then to calculate the visual responses by summing products of R and the standard values for distribution of the sensitivity of the three-color responses.

The tristimulus method has theoretical advantages where the materials to be measured are fluorescent, but there are serious practical problems in assuming that a tristimulus colorimeter exactly matches human vision, that is, in eliminating color blindness from the instrument.

Two commonly used types of color measurement equipment are a colorimeter and a spectrophotometer. A tristimulus colorimeter has three main components

- a source of illumination (usually a lamp functioning at a constant voltage);
- a combination of filters used to modify the energy distribution of the incident/reflected light; and
- a photoelectric detector that converts the reflected light into an electrical output.

Each color has a fingerprint reflectance pattern in the spectrum. The colorimeter measures color through three wide-band filters corresponding to the spectral sensitivity curves. Measurements made on a tristimulus colorimeter are normally comparative, the instrument being standardized on glass or ceramic standards. To achieve the most accurate measurements, it is necessary to use calibrated standards of similar colors to the materials to be measured. This "hitching post" technique enables reasonably accurate tristimulus values to be obtained even when the colorimeter is demonstrably colorblind. Tristimulus colorimeters are most useful for quick comparison of near-matching colors. They are not very accurate. Large differences are evident between the various instrument manufacturers. However, colorimeters are less expensive than spectrophotometers.

To get a precise measurement of color, it is advisable to use a spectrophotometer. A spectrophotometer measures the reflectance for each wavelength, and allows to calculate tristimulus values. The advantage over tristimulus colorimetry is that adequate information is obtained to calculate color values for any illuminant and that metamerism is automatically detected. Metamerism is a psychophysical phenomenon commonly defined incompletely as "two samples which match when illuminated by a particular light source and then do not match when illuminated by a different light source." In actuality, there are several types of metamerism, of which the sample and illuminant metamerism are most common. In sample metamerism, two color samples appear to match under a particular light source, and then do not match under a different light source. Illuminant metamerism appears when different light sources illuminate same sample and differences are revealed. The observer metamerism refers to where each individual perceives color slightly differently. The geometric metamerism arises when identical colors appear different when viewed at different angles, distances, light positions, etc.

In a spectrophotometer, the light is usually split into a spectrum by a prism or a diffraction grating before each wavelength band is selected for measurement. Instruments have also been developed in which narrow bands are selected by interference filters. The spectral resolution of the instrument depends on the narrowness of the bands utilized for each successive measurement. In theory, a spectrophotometer could be set up to compare reflected light directly with incident light, but it is more usual to calibrate against an opal glass standard that has been calibrated by an internationally recognized laboratory. Checks must also be made on the optical zero, for example, by measurements with a black light trap, because dust or other problems can give rise to stray light in an instrument (which would give false readings). Spectrophotometers contain monochromators and photodiodes that measure the reflectance curve of color every 10 nm or less. The analysis generates typically 30 or more data points, with which a precise color composition can be calculated.

A large number of suppliers provided colorimeters including such large array of equipment from Hunter Lab's Labscan XE with special adapter for small quantity of powders offers an excellent choice in preformulation work. The instrument has a 3-mm port and requires 0. 4-cm^3 powder to perform the testing. (http://www.hunterlab.com/)

LIX. ELECTROSTATICITY

When subjected to attrition, powders can acquire an electrostatic charge, the intensity of which is often proportional to physical force applied as static electrification of two dissimilar materials occurs by the making and breaking of surface contacts (tribo-electrification or friction electrification). Electrostatic charges are often used to induce adhesive character to bind drugs to carrier systems, for example, glass beads coated with HPMC containing drugs. The net charge on a powder may be either electropositive or electronegative depending on the direction of electron transfer. The mass charge density can vary from 10−5 to 100 μC/kg depending on the

stress, ranging from gentle sieving to micronization process. This can be determined using electric detectors to determine polarity as well as the electrostatic field. The electrostaticity results in significant changes in the powder flow properties.

Studies on tribo-electrification and potential charge buildup on equipment and particle surfaces and subsequent adhesion due to static charge often overlook the fact that all materials (whether they have a net surface charge or not) exhibit surface energy forces, that are very short range, but come into play once surfaces are "touching." These van der Waals forces are due to the dispersive and polar surface energies inherent at material boundaries. Dry powders with mass-median particle sizes larger than around 100 to 200 μm, seldom exhibit strong "cohesive" powder behavior, and such powders are usually described as "free flowing." As particle size decreases, however, the amount of surface area per unit mass increases, and surface-energy forces have a greater influence on bulk powder flow characteristics. For contacting particles that are smaller than 2 to 20 μm, such forces can be strong enough to cause small amounts of plastic deformation on particle surfaces near the points of contact—even with no applied external loads. The bulk behavior of such fine powders can be dominated by their "cohesivity." It is well known that powders comprised of finer particles are more cohesive, and, when very cohesive powders are placed in a rotating drum, they do not usually flow easily, nor do they form a smooth top surface. Instead, cohesive powders build up large overhanging "chunks" that can break off and collapse or cascade in random avalanches onto the material further down the slope. Placing the rotating drum in a centrifuge at an elevated G-level can cause a "nonflowable" cohesive powder to flow.

LX. CAKING

Powders cake due agglomeration as a result of factors such as static electricity, hygroscopicity, particle size, impurities of the powder and storage conditions, stress temperature, RH, and storage time, etc. The mechanisms involved in caking are based on the formation of five types of interparticle bonds such as bonding resulting from mechanical tangling, bonding resulting from steric effects, bonds via static electricity, bonds due to free liquid and bonds due to solid bridges. During the process of micronization, the formation of localized amorphous zones can lead to caking as these zones are more reactive to factors described above specially when exposed to moisture; the mechanisms involve moisture sorption due to surface sintering and recrystallization at well below the critical relative humidity. In most instances, increase in relative humidity begin to show some impact at values above 20% resulting in most dramatic effects above 75% to 80% relative humidity for powders that are subject to humidity effects.

LXI. POLYMORPHISM

Because polymorphism can have an effect on so many aspects of drug development, it is important to fix the polymorph (usually the stable form) as early as possible in the development cycle. Whereas, it is not necessary to create additional solid state forms by techniques or conditions unrelated to the synthetic process for the purpose of clinical trials, regulatory submission of a thorough study of the effects of solvent, temperature and possibly pressure on the stability of the solid state forms is advised. A conclusion that polymorphism does not occur with a compound must be substantiated by crystallization experiments from a range of solvents. This should also include solvents that may be involved in the manufacture of the drug product, for example, during granulation.

Whilst it is hoped that the issue of polymorphism is resolved during prenomination and early development, it can remain a concern when the synthesis of the drug is scaled-up into a larger reactor or transferred to another production site. It is not unlikely that a metastable form identified in prenomination may not be reproduced in later batches products because of some unrecorded conditions in the early phases of development. Related substances whether identified or not can significantly alter the predominance of a specific polymorph. To develop a reliable, commercial recrystallization process, the following scheme should be followed in the production of candidate drugs:

1. Selection of solvent system
2. Characterization of the polymorphic forms
3. Optimization of process times, temperature, solvent compositions, etc.
4. Examination of the chemical stability of the drug during processing
5. Manipulation of the polymorphic form, if necessary

Many analytical techniques have been used to quantitate mixtures of polymorphs, for example, XRPD has been used to quantitate the various polymorphs. Assay development requires creation of calibration curves and validation, which can be a difficult task where mixed polymorphs are present and requires study that there is no polymorphic transformation during analysis or change in the hydration of crystals, if that is also a concomitant problem. Whereas at the preformulation stage, the dosage form considerations are still developing, there is need to answer questions like how would a polymorph change should this be subject to manufacturing equipment stress like granulation or drying of granules, wet or dry granulation, and compression. In addition to the polymorphism of active drugs, the excipients like magnesium stearate can be present in various polymorphic forms that can significantly alter the behavior of active drug in the formulation stages. Studies using XRPD, IR, or SEM should be used for excipients as well as the active drug.

LXII. STABILITY STUDIES TO SELECT OPTIMAL DRUG AND EXCIPIENT COMBINATIONS

- Rapid screens of salts, solvates, hydrates, polymorphs and cocrystals.
- Large-scale preformulation and formulation studies.
- Characterization of polymers, food ingredients, and fine particles.
- Process optimization monitoring of surface and bulk chemistry.
- Quality control of incoming raw materials.
- Investigation of batch-to-batch variations in material formulations.
- At-line PAT support of production performance to specifications.

Whereas microcalorimetery remains the workhorse of studies, the use of inverse gas chromatography (IGC) is becoming more popular to determine the changes to drug substance upon micronization. The IGC differs from traditional gas chromatography insofar as the stationary phase is the

powder under investigation. The behavior of pharmaceutical solids, during either processing or use, can be noticeably affected by the surface energetics of the constituent particles. Several techniques exist to measure the surface energy, for example, sessile drop, and dynamic contact angle measurements. IGC is an alternative technique, where the powder surface is characterized by the retention behavior of minute quantities of well-characterized vapors that are injected into a column containing the material of interest. Recently published articles using IGC on pharmaceutical powders have ranged from linking surface energetic data with triboelectric charging, to study the effect of surface moisture on surface energetics. Molecular modeling has also recently been used to explore the links between IGC data and the structural and chemical factors that influence surface properties, thereby achieving predictive knowledge regarding powder behavior during processing. In this type of study, a range of nonpolar and polar adsorbates (probes) are used, for example, alkanes, from hexane to decane, acetone, diethyl ether, or ethyl acetate. The retention volume, that is, the net volume of carrier gas (nitrogen) required to elute the probe, is then measured.

IGC is a gas-phase technique for characterizing surface and bulk properties of solid materials. The principles of IGC are very simple, being the reverse of a conventional gas chromatographic (GC) experiment. A cylindrical column is uniformly packed with the solid material of interest, typically a powder, fiber, or film. A pulse or constant concentration of gas is then injected down the column at a fixed carrier gas flow rate, and the time taken for the pulse or concentration front to elute down the column is measured by a detector. A series of IGC measurements with different gas-phase probe molecules then allows access to a wide range of physicochemical properties of the solid sample.

Appendix I

Dissolution Testing Requirements of Compressed Dosage Forms

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Abacavir sulfate	Tablet	II (paddle)	75	0.1 N HCl	900	5, 10, 15, and 30	03/22/2006
Abacavir sulfate/Lamivudine	Tablet	II (paddle)	75	0.1 N HCl	900	10, 20, 30, and 45	01/03/2007
Acamprosate calcium	Tablet (delayed release)	I (basket)	180	Acid stage: 0.1 N HCl buffer stage: "citrate-sodium hydroxide" buffer pH 6.8 (150 mL of 2N NaOH, 21.014 g of citric acid and ultra-pure water to 1000 mL) (method B)	1000	120 (acid) 30, 60, 90, 120, and 180 (buffer)	12/20/2005
Acarbose	Tablet	II (paddle)	75	Water (deaerated)	900	10, 15, 20, 30, and 45	03/22/2006
Acetaminophen/butalbital	Tablet	II (paddle)	50	Water (deaerated)	900	15, 30, 45, 60, and 90	01/03/2007
Acetaminophen/butalbital/caffeine	Tablet			Refer to USP			01/14/2008
Acetaminophen/caffeine/ cihydrocodeine bitartrate	Tablet	II (paddle)	50	Water	900	10, 15, 30, 45, and 60	07/25/2007
Acetaminophen/oxycodone	Tablet			Refer to USP			01/14/2008
Acetaminophen/pentazocine HCl	Tablet	I (basket)	100	Water (deaerated)	900	10, 20, 30, 45, and 60	01/12/2004
Acetaminophen/tramadol HCl	Tablet	II (paddle)	50	0.1 N HCl	900	5, 10, 15, 20, and 30	03/04/2006
Acyclovir	Tablet			Refer to USP			06/18/2007
Albuterol sulfate	Tablet (extended release)	II (paddle)	50	0.1 N HCl	900	1, 2, 4, and 9 hr	04/09/2007
AlendronatesSodium	Tablet			Refer to USP			01/14/2008
Alfuzosin HCl	Tablet (extended release)	II (paddle)	100	0.01 N HCl	900	1, 2, 12, and 20 hr	06/18/2007
Allopurinol	Tablet			Refer to USP			07/25/2007
Almotriptan malate	Tablet	II (paddle)	50	0.1 N HCl	900	5, 10, 15, and 30	01/20/2006
Alosetron HCl	Tablet	II (paddle)	50 (for 1 mg) and 75 (for 0.5 mg)	Water (deaerated)	500	10, 20, 30, and 45	01/26/2006
Alprazolam	Tablet			Refer to USP			06/18/2007
Alprazolam	Tablet (extended release)	I (basket)	100	1% phosphate buffer, pH 6.0	500	1, 4, 8, and 16 hr	02/08/2007
Amantadine HCl	Tablet	II (paddle)	50	Water (deaerated)	500	10, 20, 30, 45, and 60	01/12/2004
Amiodarone HCl (test 1)	Tablet	II (paddle)	100	1% SLS in water	1000	10, 20, 30, 45, 60, and 90	01/12/2004
Amiodarone HCl (test 2)	Tablet	I (basket)	50	Acetate buffer, pH 4.0, with 1% Tween 80	900	10, 20, 30, 45, 60, and 90	01/12/2004
Amitriptyline HCl	Tablet			Refer to USP			01/14/2008
Amlodipine besylate	Tablet	II (paddle)	75	0.01 N HCl	500	10, 20, 30, 45, and 60	01/14/2004

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Amlodipine besylate/valsartan	Tablet	II (paddle)	50	For amlodipine: 0.1 N HCl, pH 1.0. For valsartan: 0.067 M phosphate buffer, pH 6.8	900 (for both Amlodipine and Valsartan)	10, 15, 30, and 45	02/19/2008
Amoxicillin/clavulanate potassium	Tablet (chewable)			Refer to USP			01/14/2008
Anastrozole	Tablet	II (paddle)	50	Water	900	5, 10, 15, 30, and 45	01/03/2007
Aripiprazole	Tablet	II (paddle)	60	pH 1.2 USP buffer (hydrochloric acid)	900	10, 20, 30, and 45	12/20/2005
Armodafinil	Tablet	II (paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	01/14/2008
Aspirin/caffeine/ orphenadrine citrate	Tablet	I (basket)	75	Water (deaerated)	900	10, 20, 30, 45, and 60	01/15/2004
Aspirin/hydrocodone bitartrate	Tablet	II (paddle)	75	Acetate buffer, pH 4.5	900	10, 20, 30, 45, 60, and 90	01/15/2004
Aspirin/meprobamate	Tablet	I (basket)	100	Water (deaerated)	900	10, 20, 30, 45, 60, and 90	01/15/2004
Aspirin/methocarbamol	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, 45, 60, and 90	01/15/2004
Atenolol	Tablet			Refer to USP			07/25/2007
Atorvastatin calcium	Tablet	II (paddle)	75	0.05 M phosphate buffer, pH 6.8	900	5, 10, 15, and 30	01/15/2004
Atovaquone	Tablet	II (paddle)	50	40% isopropanol buffered to pH 8.0 with potassium dihydrogen phosphate	900	10, 20, 30, 45, 60, and 90	06/18/2007
Atovaquone/proguanil HCl	Tablet	II (paddle) with PEAK vessels	50	40% isopropranol buffered to pH 8.0 with potassium dihydrogen phosphate	900	15, 30, 45, and 60	08/17/2006
Azithromycin	Tablet	II (paddle)	75	0.1 M phosphate buffer, pH 6.0	900	10, 20, 30, and 45	01/14/2008
Benazepril HCl	Tablet	II (paddle)	50	Water (deaerated)	500	10, 20, 30, and 45	01/16/2004
Benazepril HCl/hydrochlorothiazide	Tablet	I (basket)	100	0.1 N HCl	500	10, 20, 30, and 45	01/16/2004
Bendroflumethiazide/nadolol	Tablet			Refer to USP			07/25/2007
Benzphetamine HCl	Tablet	II (paddle)	50	Water	900	10, 20, 30, and 45	06/20/2007
Bepridil HCl	Tablet	I (basket)	100	0.1 N HCl	900	10, 20, 30, 45, and 60	01/16/2004
Bicalutamide	Tablet	II (paddle)	50	1% SLS in water	1000	10, 20, 30, 45, and 60	12/15/2005
Bisoprolol fumarate	Tablet			Refer to USP			06/18/2007
Bisoprolol fumarate/ hydrochlorothiazide	Tablet	II (paddle)	75	0.1 N HCl	900	5, 10, 20, 30, and 45	01/20/2004
Bromocriptine mesylate	Tablet			Refer to USP			07/25/2007

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Buprenorphine HCl	Tablet (sublingual)	I (basket)	100	Water	500	2, 5, 8, 10, 15, and until at least 80% of the labeled content is dissolved	04/09/2007
Bupropion HCl	Tablet (extended release)			Refer to USP			07/25/2007
Cabergoline	Tablet	II (paddle)	50	0.1 N HCl	500	5, 10, 15, and 30	01/20/2004
Calcium acetate	Tablet			Refer to USP			01/14/2008
Candesartan cilexetil	Tablet	II (paddle)	50	0.35% polysorbate 20 in 0.05 M phosphate buffer, pH 6.5	900	10, 20, 30, 45, and 60	06/20/2007
Candesartan cilexetil (16 mg)/ hydrochlorothiazide (12.5)	Tablet	II (paddle)	50	0.35% polysorbate 20 in phosphate buffer pH 6.5	900	10, 20, 30, 45, and 60	03/04/2006
Candesartan cilexetil (32 mg)	Tablet	II (paddle)	50	0.70% Polysorbate 20 in 0.05 M phosphate buffer, pH 6.5	900	10, 20, 30, 45, and 60	06/20/2007
Candesartan cilexetil (32 mg)/ hydrochlorothiazide (12.5)	Tablet	II (paddle)	50	0.70% polysorbate 20 in phosphate buffer pH 6.5	900	15, 20, 30, 45, and 60	03/04/2006
Capecitabine	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	01/23/2004
Carbamazepine	Tablet (extended release)			Refer to USP			01/14/2008
Carbidopa/entacapone/levodopa	Tablet	I (basket)	Carbidopa and Levodopa: 50; Entacapone: 125	For both Carbidopa and Levodopa: 0.1 N HCl. For Entacapone: phosphate buffer pH 5.5	Carbidopa and Levodopa: 750 mL. Entacapone: 900 mL	10, 20, 30, 45, and 60	01/03/2007
Carbidopa/levodopa	Tablet			Refer to USP			01/14/2008
Carbidopa/levodopa	Tablet (orally disintegrating)	II (paddle)	50	0.1 N HCl	750	5, 10, 15, 30, and 45	07/25/2007
Carvedilol	Tablet	II (paddle)	50	SGF without enzyme	900	10, 20, 30, and 45	01/21/2004
Cefditoren pivoxil	Tablet	II (paddle)	75	Simulated gastric fluid without enzyme	900	5, 10, 15, 20, and 30	02/09/2006
Cefpodoxime proxetil	Tablet			Refer to USP			07/25/2007
Cefprozil	Tablet			Refer to USP			07/25/2007
Cefuroxime axetil	Tablet			Refer to USP			07/25/2007
Cetirizine HCL	Tablet (regular and chewable)	II (paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	03/04/2006
Cetirizine HCl/pseudoephedrine HCl	Tablet (extended release)	I (basket)	100	0.1 N HCl	500	0.17, 0.25, 0.5, 1, 2, 6, and 8 hr	06/18/2007

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Chlorambucil	Tablet	II (paddle)	75	0.1N HCl	900	10, 20, 30, and 45	08/17/2006
Chlorpheniramine maleate	Tablet (extended release)	III (reciprocating cylinder)	27 dpm	Row 1: test fluid 1 (0.1N HCl) for first hour. Row 2: test fluid 2 (phosphate buffer, pH 7.5) for fifth hour	Row 1: 250 mL. Row 2: 250 mL	1 hr for test fluid 1, and 4 hr for test fluid 2	07/25/2007
Chlorpheniramine maleate/Ibuprofen/pseudoephedrine HCl	Tablet	II (paddle)	50	0.05 M phosphate buffer, pH 6.5	900	10, 20, 30, and 45	02/20/2004
Chlorzoxazone	Tablet			Refer to USP			01/14/2008
Cilostazol	Tablet	II (paddle)	75	0.3% SLS in water	900	15, 30, 45, 60, and 90	08/17/2006
Cinacalcet HCl	Tablet	II (paddle)	75	0.05 N HCl	900	10, 20, 30, and 45	01/26/2006
Ciprofloxacin HCl	Tablet (extended release)	I (basket)	100	0.1 N HCl	900	1, 2, 4, and 7 hr or until at least 80% released	01/14/2008
Ciprofloxacin/ciprofloxacin HCl (AB)	Tablet (extended release)	II (paddle)	50	0.1 N HCl	900	15, 30, 60, and 120	01/14/2008
Citalopram HBr	Tablet			Refer to USP			01/14/2008
Clarithromycin	Tablet			Refer to USP			07/25/2007
Clonazepam	Tablet (orally disintegrating)	II (paddle)	50	Water	900	5, 10, 15, 30, and 45	07/25/2007
Clonidine HCl	Tablet			Refer to USP			06/18/2007
Clopidogrel bisulfate	Tablet			Refer to USP			07/25/2007
Clotrimazole	Tablet (vaginal)	II (paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	01/24/2004
Cyclobenzaprine HCl	Tablet			Refer to USP			07/25/2007
Cyclophosphamide	Tablet	I (basket)	100	Water (deaerated)	900	10, 20, 30, 45, and 60	01/24/2004
Darifenacin hydrobromide	Tablet (extended release)	I (basket)	100	0.01M HCl comparative dissolution data should also be provided in 900 ml pH 4.5 buffer, pH 6.8 buffer, and water using apparatus I (basket) at 100 RPM.	900	1, 4, 8, 12, 16, 20, and 24 hr	01/20/2006
Darunavir ethanolate	Tablet	II (paddle)	75	2% Tween-20 in 0.05 M sodium phosphate buffer, pH 3.0	900	10, 20, 30, and 45	09/13/2007
Deferasirox	Tablet (for suspension oral)	II (paddle)	50	Phosphate buffer pH 6.8 with 0.5% Tween 20	900	10, 20, 30, and 45	06/21/2006
Delavirdine Mesylate	Tablet	II (paddle)	50	0.05 M phosphate buffer, pH 6.0 containing 0.6% w/v SDS	900	10, 20, 30, 45, and 60	12/03/2007
Demeclocycline HCl	Tablet			Refer to USP			07/25/2007

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Desloratadine	Tablet	II (paddle)	50	0.1 N HCl	500	15, 20, 30, and 45	03/04/2006
Desloratadine	Tablet (orally disintegrating)	II (paddle)	50	0.1 N HCl	900	3, 6, 10, and 15	06/18/2007
Desmopressin acetate	Tablet	II (paddle)	75	Water (deaerated)	500	10, 20, 30, and 45	12/15/2005
Desogestrel/ethinyl estradiol	Tablet	II (paddle)	50	0.05% SLS in water	500	10, 20, 30, and 45	01/28/2004
Dexmethylphenidate HCl	Tablet	I (basket)	100	Water	900	10, 15, 30, and 45	06/18/2007
Diazepam	Tablet			Refer to USP			07/25/2007
Diclofenac potassium	Tablet	II (paddle)	50	SIF without enzyme	900	10, 20, 30, 45, 60, and 90	01/27/2004
Diclofenac sodium/misoprostol enteric coated (arthrotec)	Tablet (delayed release)	II (paddle) (diclo) II (paddle) (miso)	100 (diclo) 50 (miso)	Diclofenac: acid stage: 0.1 N HCl buffer stage: 750 mL 0.1N HCL + 250 mL 0.2M phos.buffer, pH 6.8 (method A) Misoprostol: water (deaerated)	Diclo: Acid: 750 Buffer:1000 Miso: 500	Diclo.: 120 (acid) 15, 30, 45, and 60 (buffer). Miso: 10, 20, and 30	12/15/2005
Didanosine	Tablet (chewable)	II (paddle)	75	Water (deaerated)	900	10, 20, 30, and 45	01/26/2004
Digoxin	Tablet			Refer to USP			06/18/2007
Diltiazem HCl	Tablet (extended release)	II (paddle)	100	Phosphate buffer, pH 5.8	900	2, 8, 14, and 24 hr	02/19/2008
Diphenhydramine citrate/ibuprofen	Tablet	II (paddle)	50	50 mM phosphate buffer, pH 6.5	900	10, 20, 30, and 45	01/14/2008
Dipyridamole	Tablet			Refer to USP			06/18/2007
Disulfiram	Tablet	II (paddle)	100	2% SDS	900	15, 30, 45, 60, 75, 90, 105, and 120	06/18/2007
Divalproex sodium	Tablet (delayed release)			Refer to USP			07/25/2007
Divalproex sodium	Tablet (extended release)	II (paddle)	100	Acid phase: 0.1 N HCl for 45 min; drug release: 0.05 M phosphate buffer with 75 mM SDS after 45 min	Acid phase:500 mL; Drug release: 900 mL	3, 9, 12, and 21 hr	06/18/2007
Donepezil HCl	Tablet	II (paddle)	50	0.1 N HCl	900	10, 20, 30, and 40	01/27/2004
Donepezil HCl	Tablet (orally disintegrating (ODT))	II (paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	03/04/2006
Doxazosin mesylate	Tablet	II (paddle)	50	0.01 N HCl	900	10, 20, 30, 45, and 60	01/27/2004
Doxazosin mesylate	Tablet (extended release)	II (paddle)	75	SGF without enzyme	900	4, 8, and 16 hr	01/03/2007

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Doxycycline	Tablet	II (paddle)	75	0.01 N HCl	900	15, 30, 45, 60, and 90	01/14/2008
Drospirenone/estradiol	Tablet	II (paddle)	50	Water	900	10, 20, 30, and 45	01/03/2007
Efavirenz	Tablet	II (paddle)	50	2% SLS in water	1000	10, 15, 30, 45, and 60	06/18/2007
Efavirenz 600 mg; emtricitabine 200 mg; tenofovir disoproxil fumarate 300 mg	Tablet	II (paddle)	100	2% SLS in water	1000	10, 20, 30, and 45	01/03/2007
Emtricitabine/tenofovir disoproxil fumarate	Tablet	II (paddle)	50	0.01 N HCl	900	5, 10, 15, 30, and 45	01/03/2007
Entacapone	Tablet	II (paddle)	50	Phosphate buffer, pH 5.5	900	10, 20, 30, and 45	01/29/2004
Entecavir	Tablet	II (paddle)	50	Phosphate buffer pH 6.8 (50 mM)	1000	10, 20, 30, and 45	06/21/2006
Eplerenone	Tablet	II (paddle)	50	0.1 N HCl	1000	10, 20, 30, and 45	12/19/2005
Eprosartan mesylate/hydrochlorothiazide	Tablet	II (paddle)	75	0.2 M phosphate buffer, pH 7.5	1000	10, 20, 30, and 45	02/19/2008
Erlotinib HCl	Tablet	II (paddle)	75	0.1 N HCl containing 1% SDS	1000	15, 30, 45, and 60	03/22/2006
Escitalopram oxalate	Tablet	II (paddle)	75	0.1 N HCl	900	10, 20, 30, and 45	02/20/2004
Estazolam	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	01/27/2004
Esterified estrogens	Tablet	II (paddle)	50	Water	900	15, 30, 45, 60, 90, 120, and 180	02/19/2008
Estradiol	Vaginal ring	Incubator shaker	130	0.9% saline	250	1, 9, 16, 17, 18, 19, and 45 days	01/03/2007
Estradiol/norgestimate (1/0.09 mg)	Tablet	II (paddle)	50	0.3% SLS in water	500	10, 20, 30, and 45	07/09/2004
Eszopiclone	Tablet	II (paddle)	50	0.1 N HCl	500	10, 20, 30, and 45	09/13/2007
Ethambutol HCl	Tablet			Refer to USP			01/14/2008
Ethinyl estradiol/levonorgestrel	Tablet			Refer to USP			02/19/2008
Ethinyl estradiol/levonorgestrel (AB)	Tablet			Refer to USP			02/19/2008
Ethinyl estradiol/norethindrone	Tablet (chewable)	II (paddle)	75	0.09% sodium lauryl sulfate in 0.1 N HCl	500	10, 20, 30, and 45	01/14/2008
Ethinyl estradiol/norgestimate	Tablet	II (paddle)	75	0.05% Tween 20 in water	600	5, 10, 20, and 30	01/14/2008
Ethinyl estradiol/norgestimate (AB)	Tablet	II (paddle)	75	0.05% Tween 20 in water	600	10, 20, 30, and 45	01/14/2008
Ethinyl estradiol/norgestrel	Tablet	II (paddle)	75	Water with 5 ppm of Tween 80	500	10, 20, 30, 45, 60, and 90	01/28/2004
Etidronate disodium	Tablet			Refer to USP			06/18/2007
Etodolac	Tablet			Refer to USP			01/14/2008
Exemestane	Tablet	I (basket)	100	0.5%(w/v) SLS solution	900	10, 20, 30, and 45	08/17/2006

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Ezetimibe	Tablet	II (paddle)	50	0.45% SLS in 0.05 M acetate buffer, pH 4.5	500	10, 20, 30, and 45	01/14/2008
Ezetimibe/simvastatin	Tablet	II (paddle)	50	0.01M sodium phosphate, pH 7.0/0.5% SDS	900	5, 10, 20, and 30	01/03/2007
Famciclovir	Tablet	II (paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	04/09/2007
Famotidine	Tablet			Refer to USP			06/18/2007
Famotidine	Tablet (chewable)	II (paddle)	50	0.1 M phosphate buffer, pH 4.5	900	10, 20, 30, 45, and 60	01/29/2004
Famotidine	Tablet (orally disintegrating)	II (paddle)	50	Water (deaerated)	900	2, 4, 6, 8, and 10	01/29/2004
Famotidine/antacid combination berry and mint flavors	Tablet (chewable)	III (20 mesh top screen, 40 mesh bottom screen)	30 DPM	0.1 M acetate buffer, pH 4.5	900	10, 20, 39, and 45	03/04/2006
Felbamate	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, 45, 60, and 90	01/28/2004
Felodipine	Tablet (extended release)			Refer to USP			01/14/2008
Fenofibrate	Tablet	II (paddle)	50	0.05 M SLS in water	1000	10, 20, 30, and 45	01/29/2004
Fexofenadine HCl	Tablet	II (paddle)	50	0.001 N HCl	900	5, 10, 20, 30, and 45	02/19/2004
Finasteride	Tablet			Refer to USP			07/25/2007
Flavoxate HCl	Tablet	I (basket)	100	0.1 N HCl	900	5, 10, 20, and 30	01/29/2004
Fluconazole	Tablet	II (paddle)	50	Water (deaerated)	900 (for 150, 200, 300, and 400 mg tabs) 500 (for 50 and 100 mg tabs)	10, 20, 30, 45, and 60	03/04/2006
Fluoxetine HCl	Tablet	I (basket)	100	0.1 N HCl	1000	5, 10, 15, and 30	01/03/2007
Fluvastatin sodium	Tablet (extended release)	I (basket)	50	Water	900	0.5, 2, 4, and 8 hr	06/18/2007
Fluvoxamine maleate	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	01/03/2007
Fosamprenavir calcium	Tablet	II (paddle)	75	250 mM sodium acetate/acetic acid buffer pH 3.5	900	10, 20, 30, and 45	12/16/2005
Fosinopril sodium	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	01/30/2004
Fosinopril sodium/hydrochlorothiazide	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, 45, and 60	01/30/2004

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Gabapentin	Tablet	II (paddle)	50	0.06 N HCl	900	10, 20, 30, and 45	01/30/2004
Galantamine HBr	Tablet	II (paddle)	50	Water (deaerated)	500	5, 10, 20, and 30	03/04/2006
Gemfibrozil	Tablet			Refer to USP			07/25/2007
Gemifloxacin mesylate	Tablet	II (paddle)	50	0.01 N HCl	900	10, 20, 30, and 45	01/03/2007
Glimepiride	Tablet	II (paddle)	75	Phosphate buffer, pH 7.8	900	5, 10, 15, and 30	07/23/2004
Glimepiride/rosiglitazone maleate	Tablet	II (paddle)	75	0.01 M HCl with 0.5% sodium dodecyl sulfate	900	5, 10, 15, 30, 45, and 60	01/03/2007
Glipizide/metformin HCL	Tablet	II (paddle)	50	Phosphate buffer, pH 6.8	1000	10, 20,30, 45, and 60	03/04/2006
Glyburide (micronized)	Tablet	II (paddle)	50	0.05 M phosphate buffer, pH 7.5	900	10, 20, 30, 45, and 60	02/02/2004
Glyburide (nonmicronized)	Tablet	II (paddle)	75	0.05 M borate buffer, pH 9.5	500	10, 20, 30, 45, and 60	02/02/2004
Glyburide/metformin HCl	Tablet			Refer to USP			01/14/2008
Glycopyrrolate	Tablet			Refer to USP			07/25/2007
Granisetron HCl	Tablet	II (paddle)	50	Phosphate buffer, pH 6.5	500	10, 20, 30, 45, and 60	06/05/2006
Guaifenesin	Tablet (extended release)	I (basket)	75	0.1 N HCl	900	1, 2, 4, 6, and 12 hr	01/03/2007
Homatropine methylbromide/hydrocodone bitartrate	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	02/03/2004
Hydrochlorothiazide	Tablet			Refer to USP			07/25/2007
Hydrochlorothiazide/lisinopril	Tablet	II (paddle)	50	0.1 N HCl	900	10, 20, 30, 45, and 60	02/03/2004
Hydrochlorothiazide/losartan potassium	Tablet	I (basket)	100	Water (deaerated)	900	10, 20, 30, 45, and 60	02/03/2004
Hydrochlorothiazide/Moexipril HCl	Tablet	II (paddle)	50	0.1 N HCl	900	5, 10, 15, and 30	02/10/2004
Hydrochlorothiazide/olmesartan medoxomil	Tablet	II (paddle)	50	0.05 M phosphate buffer, pH 6.8	900	5, 10, 15, 20, 30, 45, and 60	07/09/2007
Hydrochlorothiazide/quinapril HCl	Tablet	I (basket)	100	Water (deaerated)	900	5, 10, 20, and 30	02/03/2004
Hydrochlorothiazide/valsartan	Tablet	II (paddle)	50	Phosphate buffer pH 6.8	1000	10, 20, 30, and 45	02/03/2004
Hydrocodone bitartrate/ibuprofen	Tablet	II (paddle)	50	Phosphate buffer, pH 7.2	900	5, 10, 15, and 30	02/04/2004
Hydromorphone HCl	Tablet			Refer to USP			07/25/2007
Hydroxyzine HCl	Tablet			Refer to USP			07/25/2007
Ibandronate sodium	Tablet	II (paddle)	50	Water	500	5, 10, 15, 30, and 45	01/03/2007
Ibuprofen	Tablet			Refer to USP			07/25/2007

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Ibuprofen (chewable Tab)	Tablet (chewable)	II (paddle)	50	0.05 M phosphate buffer, pH 7.2	900	10, 20, 30, and 45	02/04/2004
Ibuprofen/oxycodone HCl	Tablet	I (basket)	100	Phosphate buffer, pH 7.2	500	10, 20, 30, and 45	04/09/2007
Imipramine HCl	Tablet			Refer to USP			01/14/2008
Irbesartan	Tablet	II (paddle)	50	0.1 N HCl	1000	10, 20, 30, and 45	12/14/2004
Irbesartan/HCTZ	Tablet	II (paddle)	50	0.1 N HCl	1000	10, 20, 30, 45, and 60	01/03/2007
Isocarboxazid	Tablet	II (paddle)	50	0.1 N HCl	900	10, 20, 30, 45, and 60	02/04/2004
Isosorbide mononitrate	Tablet	II (paddle)	50	Water (deaerated)	900	5, 10, 15, and 30	02/04/2004
Isosorbide mononitrate	Tablet (extended release)	II (paddle)	50	0.1N HCl containing 0.2% NaCl	500	1, 2, 6, 10, and 12	01/03/2007
Isradipine (10 mg)	Tablet (extended release)	II (paddle)	50	0.2% lauryl dimethylamine oxide (LDAO) in water	1000	2, 4, 8, 12, 16, and 24 hr	02/25/2004
Isradipine (5 mg)	Tablet (extended release)	II (paddle)	50	0.2% lauryl dimethylamine oxide (LDAO) in water	500	2, 4, 8, 12, 16, and 24 hr	02/25/2004
Ivermectin	Tablet	II (paddle)	50	0.5% SDS in 0.01 M monobasic sodium phosphate, pH 7.0	900	10, 20, 30, 45, and 60	02/04/2004
Ketoconazole	Tablet	I (basket)	100	Simulated gastric fluid w/o pepsin	800	15, 30, 45, 60, and 90	01/03/2007
Ketoprofen	Tablet	II (paddle)	50	SIF buffer without enzyme, pH 7.4	900	10, 20, 30, 45, and 60	02/05/2004
Lamivudine (for 100 mg and 150 mg)	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	03/22/2006
Lamivudine (for 300 mg only)	Tablet	II (paddle)	75	0.1 N HCl	900	5, 10, 15, and 30	03/22/2006
Lamivudine 150 mg/zidovudine 300 mg Tablets and abacavir sulfate 300 mg Tablets-co-packaged	Tablet	II (paddle)	75	0.1 N HCl	900	5, 10, 15, 20, 30, and 40	01/03/2007
Lamivudine/stavudine/nevirapine	Tablet	II (paddle)	75	0.1 N HCl	900	10, 20, 30, 45, and 60	01/03/2007
Lamivudine/zidovudine	Tablet	II (paddle)	75	0.1 N HCl	900	10, 20, 30, and 45	02/20/2004
Lamivudine/zidovudine + efavirenz	Tablet (copackage)	II (paddle)	Lamivudine and zidovudine: 75 efavirenz: 50	Lamivudine and zidovudine: 0.1 N HCl efavirenz: 2% SLS in water	Lamivudine and zidovudine: 1000 efavirenz: 900	10, 20, 30, and 45	01/03/2007
Lamivudine/zidovudine + nevirapine	Tablet (copackage)	II (paddle)	50	Lamivudine and zidovudine: water nevirapine: 0.06 M HCl (pH 1.2)	900	10, 15, 30, 45, and 60	01/03/2007
Lamivudine/zidovudine/nevirapine	Tablet	II (paddle)	50	0.01 N HCl	900	10, 15, 30, 45, and 60	01/03/2007
Lamotrigine	Tablet (chewable dispersible)	II (paddle)	50	0.1 N HCl	900	5, 10, 15, 20, and 30	01/14/2008

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Lamotrigine	Tablet (regular)	II (paddle)	50	0.1 N HCl	900	5, 10, 15, 20, and 30	03/04/2006
Lanthanum carbonate	Tablet (chewable)	Reciprocating cylinder (apparatus 3 modified)	10 dpm (dip rate per minute)	0.25 N HCl	900 (modified from the standard apparatus 3 vessel to achieve sink condition)	10, 20, 30, and 45	01/03/2007
Leflunomide	Tablet	II (paddle)	100	Water (deaerated)	1000	10, 20, 30, and 45	02/05/2004
Leflunomide (100 mg)	Tablet	II (paddle)	100	Water (deaerated) + 0.6% polyoxyethylene lauryl ether	1000	10, 20, 30, and 45	05/31/2007
Levetiracetam	Tablet	II (paddle)	50	Water (deaerated)	900	5, 10, 15, and 30	02/05/2004
Levofloxacin	Tablet	I (basket)	100	0.1 N HCl	900	10, 20, 30, and 45	06/18/2007
Levonorgestrel	Tablet	II (paddle)	75	0.1 N HCl with 0.1% SLS	1000	10, 20, 30, 45, 60, and 90	02/05/2004
Levothyroxine sodium	Tablet			Refer to USP			07/25/2007
Lidocaine	Topical Patch	Paddle over disk (apparatus 5)	50	Acetic acid/sodium acetate buffer, pH 4.0 at 32°C	500	10, 20, 30, 60, 120, and 180	01/03/2007
Linezolid	Tablet	II (paddle)	50	0.05 M phosphate buffer, pH 6.8	900	5, 10, 20, 30, and 45	01/14/2008
Liothyronine sodium	Tablet			Refer to USP			06/18/2007
Lisinopril	Tablet			Refer to USP			01/14/2008
Lithium carbonate	Tablet (extended release)			Refer to USP			01/14/2008
Lomefloxacin HCl	Tablet	II (paddle)	50	0.01 N HCl	900	10, 20, 30, and 45	02/05/2004
Lopinavir/ritonavir	Tablet (combination)	II (paddle)	75	0.06 M polyoxyethylene 10 lauryl ether	900	15, 30, 60, 90, and 120	09/13/2007
Loratadine (orally disintegrating tablet)	Tablet (orally disintegrating)	I (basket)	50	SGF without enzyme	900	2, 4, 6, and 10	02/05/2004
Lorazepam	Tablet			Refer to USP			01/14/2008
Losartan potassium	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	02/06/2004
Lovastatin/niacin	Tablet (extended release)	I (basket)	100	For Niacin: water; for Lovastatin: 0.05 M phosphate buffer, pH 7.0 with 0.5% sodium dodecyl sulfate	900	For Niacin: 0.5, 1, 2, 3, 6, 9, 12, 20, and 24 hr; for Lovastatin: 15, 30, 45, and 60 min	01/14/2008

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Magnesium hydroxide/ omeprazole/sodium bicarbonate	Tablet (chewable)	II (paddle)	150	0.029 M sodium phosphate buffer w/ 0.5% SDS, pH 7.4	900	15, 30, 45, and 60	02/19/2008
Mefloquine HCl	Tablet	I (basket)	100	SGF without enzyme	900	10, 20, 30, 45, and 60	02/06/2004
Meloxicam	Tablet	II (paddle)	75	Phosphate buffer, pH 7.5	900	10, 20, 30, 45, and 60	02/20/2004
Memantine HCL	Tablet	I (basket)	100	0.1 N HCl with NaCl (12 g NaCl in 6 L water adjust pH to 1.2 with HCl)	900	10, 20, 30, and 45	12/16/2005
Mercaptopurine	Tablet	II (paddle)	50	0.1 N HCl	900	20, 30, 45, 60, 90, and 120	02/06/2004
Mesalamine	Tablet (delayed release)			Refer to USP			12/03/2007
Mesna	Tablet	II (paddle)	50	0.06 N HCl	500	5, 10, 15, 20, and 30	02/09/2004
Metaxalone	Tablet	II (paddle)	100	0.5% SLS in water	900	30, 60, 90, and 120	02/06/2004
Metformin HCl	Tablet (extended release)	I (basket)	100	Phosphate buffer, pH 6.8	1000	1, 3, 6, and 10 hr	04/09/2007
Metformin HCl/pioglitazone HCl	Tablet	II (paddle)	50	pH 2.5 McIlvaine buffer (0.1 M citric acid adjusted to pH 2.5 with 0.2 M Na_2HPO_4)	900	10, 20, 30, and 45	01/03/2007
Methimazole	Tablet			Refer to USP			01/14/2008
Metoclopramide	Tablet			Refer to USP			07/25/2007
Metolazone	Tablet	II (paddle)	75	2% SLS in 0.05 M sodium phosphate buffer, pH 7.5	900	30, 60, 90, 120, and 150	02/10/2004
Metoprolol succinate	Tablet (extended release)			Refer to USP			07/25/2007
Metoprolol tartrate	Tablet			Refer to USP			07/25/2007
Midodrine HCl	Tablet	II (paddle)	50	0.1 N HCl	900	5, 10, 15, and 30	02/06/2004
Mifepristone	Tablet	II (paddle)	75	0.01 N HCl	900	5, 10, 15, 20, and 30	01/14/2008
Minocycline HCl	Tablet			Refer to USP			07/25/2007
Minocycline HCl	Tablets ER	I (basket)	100	0.1 N HCl	900	1, 2, 4, and 6 hr and until 80% of drug released	01/14/2008
Mirtazapine	Tablet	II (paddle)	50	0.1 N HCl	900	5, 10, 15, and 30	02/10/2004
Mirtazapine	Tablet (orally disintegrating (ODT))	II (paddle)	50	0.1 N HCl	900	5, 10, 15, 20, and 30	03/04/2006
Misoprostol	Tablet	II (paddle)	50	Water (deaerated)	500	5, 10, 20, and 30	02/10/2004

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Modafinil	Tablet	II (paddle)	50	0.1 N HCl	900	10, 20, 30, 45, and 60	02/10/2004
Moexipril HCl	Tablet	II (paddle)	50	Water (deaerated)	900	5, 10, 15, and 30	02/10/2004
Molindone HCl	Tablet			Refer to USP			07/25/2007
Montelukast sodium	Tablet	II (paddle)	50	0.5% SDS in water	900	5, 10, 20, and 30	04/09/2007
Montelukast sodium	Tablet (chewable)	II (paddle)	50	0.5% SDS in water	900	5, 10, 20, and 30	03/04/2006
Moxifloxacin	Tablet	II (paddle)	50	0.1 N HCl	900	15, 30, 45, and 60	06/18/2007
Mycophenolate Mofetil	Tablet	II (paddle)	50	0.1 N HCl	900	5, 10, 15, and 30	02/10/2004
Nabumetone	Tablet			Refer to USP			07/25/2007
Naproxen	Tablet			Refer to USP			07/25/2007
Naratriptan HCl	Tablet			Refer to USP			07/25/2007
Nateglinide	Tablet	II (paddle)	50	0.01 N HCl with 0.5% (w/v) SLS	1000	10, 20, 30, and 45	01/03/2007
Nefazodone HCl	Tablet	II (paddle)	50	0.1 N HCl	900	10, 20, 30, 45, and 60	01/03/2007
Nelfinavir mesylate	Tablet	II (paddle)	50	0.1 N HCl	900	5, 10, 15, 20, 30, 45, 60, and 90	01/03/2007
Neomycin Sulfate	Tablet	II (paddle)	50	0.05 M phosphate buffer, pH 6.8	900	15, 30, 45, and 60	01/14/2008
Nevirapine	Tablet			Refer to USP			09/13/2007
Nifedipine	Tablet (extended release)			Refer to USP			07/25/2007
Nitazoxanide	Tablet	II (paddle)	75	Phosphate buffer at pH 7.5 with 6% hexadecyltrimethyl ammonium bromide, bath temperature at 25°C	900	10, 20, 30, 45, and 60	01/03/2007
Norethindrone (AB1)	Tablet	II (paddle)	75	0.1 N HCl, 0.02% SLS	900	15, 30, 45, 60, and 75	01/03/2007
Norethindrone (AB2)	Tablet	II (paddle)	75	0.09% SLS in 0.1 N HCl (same as norethindrone/EE USP method)	500	15, 30, 45, and 60	01/03/2007
Nystatin	Tablet	II (paddle)	75	Water with 0.1% SLS	900	15, 30, 45, 60, and 90	01/03/2007
Ofloxacin	Tablet	I (basket)	100	0.1 N HCl	900	10, 20, 30, and 45	02/12/2004
Olanzapine	Tablet	II (paddle)	50	0.1 N HCl	900	5, 10, 20, and 30	02/12/2004
Olanzapine (orally disintegrating)	Tablet (orally disintegrating)	II (paddle)	50	0.1 N HCl	900	5, 10, 15, and 30	02/12/2004
Olmesartan	Tablet	II (paddle)	50	0.05 M phosphate buffer, pH 6.8	900	10, 20, 30, and 45	07/09/2007

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Omeprazole magnesium	Tablet OTC (delayed release)	II (paddle)	100	Tablets are preexposed to 300 mL of 0.1M HCL for 2 hr and then 700 mL of 0.086 M Na_2HPO_4 is added to the medium containing the capsule to give 1000 mL with pH 6.8	300 mL for the acid stage; 1000 mL for the buffer stage	Sampling started at the buffer stage 10, 20, 30, 45, and 60	01/03/2007
Ondansetron	Tablet (orally disintegrating)			Refer to USP			06/18/2007
Ondansetron HCl	Tablet	II (paddle)	50	Water (deaerated)	500	5, 10, 15, and 30	02/12/2004
Orphenadrine citrate	Tablet (extended release)	II (paddle)	50	0–1 hr: 0.1N HCl. After 1 hr: pH 7.5 buffer	800 mL for HCl, and 900 mL for buffer	0.5, 1, 2, 4, 10, and 12 hr	07/25/2007
Oxaprozin	Tablet	II (paddle)	75	0.05 M phosphate buffer, pH 7.4	1000	10, 20, 30, 45, and 60	02/12/2004
Oxcarbazepine (150 mg)	Tablet	II (paddle)	6	0.3% SDS in water	900	10, 20, 30, 45, 60, and 90	02/12/2004
Oxcarbazepine (300 mg)	Tablet	II (paddle)	60	0.6% SDS in water	900	10, 20, 30, 45, 60, and 90	02/12/2004
Oxcarbazepine (600 mg)	Tablet	II (paddle)	60	1% SDS in water	900	10, 20, 30, 45, 60, and 90	02/12/2004
Oxybutynin	Transdermal	Paddle over disk (apparatus 5)	50	Phosphate buffer, pH 4.5 at 32°C	900	1, 4, and 24 hr	01/03/2007
Oxybutynin chloride	Tablet (extended release)			Refer to USP			
Oxycodone HCl	Tablet			Refer to USP			01/14/2008
Oxycodone hydrochloride	Tablet (extended release)	I (basket)	100	SGF w/o enzymes	900	1, 4, 8, 12, and 15 hr	04/09/2007
Oxymorphone HCl	Tablet (extended release)	II (paddle)	50	pH 4.5 phosphate buffer	900	1, 4, 6, 10, and 14 hr	12/03/2007
Oxymorphone HCl	Tablets	II (paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	01/14/2008
Paliperidone	Tablet (extended release)	Reciprocating disk (apparatus 7)	30 cycles per minute	NaCl 0.2% w/w in 0.0825 N HCl pH 1.0	50	2, 8, 14, 18, and 24 hr	12/03/2007
Pantoprazole sodium	Tablet (delayed release)	II (paddle)	100	Acid stage: 0.1 N HCl for 2 hr Buffer stage: phosphate buffer, pH 6.8	1000	1, 2 hr (acid stage) 10, 20, 30, 45, and 60 (buffer stage)	03/04/2006
Paroxetine HCl	Tablet			Refer to USP			01/14/2008
Pemoline	Tablet	II (paddle)	75	Water (deaerated)	900	10, 20, 30, 45, 60, and 90	02/13/2004

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Pergolide Mesylate	Tablet	II (paddle)	50	Simulated gastric fluid TS with cysteine without enzymes	500	10, 20, 30, and 45	03/04/2006
Perindopril erbumine	Tablet	II (paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	06/20/2007
Phenytoin	Tablet (chewable)			Refer to USP			01/14/2008
Pilocarpine HCl	Tablet	II (paddle)	50	0.1 N HCl	500	10, 20, 30, 45, and 60	01/20/2004
Pimozide	Tablet			Refer to USP			02/19/2008
Pioglitazone HCl	Tablet	II (paddle)	75	HCl-0.3 M KCl buffer, pH 2.0	900	5, 10, 15, and 30	02/13/2004
Potassium chloride	Tablet (extended release)			Refer to USP			07/25/2007
Pramipexole dihydrochloride	Tablet	II (paddle)	50	0.023 M Citrate/0.155 M phosphate buffer, pH 6.8	500	5, 10, 15, 30, and 45	10/09/2007
Pravastatin sodium	Tablet	II (paddle)	50	Water (deaerated)	900	5, 10, 20, and 30	02/13/2004
Primidone	Tablet			Refer to USP			01/14/2008
Promethazine HCl	Tablet			Refer to USP			07/25/2007
Propafenone HCl	Tablet	II (paddle)	75	0.1 N HCl	900	10, 20, 30, and 45	02/13/2004
Protriptyline HCl	Tablet			Refer to USP			01/14/2008
Pseudoephedrine HCl	Tablet (extended release)			Refer to USP			01/14/2008
Quetiapine fumarate	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	02/18/2004
Quinapril HCl	Tablet			Refer to USP			07/25/2007
Rabeprazole sodium	Tablet (delayed release)	II (paddle)	100	700 mL 0.1 N HCl (acid stage), after 2 hr add 300 mL of 0.6 M Tris–HCl buffer, pH 8.0 (buffer stage). Stabilize the samples with the addition of 0.5 N NaOH	Acid: 700 buffer: 1000	10, 20, 30, and 45	04/09/2007
Raloxifene HCl	Tablet	II (paddle)	50	0.1% polysorbate 80 in water	1000	10, 20, 30, and 45	02/18/2004
Ranitidine HCl	Tablet			Refer to USP			07/25/2007
Repaglinide	Tablet			Refer to USP			07/25/2007
Ribavirin	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	02/18/2004
Rifapentine	Tablet	II (paddle)	50	0.8% SLS in phosphate buffer, pH 7.0	900	10, 20, 30, 45, 60, and 90	02/25/2004
Riluzole	Tablet	II (paddle)	50	0.1 N HCl	900	10, 20, 30, 45, and 60	02/18/2004
Rimantadine HCl	Tablet	II (paddle)	50	Water	900	10, 20, 30, and 45	01/03/2007

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Risedronate sodium	Tablet	II (paddle)	50	Water (deaerated)	500	10, 20, 30, and 45	02/20/2004
Risedronate sodium (75 mg)	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	09/13/2007
Risedronate sodium/ Calcium Carbonate	Tablet (Copackaged)	For Risedronate Tablets: Paddle	For Risedronate Tablets: 50	For Risedronate tablets: water. For Calcium Carbonate tablets: using USP method.	For Risedronate Tablets: 500 mL	10, 20, 30, and 45	01/03/2007
Risperidone	Tablet	II (paddle)	50	0.1 N HCl	500	10, 20, 30, 45, and 60	03/04/2006
Risperidone	Tablet (orally disintegrating)	II (paddle)	50	0.1 N HCl	500	5, 10, and 15	07/23/2004
Rizatriptan benzoate	Tablet	II (paddle)	50	Water (deaerated)	900	5, 10, 15, and 30	02/18/2004
Rizatriptan benzoate	Tablet (orally disintegrating)	II (paddle)	50	Water (deaerated)	900	5, 10, and 15	02/18/2004
Ropinirole HCl	Table	I (basket)	50	Citrate buffer, pH 4.0	500	5, 10, 15, and 30	01/03/2007
Rosiglitazone maleate	Tablet	II (paddle)	50	0.01 M acetate buffer, pH 4.0	900	10, 20, 30, and 45	02/24/2004
Rosuvastatin calcium	Tablet	II (paddle)	50	0.05 M citrate buffer pH 6.6	900	10, 20, 30, and 45	12/20/2005
Saquinavir mesylate	Tablet	II (paddle)	50	Citrate buffer (pH 3.0)	900	10, 20, 30, and 45	09/13/2007
Sertraline HCl	Tablet	II (paddle)	75	0.05 M sodium acetate buffer, pH 4.5	900	10, 20, 30, and 45	02/20/2004
Sildenafil citrate	Tablet	I (basket)	100	0.01 N HCl	900	5, 10, 15, and 30	03/04/2006
Simvastatin	Tablet			Refer to USP			06/18/2007
Sirolimus	Tablet	Basket (20 mesh)	120	0.4% SLS in water	500	10, 20, 30, 45, 60, and 120	03/14/2007
Solifenacin succinate	Tablet	II (paddle)	50	Water	900	10, 15, 30, and 45	02/19/2008
Sulfamethoxazole/trimethoprim	Tablet			Refer to USP			01/14/2008
Sumatriptan succinate	Tablet	II (paddle)	30	0.01 M HCl	900	5, 10, 15, and 30	03/04/2006
Tadalafil	Tablet	II (paddle)	50	0.5% sodium lauryl sulfate	1000	10, 20, 30, and 45	01/26/2006
Telithromycin	Tablet	II (paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	01/03/2007
Telmisartan	Tablet	II (paddle)	75	Phosphate buffer, pH 7.5	900	10, 20, 30, and 45	03/04/2006
Tenofovir disoproxil fumarate	Tablet	II (paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	01/03/2007
Terazosin HCl	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, 45, and 60	02/20/2004
Terbinafine HCl	Tablet	II (paddle)	50	Citrate buffer, pH 3.0 adjusted with HCl	500	10, 20, 30, and 45	02/20/2004
Testosterone	Tablet Buccal (extended release)	II (paddle, may use sinker)	60	1% sodium dodecyl sulfate in double distilled water	1000	1, 2, 4, 6, 10, 12, and 24 hr	01/03/2007
Theophylline (100 and 200 mg)	Tablet (extended release)	II (paddle)	50	SGF, pH 1.2 during first hour. SIF, pH 7.5 from end of hour 1 through 12th hour	900	1, 4, 8, and 12 hr	01/03/2007

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Theophylline (450 mg)	Tablet (extended release)	II (paddle)	50	SGF, pH 1.2 during first hour. SIF, pH 7.5 from end of hour 1 through 12th hour	900	1, 4, 8, and 12 hr	01/03/2007
Tiagabine HCl	Tablet	II (paddle)	50	Water	900	5, 10, 15, 20, and 30	01/03/2007
Ticlopidine HCl	Tablet	II (paddle)	50	Water (deaerated)	900	10, 20, 30, 45, and 60	02/19/2004
Tinidazole	Tablet	I (basket)	100	Water (deaerated)	900	10, 20, 30, and 45	01/03/2007
Tizanidine HCl	Tablet	I (basket)	100	0.1 N HCl	500	5, 10, 15, and 30	02/20/2004
Tolcapone	Tablet	II (paddle)	75	Borate buffer, pH 6.8 with 1% SLS	900	10, 20, 30, and 45	02/20/2004
Tolterodine tartrate	Tablet	II (paddle)	50	SGF without enzymes, pH 1.2	900	5, 10, 15, and 30	02/20/2004
Topiramate	Tablet	II (paddle)	50	Water (deaerated)	900	5, 10, 20, and 30	02/19/2004
Toremifene citrate	Tablet	II (paddle)	50	0.02 N HCl	1000	10, 20, 30, and 45	02/20/2004
Torsemide	Tablet	II (paddle)	50	0.1 N HCl	900	5, 10, 15, and 30	02/20/2004
Tramadol HCl	Tablet	I (basket)	100	0.1 N HCl	900	10, 20, 30, and 45	02/19/2004
Tramadol HCl	Tablet (extended release)	I (basket)	75	0.1 N HCl	900	2, 4, 8, 10, and 16 hr	01/03/2007
Trandolapril	Tablet	II (paddle)	50	Water (deaerated)	500	10, 20, 30, 45, and 60	02/20/2004
Trospium chloride	Tablet	II (paddle)	50	0.1 N HCl	1000	10, 20, 30, and 45	12/03/2007
Valganciclovir HCl	Tablet	II (paddle)	50	0.1 N HCl	900	10,15, 30, 45, and 60	06/18/2007
Valsartan (Tablet and Capsule)	Tablet	II (paddle)	50	0.067 M phosphate buffer, pH 6.8	1000	10, 20, 30, and 45	12/13/2004
Vardenafil HCl	Tablet	II (paddle)	50	0.1 N HCl	900	5, 10, 15, and 30	12/20/2005
Varenicline tartrate	Tablet	I (basket)	100	0.01 N HCl	500	5, 10, 15, and 30	12/03/2007
Venlafaxine HCl	Tablet	II (paddle)	50	Water (deaerated)	900	5, 10, 15, and 30	02/19/2004
Zafirlukast	Tablet	II (paddle)	50	1% w/v aqueous sodium dodecyl sulfate	1000	10. 30, 30, and 45	10/09/2007
Zalcitabine	Tablet			Refer to USP	900		02/19/2008
Zidovudine	Tablet			Refer to USP			07/25/2007
Zileuton	Tablet	II (paddle)	50	0.05 M SLS in water	900	10, 20, 30, 45, and 60	02/19/2004
Zolmitriptan	Tablet (orally disintegrating)	II (paddle)	50	0.1 N HCl	500	5, 10, 15, and 30	06/18/2007
Zolpidem tartrate	Tablet	II (paddle)	50	0.01 N HCl, pH 2.0	900	5, 10, 15, and 30	02/19/2004
Zolpidem tartrate	Tablet (extended release)	I (basket)	100	0.01 N HCl	500	15, 30, 90, 120, and 240	04/09/2007

Appendix II

Approved Excipients in Compressed Solid Dosage Forms

Ingredient	Dosage form	Quantity	Unit
Acacia	Oral-21; tablet	5	mg
Acacia	Oral-28; tablet	5	mg
Acacia	Buccal/sublingual; tablet	9.1	mg
Acacia	Oral; tablet, delayed action, enteric coated	10	mg
Acacia	Oral; tablet, repeat action	11.542	mg
Acacia	Oral; tablet, film coated	14.9	mg
Acacia	Oral-20; tablet	33.5	mg
Acacia	Oral; tablet, sustained action	34.4	mg
Acacia	Oral; tablet	70	mg
Acacia	Oral; tablet (immed./comp. release), uncoated, chewable	80	mg
Acacia	Oral; tablet, coated	156	mg
Acacia mucilage	Oral; tablet, coated	27.2	mg
Acesulfame potassium	Buccal; gum, chewing	2	mg
Acesulfame potassium	Sublingual; tablet	3	mg
Acesulfame potassium	Oral; tablet (immed./comp. release), uncoated, chewable	3.75	mg
Acesulfame potassium	Oral; tablet	4.4	mg
Acesulfame potassium	Oral; troche	6	mg
Acesulfame potassium	Oral; tablet, film coated	8.19	mg
Acetic acid, glacial	Oral; tablet	0.002	mg
Acetic anhydride	Oral; tablet, sustained action	0.11	mg
Acetylated monoglycerides	Oral; tablet, coated	0.28	mg
Acetylated monoglycerides	Oral; tablet, film coated	2.1	mg
Acetylated monoglycerides	Oral; tablet, sustained action	2.48	mg
Acetylated monoglycerides	Oral; tablet	3.74	mg
Acetylated monoglycerides	Oral; tablet, delayed action, enteric coated	5.17	mg
Acetyltributyl citrate	Oral; tablet	0.56	mg
Acetyltributyl citrate	Oral; tablet, enteric coated particles	18.7	mg
Acetyltributyl citrate	Oral; tablet, sustained action	57.35	mg
Acrylates copolymer	Oral; tablet (immed./comp. release), uncoated, chewable	5.05	mg
Acrylates copolymer	Oral; tablet	9.88	mg
Acrylates copolymer	Oral; tablet, orally disintegrating, delayed release	11.88	mg
Acrylates copolymer	Oral; tablet, sustained action, coated	25.18	mg
Acrylates copolymer	Oral; tablet, extended release	29.41	mg
Adipic acid	Vaginal; insert	57	mg
Agar	Oral; tablet	0.203	mg

Ingredient	Dosage form	Quantity	Unit
Albumins	Oral; tablet, film coated	4.5	mg
Alcohol	Oral; tablet, delayed action, enteric coated	71.5	mg
Alcohol	Oral; tablet	196	mg
Alcohol, dehydrated	Oral; tablet, film coated	0.75	mg
Alcohol, denatured	Oral; tablet	0.24	mg
Alginic acid	Oral; tablet, sustained action	22.25	mg
Alginic acid	Oral; tablet	32	mg
Alginic acid	Oral; tablet, film coated	52.8	mg
Alginic acid	Oral; tablet, coated	60	mg
Alginic acid	Oral; tablet (immed./comp. release), uncoated, chewable	400	mg
Alpha-tocopherol	Oral; tablet	0.3	mg
Aluminum hydroxide	Oral; tablet	15	mg
Aluminum hydroxide gel	Oral; tablet	85	mg
Aluminum hydroxide gel, dried	Oral; tablet	0.173	mg
Aluminum silicate	Oral; tablet	19.25	mg
Aluminum silicate	Oral; tablet, sustained action, coated	47	mg
Aluminum silicate	Oral; tablet, coated	50	mg
Aluminum silicate	Oral; tablet, sustained action	94	mg
Aluminum stearate	Oral; tablet	2.8	mg
Aluminum stearate	Oral; tablet, sustained action	105	mg
Alzamer-39	Oral; tablet, sustained action	10	mg
Alzamer-50	Oral; tablet, sustained action	10	mg
Alzamer-50	Oral; tablet, controlled release	32	mg
Amberlite	Oral; tablet	20	mg
Amberlite	Oral; tablet, film coated	25	mg
Amberlite IRP-69M	Oral; tablet, sustained release, film coated	18	mg
Amberlite XE-88	Oral; tablet	2.4	mg
Amberlite XE-88	Oral; tablet, coated	9	mg
Ammonium calcium alginate	Oral; tablet	10.72	mg
Ammonium chloride	Oral; tablet	4.2	mg
Ammonium chloride	Oral; tablet, film coated	8	mg
Ammonium phosphate	Sublingual; tablet	0.2	mg
Ammonium phosphate	Oral; tablet	0.4	mg
Ammonium phosphate	Oral; tablet, sustained action	0.4	mg
Anise oil	Oral; pastille	16	mg
Aquacoat	Oral; tablet	2.25	mg
Aquacoat	Oral; tablet (immed./comp. release), uncoated, chewable	13.5	mg
Aquacoat ECD	Oral; tablet	3.453	mg
Aquacoat ECD	Oral; tablet, sustained action	27.4	mg
Ascorbic acid	Oral; tablet, film coated	20	mg
Ascorbic acid	Oral; tablet	28.44	mg
Ascorbyl palmitate	Oral; tablet	0.515	mg
Aspartame	Buccal; patch, controlled release	1.1	mg

Ingredient	Dosage form	Quantity	Unit
Aspartame	Oral; tablet (immed./comp. release), film coated	5.1	mg
Aspartame	Oral; troche	6.1	mg
Aspartame	Oral; tablet, orally disintegrating, delayed release	9	mg
Aspartame	Oral; tablet	20	mg
Aspartame	Oral; tablet, film coated	20	mg
Aspartame	Oral; tablet (immed./comp. release), uncoated, effervescent	30	mg
Aspartame	Oral; tablet, orally disintegrating	36	mg
Aspartame	Oral; tablet (immed./comp. release), uncoated, chewable	65	mg
Barium sulfate	Vaginal; intrauterine device	1.42	mg
Beeswax	Oral; tablet, delayed action, enteric coated	0.1	mg
Beeswax	Oral; tablet	0.44	mg
Beeswax	Oral; tablet, coated	0.53	mg
Bentonite	Oral; tablet, coated	3.6935	mg
Bentonite	Oral; tablet	23	mg
Benzyl alcohol	Oral; tablet	1.06	mg
Benzyl alcohol	Oral; tablet, sustained action, coated	1.25	mg
Benzyl alcohol	Oral; tablet, delayed action, enteric coated	2.31	mg
Betadex	Oral-28; tablet	0.146	mg
Betadex	Oral; tablet, film coated	82.5	mg
Betadex	Oral; tablet	89.17	mg
Bismuth subcarbonate	Oral; tablet	0.0044	mg
Bismuth subcarbonate	Oral; tablet, sustained action	0.044	mg
Butylated hydroxyanisole	Oral; tablet, film coated	0.4	mg
Butylated hydroxyanisole	Oral; tablet	0.5	mg
Butylated hydroxyanisole	Sublingual; tablet	0.5	mg
Butylated hydroxytoluene	Oral; tablet, extended release	0.11	mg
Butylated hydroxytoluene	Oral; tablet (immed./comp. release), film coated	0.15	mg
Butylated hydroxytoluene	Buccal; gum, chewing	0.21	mg
Butylated hydroxytoluene	Oral; tablet, controlled release	0.21	mg
Butylated hydroxytoluene	Oral; tablet, sustained action	0.24	mg
Butylated hydroxytoluene	Oral; tablet, film coated	0.36	mg
Butylated hydroxytoluene	Oral; tablet	0.4	mg
Butylparaben	Oral; tablet, coated	0.004	mg
Butylparaben	Oral; tablet, repeat action	0.006	mg
Butylparaben	Oral; tablet, sustained action	0.04	mg
Calcium acetate	Oral-21; tablet	10	mg
Calcium acetate	Oral-28; tablet	10	mg
Calcium alginate and ammonium alginate	Oral; tablet	20	mg
Calcium carbonate	Oral; tablet, delayed action, enteric coated	8.4	mg
Calcium carbonate	Oral-21; tablet, coated	8.607	mg
Calcium carbonate	Oral-28; tablet, coated	8.607	mg
Calcium carbonate	Oral-28; tablet	9.59	mg
Calcium carbonate	Oral; tablet, coated	64.8	mg

Ingredient	Dosage form	Quantity	Unit
Calcium carbonate	Oral; tablet (immed./comp. release), film coated	132	mg
Calcium carbonate	Buccal; gum, chewing	145.5	mg
Calcium carbonate	Oral; tablet, film coated	225	mg
Calcium carbonate	Oral; tablet, sustained action	229.7	mg
Calcium carbonate	Oral; tablet	265.2	mg
Calcium carbonate	Oral; tablet (immed./comp. release), uncoated, chewable	550	mg
Calcium citrate	Oral; tablet	98.95	mg
Calcium cyclamate	Oral; tablet (immed./comp. release), uncoated, chewable	5	mg
Calcium hydroxide	Oral; tablet	35	mg
Calcium lactate	Vaginal; tablet	30	mg
Calcium phosphate	Oral-21; tablet	86	mg
Calcium phosphate	Oral; tablet, coated	93.6	mg
Calcium phosphate	Oral; tablet	160	mg
Calcium phosphate	Oral; tablet, film coated	362	mg
Calcium phosphate, dibasic	Oral; tablet, delayed action, enteric coated	46	mg
Calcium phosphate, dibasic	Oral; tablet (immed./comp. release), uncoated, chewable	50	mg
Calcium phosphate, dibasic	Oral-21; tablet	104.5	mg
Calcium phosphate, dibasic	Oral-28; tablet	104.5	mg
Calcium phosphate, dibasic	Oral; tablet (immed./comp. release), film coated	138.84	mg
Calcium phosphate, dibasic	Oral; tablet, coated	293.2	mg
Calcium phosphate, dibasic	Oral; tablet, sustained action	335	mg
Calcium phosphate, dibasic	Oral; tablet, film coated	525.56	mg
Calcium phosphate, dibasic	Oral; tablet	850	mg
Calcium phosphate, dibasic monohydrate	Oral; tablet	109.3	mg
Calcium phosphate, dibasic, dihydrate	Oral; tablet, extended release	108	mg
Calcium phosphate, dibasic, dihydrate	Oral; tablet, sustained action	189	mg
Calcium phosphate, dibasic, dihydrate	Oral; tablet, coated	488.7	mg
Calcium phosphate, dibasic, dihydrate	Oral; tablet	512	mg
Calcium phosphate, dibasic, dihydrate	Oral; tablet, film coated	635.5	mg
Calcium phosphate, tribasic	Oral; tablet, coated	21	mg
Calcium phosphate, tribasic	Oral; tablet (immed./comp. release), film coated	21.8	mg
Calcium phosphate, tribasic	Buccal/sublingual; tablet	99.2	mg
Calcium phosphate, tribasic	Oral; tablet, sustained action	100	mg
Calcium phosphate, tribasic	Oral; tablet (immed./comp. release), uncoated, chewable	130	mg
Calcium phosphate, tribasic	Oral; tablet	282	mg
Calcium phosphate, tribasic	Oral; tablet, delayed action, enteric coated	333.3	mg
Calcium pyrophosphate	Oral; tablet	298.04	mg
Calcium silicate	Oral; tablet, sustained action	15	mg
Calcium silicate	Oral; tablet, coated	143	mg
Calcium silicate	Oral; tablet	146.13	mg
Calcium silicate	Oral; tablet, film coated	182.7	mg
Calcium stearate	Oral-21; tablet	0.7	mg
Calcium stearate	Oral-28; tablet	0.7	mg

Ingredient	Dosage form	Quantity	Unit
Calcium stearate	Buccal/sublingual; tablet	1.42	mg
Calcium stearate	Sublingual; tablet	2	mg
Calcium stearate	Oral; tablet, delayed action, enteric coated	3.2	mg
Calcium stearate	Oral; tablet, film coated	16	mg
Calcium stearate	Oral; tablet, sustained action	24	mg
Calcium stearate	Oral; tablet	42.9	mg
Calcium stearate	Oral; tablet (immed./comp. release), uncoated, chewable	47.5	mg
Calcium sulfate	Oral-28; tablet	10.7	mg
Calcium sulfate	Oral; tablet, delayed action, enteric coated	75	mg
Calcium sulfate	Oral; tablet, coated	170	mg
Calcium sulfate	Oral; tablet, repeat action	235	mg
Calcium sulfate	Oral; tablet, sustained action	340	mg
Calcium sulfate	Oral; tablet	436.9	mg
Calcium sulfate	Oral; tablet, film coated	443	mg
Calcium sulfate dihydrate	Oral; tablet, sustained action, coated	29.7	mg
Calcium sulfate dihydrate	Oral; tablet, delayed action, enteric coated	87.2	mg
Calcium sulfate dihydrate	Oral-28; tablet	105.4	mg
Calcium sulfate dihydrate	Oral; tablet, coated	214.24	mg
Calcium sulfate dihydrate	Oral; tablet, repeat action	242.946	mg
Calcium sulfate dihydrate	Oral; tablet	279.309	mg
Calcium sulfate dihydrate	Oral; tablet, film coated	341	mg
Calcium sulfate, anhydrous	Oral-28; tablet	10.7	mg
Calcium sulfate, anhydrous	Oral; tablet, repeat action	86.531	mg
Calcium sulfate, anhydrous	Oral; tablet	174.5	mg
Candelilla wax	Oral; tablet, sustained action	0.16	mg
Candelilla wax	Oral; tablet (immed./comp. release), film coated	0.32	mg
Candelilla wax	Oral; tablet, extended release	0.37	mg
Candelilla wax	Oral; tablet	0.3708	mg
Candelilla wax	Oral; tablet, sustained action, coated	0.58	mg
Candelilla wax	Oral; tablet, film coated	0.8	mg
Carbomer 934	Oral; tablet, sustained action	90	mg
Carbomer 934P	Oral; tablet, orally disintegrating	0.3	mg
Carbomer 934P	Oral; tablet, sustained action	1.5	mg
Carbomer 934P	Oral; tablet, sustained action, coated	3	mg
Carbomer 934P	Buccal; tablet	9.375	mg
Carbomer 934P	Oral; tablet, extended release	15	mg
Carbomer 974P	Oral; tablet, controlled release	6.25	mg
Carbomer 974P	Oral; tablet, sustained action	6.25	mg
Carbon	Oral; tablet	0.006	mg
Carbon	Oral; tablet, coated	0.011	mg
Carboxymethyl starch	Oral; tablet	25	mg
Carboxymethylcellulose	Oral; tablet	3	mg
Carboxymethylcellulose calcium	Oral; tablet, delayed action, enteric coated	13.3	mg

Ingredient	Dosage form	Quantity	Unit
Carboxymethylcellulose calcium	Oral; tablet	29	mg
Carboxymethylcellulose calcium	Oral; tablet, film coated	241.842	mg
Carboxymethylcellulose sodium	Oral; tablet, coated	2.2	mg
Carboxymethylcellulose sodium	Oral; tablet, extended release	15	mg
Carboxymethylcellulose sodium	Oral; tablet (immed./comp. release), uncoated, chewable	24.75	mg
Carboxymethylcellulose sodium	Oral; tablet	48	mg
Carboxymethylcellulose sodium	Oral; tablet, film coated	50	mg
Carboxymethylcellulose sodium	Oral; tablet, sustained action	155	mg
Carboxypolymethylene	Oral; tablet, sustained action	195	mg
Carmine	Oral; tablet, film coated	0.377	mg
Carmine	Oral; tablet	6.8	mg
Carnauba wax	Oral; tablet, repeat action	0.046	mg
Carnauba wax	Oral-28; tablet	0.157	mg
Carnauba wax	Oral; tablet, sustained action, film coated	0.25	mg
Carnauba wax	Oral; tablet, coated	0.92	mg
Carnauba wax	Oral; tablet, film coated	5	mg
Carnauba wax	Oral; tablet (immed./comp. release), uncoated, chewable	31.129	mg
Carnauba wax	Oral; tablet	57.8	mg
Carnauba wax	Oral; tablet, sustained action, multilayer, film coated	75	mg
Carnauba wax	Oral; tablet, sustained action, coated	140	mg
Carnauba wax	Oral; tablet, delayed action, enteric coated	230	mg
Carnauba wax	Oral; tablet, extended release	290	mg
Carnauba wax	Oral; tablet, sustained action	300	mg
Carnauba yellow wax	Oral; tablet, sugar coated	0.09	mg
Carnauba yellow wax	Oral; tablet	0.18	mg
Carnauba yellow wax	Oral; tablet, coated	0.18	mg
Carnauba yellow wax	Oral; tablet, extended release	200	mg
Castor oil	Oral; tablet, coated	0.9	mg
Castor oil	Sublingual; tablet	1.6	mg
Castor oil	Oral; tablet	2	mg
Castor oil	Oral; tablet, film coated	3.06	mg
Castor oil	Oral; tablet, sustained action	23.27	mg
Castor oil hydrogenated	Oral-21; tablet	0.93	mg
Castor oil hydrogenated	Oral-28; tablet	0.93	mg
Castor oil hydrogenated	Oral; tablet, delayed action, enteric coated	1.3	mg
Castor oil hydrogenated	Sublingual; tablet	1.6	mg
Castor oil hydrogenated	Oral; tablet, film coated	3.3	mg
Castor oil hydrogenated	Oral; tablet, sustained action, coated	5	mg
Castor oil hydrogenated	Oral; tablet	37.6	mg
Castor oil hydrogenated	Oral; tablet, sustained action	295	mg
Cellacefate	Oral; tablet, film coated	15.6	mg
Cellacefate	Oral; tablet	37	mg
Cellacefate	Oral; tablet, delayed action, enteric coated	70	mg

Ingredient	Dosage form	Quantity	Unit
Cellacefate	Oral; tablet, sustained action	70	mg
Cellulose	Buccal/sublingual; tablet	4.5	mg
Cellulose	Oral; tablet, delayed action, enteric coated	16	mg
Cellulose	Oral-21; tablet	20	mg
Cellulose	Oral-28; tablet	20	mg
Cellulose	Oral; tablet, coated	40.2	mg
Cellulose	Oral; tablet, sustained action, coated	42.25	mg
Cellulose	Oral; tablet, sustained action	110.6	mg
Cellulose	Oral; tablet, film coated	391.7	mg
Cellulose	Oral; tablet	1120	mg
Cellulose acetate	Oral; tablet	2.45	mg
Cellulose acetate	Oral; tablet (immed./comp. release), uncoated, chewable	6.86	mg
Cellulose acetate	Oral; tablet, extended release	23.56	mg
Cellulose acetate	Oral; tablet, controlled release	27.39	mg
Cellulose acetate	Oral; tablet, sustained action	39	mg
Cellulose acetate	Oral; tablet, sustained action, coated	44.6	mg
Cellulose acetate CA-320S	Oral; tablet, extended release	36.02	mg
Cellulose acetate CA-398-10	Oral; tablet, extended release	47.49	mg
Cellulose microcrystalline, aqueous	Oral; tablet, delayed action, enteric coated	199.6	mg
Cellulose microcrystalline, aqueous	Oral; tablet	240	mg
Cellulose microcrystalline, aqueous	Oral; tablet, film coated	262.19	mg
Cellulose microcrystalline/ carboxymethylcellulose sodium	Oral; tablet	160	mg
Cellulose, microcrystalline	Oral; tablet, for solution	0.75	mg
Cellulose, microcrystalline	Oral; tablet, sugar coated	4.64	mg
Cellulose, microcrystalline	Oral-28; tablet, coated	10	mg
Cellulose, microcrystalline	Oral; tablet, multilayer, extended release	17.3	mg
Cellulose, microcrystalline	Oral; tablet, repeat action	25	mg
Cellulose, microcrystalline	Oral-21; tablet	28.488	mg
Cellulose, microcrystalline	Oral-28; tablet	28.488	mg
Cellulose, microcrystalline	Oral; tablet, orally disintegrating, delayed release	30	mg
Cellulose, microcrystalline	Oral; tablet, multilayer, coated	34	mg
Cellulose, microcrystalline	Sublingual; tablet	43.2	mg
Cellulose, microcrystalline	Oral; tablet, uncoated, troche	60	mg
Cellulose, microcrystalline	Oral; tablet, sustained release, film coated	62.4	mg
Cellulose, microcrystalline	Oral; tablet, sustained action, coated	100	mg
Cellulose, microcrystalline	Oral; tablet, delayed action	150	mg
Cellulose, microcrystalline	Oral; tablet, controlled release	152	mg
Cellulose, microcrystalline	Oral; tablet (immed./comp. release), film coated	240	mg
Cellulose, microcrystalline	Oral; tablet, sustained action, film coated	307.52	mg
Cellulose, microcrystalline	Oral; tablet, coated	356	mg
Cellulose, microcrystalline	Oral; tablet, sustained action	363.7	mg
Cellulose, microcrystalline	Oral; tablet, delayed action, enteric coated	375.26	mg
Cellulose, microcrystalline	Vaginal; tablet	390	mg

Ingredient	Dosage form	Quantity	Unit
Cellulose, microcrystalline	Oral; tablet, enteric coated particles	391	mg
Cellulose, microcrystalline	Oral; tablet, orally disintegrating	392.86	mg
Cellulose, microcrystalline	Oral; tablet, extended release	397.7	mg
Cellulose, microcrystalline	Oral; tablet, film coated	530	mg
Cellulose, microcrystalline	Oral; tablet (immed./comp. release), uncoated, chewable	570	mg
Cellulose, microcrystalline	Oral; tablet	1385.3	mg
Cellulose, microcrystalline 101	Oral; tablet, film coated	6.5	mg
Cellulose, microcrystalline 101	Oral; tablet, extended release	100	mg
Cellulose, microcrystalline 101	Oral; tablet	164.7	mg
Cellulose, oxidized	Oral; tablet	165.092	mg
Cellulose, powder	Oral; tablet	44	mg
Cetearyl alcohol	Oral; tablet, sustained action, film coated	62	mg
Cetearyl alcohol	Oral; tablet, sustained action	70	mg
Cetyl alcohol	Oral; tablet, sustained action	44	mg
Cetyl alcohol	Oral; tablet, sustained action, film coated	59	mg
Charcoal, activated	Oral; tablet	0.6	mg
Cherry	Oral; tablet	0.45	mg
Chromacote T 2700GN	Oral; tablet	4.74	mg
Chromacote T 2716Y	Oral; tablet	6.33	mg
Chroma-Kote T2956-Y yellow	Oral; tablet, film coated	0.912	mg
Chroma-Kote T2956-Y yellow	Oral; tablet	2.75	mg
Cinnamaldehyde	Oral; tablet	2.1	mg
Cinnamon oil	Oral; tablet (immed./comp. release), uncoated, chewable	0.001	mg
Cinnamon oil	Oral; pastille	4	mg
Citric acid	Oral; tablet, delayed action, enteric coated	1	mg
Citric acid	Oral; tablet (immed./comp. release), film coated	2.56	mg
Citric acid	Oral; tablet, orally disintegrating, delayed release	3.08	mg
Citric acid	Oral; tablet (immed./comp. release), uncoated, chewable	4.26	mg
Citric acid	Oral; tablet, extended release	5	mg
Citric acid	Sublingual; tablet	5.92	mg
Citric acid	Buccal; tablet	30	mg
Citric acid	Oral; tablet, sustained action, film coated	40	mg
Citric acid	Oral; tablet, film coated	42	mg
Citric acid	Oral; tablet, orally disintegrating	63	mg
Citric acid	Oral; tablet	78	mg
Citric acid	Oral; bar, chewable	500	mg
Citric acid monohydrate	Oral; tablet, film coated	10	mg
Citric acid monohydrate	Oral; tablet	50	mg
Citric acid, hydrous	Oral; tablet, film coated	10	mg
Coateric YPA-6-7430 white	Oral; tablet, delayed action, enteric coated	26	mg
Compressible sugar	Oral-21; tablet	8	mg
Compressible sugar	Oral-28; tablet	8	mg
Compressible sugar	Oral; tablet, coated	120	mg

Ingredient	Dosage form	Quantity	Unit
Compressible sugar	Sublingual; tablet	136	mg
Compressible sugar	Oral; tablet, sustained action	253	mg
Compressible sugar	Oral; tablet, sustained action, film coated	354	mg
Compressible sugar	Oral; tablet	360	mg
Compressible sugar	Oral; tablet (immed./comp. release), uncoated, chewable	623.5	mg
Copovidone	Oral; tablet, extended release	3.9	mg
Copovidone	Oral; tablet, orally disintegrating	4.38	mg
Copovidone	Oral; tablet, sustained action, film coated	6.1	mg
Copovidone	Oral; tablet	356.82	mg
Copovidone	Oral; tablet, film coated	853.8	mg
Corn oil	Oral; tablet, delayed action, enteric coated	0.03	mg
Corn oil	Oral; tablet, coated	0.3	mg
Corn oil	Sublingual; tablet	1.7	mg
Corn oil	Oral; tablet	20	mg
Corn syrup	Oral; tablet	14.065	mg
Cottonseed oil, hydrogenated	Oral; tablet, coated	0.6	mg
Cottonseed oil, hydrogenated	Sublingual; tablet	2	mg
Cottonseed oil, hydrogenated	Oral; tablet, delayed action, enteric coated	4	mg
Cottonseed oil, hydrogenated	Oral; tablet	34	mg
Cottonseed oil, hydrogenated	Oral; tablet, sustained action	402	mg
Croscarmellose sodium	Oral-28; tablet, coated	2	mg
Croscarmellose sodium	Oral; tablet, sugar coated	2.5	mg
Croscarmellose sodium	Oral-21; tablet	3	mg
Croscarmellose sodium	Oral-28; tablet	3	mg
Croscarmellose sodium	Sublingual; tablet	6.5	mg
Croscarmellose sodium	Oral; tablet, uncoated, troche	10	mg
Croscarmellose sodium	Oral; tablet, orally disintegrating	13	mg
Croscarmellose sodium	Oral; tablet, delayed action	14	mg
Croscarmellose sodium	Oral; tablet, extended release	15	mg
Croscarmellose sodium	Oral; tablet (immed./comp. release), uncoated, chewable	18	mg
Croscarmellose sodium	Oral; tablet, sustained action	28	mg
Croscarmellose sodium	Oral; tablet, delayed action, enteric coated	32.44	mg
Croscarmellose sodium	Oral; tablet, coated	35.2	mg
Croscarmellose sodium	Oral; tablet (immed./comp. release), film coated	50	mg
Croscarmellose sodium	Oral; tablet, film coated	165	mg
Croscarmellose sodium	Oral; tablet	180	mg
Crospovidone	Oral-21; tablet	4.45	mg
Crospovidone	Oral; tablet, multilayer, extended release	5	mg
Crospovidone	Oral; tablet, sustained action, film coated	5	mg
Crospovidone	Oral; tablet, dispersible	6	mg
Crospovidone	Sublingual; tablet	6.5	mg
Crospovidone	Oral; tablet, repeat action	10	mg
Crospovidone	Oral; tablet, orally disintegrating, delayed release	15	mg

Ingredient	Dosage form	Quantity	Unit
Crospovidone	Oral; tablet, sustained action, coated	15.4	mg
Crospovidone	Oral; tablet (immed./comp. release), film coated	17	mg
Crospovidone	Vaginal; tablet	35	mg
Crospovidone	Oral; tablet, extended release	39.2	mg
Crospovidone	Oral; tablet, delayed action, enteric coated	50	mg
Crospovidone	Oral; tablet (immed./comp. release), uncoated, chewable	100	mg
Crospovidone	Oral; tablet, enteric coated particles	130	mg
Crospovidone	Oral; tablet, sustained action	144	mg
Crospovidone	Oral; tablet, orally disintegrating	180	mg
Crospovidone	Oral; tablet, film coated	196.7	mg
Crospovidone	Oral; tablet	300	mg
Crospovidone	Oral; tablet, coated	792	mg
Crystal gum	Oral; tablet	17	mg
Cutina	Sublingual; tablet	1.6	mg
Cysteine hydrochloride	Oral; tablet, sustained action, film coated	16.2	mg
D&C black no. 1	Oral; tablet	0.08	mg
D&C blue no. 1	Oral; tablet	0.15	mg
D&C blue no. 1	Oral; tablet, film coated	0.1624	mg
D&C blue no. 1–aluminum lake	Oral; tablet	3.6	mg
D&C blue no. 2 lake	Oral; tablet, coated	0.002	mg
D&C blue no. 2 lake	Oral; tablet	0.24	mg
D&C green no. 5	Oral-21; tablet	0.0024	mg
D&C green no. 5	Oral-28; tablet	0.0024	mg
D&C green no. 5	Oral; tablet	0.015	mg
D&C red no. 19	Oral; tablet	0.005	mg
D&C red no. 27	Oral; tablet	0.04	mg
D&C red no. 3 lake	Sublingual; tablet	0.005	mg
D&C red no. 3 lake	Oral; tablet	0.5	mg
D&C red no. 30	Oral-21; tablet	0.5	mg
D&C red no. 30	Oral-28; tablet	0.5	mg
D&C red no. 30	Oral; tablet	0.75	mg
D&C red no. 30	Oral; tablet, coated	1.16	mg
D&C red no. 30	Oral; tablet (immed./comp. release), uncoated, chewable	1.46	mg
D&C red no. 30	Oral; tablet, film coated	290	mg
D&C red no. 30 lake	Oral; tablet, sustained action	0.025	mg
D&C red no. 30 lake	Oral-21; tablet	0.03	mg
D&C red no. 30 lake	Oral; tablet, delayed action, enteric coated	0.04	mg
D&C red no. 30 lake	Oral; tablet, film coated	0.064	mg
D&C red no. 30 lake	Oral; tablet, coated	0.343	mg
D&C red no. 30 lake	Oral; tablet, enteric coated particles	0.8	mg
D&C red no. 30 lake	Oral; tablet	1.5	mg
D&C red no. 30 lake	Oral; tablet (immed./comp. release), uncoated, chewable	5	mg
D&C red no. 33	Oral; tablet, coated	0.0023	mg

Ingredient	Dosage form	Quantity	Unit
D&C red no. 33	Oral; tablet	0.24	mg
D&C red no. 36	Oral; tablet	48.75	mg
D&C red no. 40	Oral; tablet	0.02	mg
D&C red no. 40 lake	Oral; tablet	0.2	mg
D&C red no. 5	Oral; tablet	0.18	mg
D&C red no. 6 lake	Oral; tablet	1.5	mg
D&C red no. 7	Oral; tablet, film coated	0.16	mg
D&C red no. 7	Oral; tablet	0.28	mg
D&C red no. 7 lake	Oral; tablet, delayed action, enteric coated	0.5	mg
D&C red no. 7 lake	Oral; tablet	0.6	mg
D&C violet no. 2 lake	Oral; tablet	0.112	mg
D&C yellow no. 10	Oral; tablet, extended release	0.03	mg
D&C yellow no. 10	Oral-28; tablet	0.09	mg
D&C yellow no. 10	Oral-21; tablet	0.12	mg
D&C yellow no. 10	Sublingual; tablet	0.23	mg
D&C yellow no. 10	Buccal; gum, chewing	1	mg
D&C yellow no. 10	Oral; tablet, delayed action, enteric coated	1.9	mg
D&C yellow no. 10	Oral; tablet, sustained action	2.01	mg
D&C yellow no. 10	Oral; tablet, coated	2.5	mg
D&C yellow no. 10	Oral; tablet	80	mg
D&C yellow no. 10	Oral; tablet, film coated	120	mg
D&C yellow no. 10 lake	Oral; tablet, sustained action	0.015	mg
D&C yellow no. 10 lake	Oral; tablet, coated	3.68	mg
D&C yellow no. 10 lake	Oral; tablet	5.2	mg
D&C yellow no. 10–aluminum lake	Oral; tablet, delayed action, enteric coated	0.05	mg
D&C yellow no. 10–aluminum lake	Oral; tablet, dispersible	0.13	mg
D&C yellow no. 10–aluminum lake	Oral; tablet, sustained action, film coated	0.16	mg
D&C yellow no. 10–aluminum lake	Sublingual; tablet	0.18	mg
D&C yellow no. 10–aluminum lake	Oral; tablet, coated	0.208	mg
D&C yellow no. 10–aluminum lake	Buccal; gum, chewing	0.35	mg
D&C yellow no. 10–aluminum lake	Oral; tablet, film coated	0.3968	mg
D&C yellow no. 10–aluminum lake	Oral-21; tablet	0.415	mg
D&C yellow no. 10–aluminum lake	Oral-28; tablet	0.415	mg
D&C yellow no. 10–aluminum lake	Oral; tablet, sustained release, film coated	0.8	mg
D&C yellow no. 10–aluminum lake	Oral; tablet, extended release	1	mg
D&C yellow no. 10–aluminum lake	Oral; tablet (immed./comp. release), uncoated, chewable	2	mg
D&C yellow no. 10–aluminum lake	Oral; tablet, sustained action	2.33	mg
D&C yellow no. 10–aluminum lake	Oral; tablet	12.5	mg
D&C yellow no. 5	Oral; tablet	0.013	mg
D&C yellow no. 5	Sublingual; tablet	0.1	mg
D&C yellow no. 5–aluminum lake	Oral; tablet (immed./comp. release), uncoated, chewable	0.285	mg
D&C yellow no. 5–aluminum lake	Oral; tablet, film coated	0.59	mg
D&C yellow no. 5–aluminum lake	Oral; tablet	2.69	mg

Ingredient	Dosage form	Quantity	Unit
D&C yellow no. 6	Oral; tablet	0.005	mg
D&C yellow no. 6 lake	Sublingual; tablet	0.01	mg
D&C yellow no. 6 lake	Oral; tablet	0.5	mg
Dextrates	Oral; tablet	86.5	mg
Dextrates	Oral; tablet, sustained action	108.5	mg
Dextrates	Oral; tablet (immed./comp. release), uncoated, chewable	1066.4	mg
Dextrin	Oral; tablet, delayed action, enteric coated	9.25	mg
Dextrin	Oral; tablet	21.7	mg
Dextrose	Oral; tablet, sustained action, coated	103.95	mg
Dextrose	Sublingual; tablet	115.775	mg
Dextrose	Oral; pastille	157	mg
Dextrose	Oral; tablet	183.66	mg
Dextrose	Oral; tablet (immed./comp. release), uncoated, chewable	398	mg
Dextrose	Oral; tablet, uncoated, troche	903.5	mg
Diacetylated monoglycerides	Oral; tablet, coated	0.63	mg
Diacetylated monoglycerides	Oral; tablet, film coated	1.143	mg
Diacetylated monoglycerides	Oral; tablet, delayed action, enteric coated	1.2	mg
Diacetylated monoglycerides	Oral; tablet	9.14	mg
Dibutyl phthalate	Oral; tablet, delayed action, enteric coated	1.7	mg
Dibutyl sebacate	Oral; tablet, sustained action	1.11	mg
Dibutyl sebacate	Oral; tablet	6	mg
Dibutyl sebacate	Oral; tablet, extended release	8	mg
Diethyl phthalate	Oral; tablet (immed./comp. release), uncoated, chewable	0.5	mg
Diethyl phthalate	Oral; tablet, coated	1.25	mg
Diethyl phthalate	Oral; tablet, film coated	2.3	mg
Diethyl phthalate	Oral; tablet	4	mg
Diethyl phthalate	Oral; tablet, sustained action	12	mg
Diethyl phthalate	Oral; tablet, delayed action, enteric coated	16.8	mg
Dihydroxyaluminum sodium carbonate	Oral; tablet (immed./comp. release), uncoated, chewable	1350	mg
Diisopropylbenzothiazyl-2-sulfenamide	Oral; tablet	77	mg
Dimethyl phthalate	Oral; tablet, sustained action	0.407	mg
Dipropylene glycol	Buccal; patch, controlled release	29.9	mg
Docusate sodium	Oral; tablet, coated	0.002	mg
Docusate sodium	Oral; tablet (immed./comp. release), film coated	0.03	mg
Docusate sodium	Oral; tablet, sustained action, film coated	0.03	mg
Docusate sodium	Oral; tablet, film coated	0.5	mg
Docusate sodium	Oral; tablet	11	mg
Docusate sodium/sodium benzoate	Oral; tablet, film coated	3	mg
Docusate sodium/sodium benzoate	Oral; tablet	7	mg
Dri Klear	Oral; tablet	1.5	mg
Dri Klear 042	Oral; tablet, film coated	5.67	mg
Dri Klear 042	Oral; tablet, coated	10	mg
Dri Klear 042	Oral; tablet	18	mg

Ingredient	Dosage form	Quantity	Unit
Dri Klear LV 609527	Oral; tablet, film coated	2.256	mg
DRY FLO	Oral; tablet	27.5	mg
dry-clear LV	Oral; tablet	19.94	mg
Dusting powder	Oral; tablet, coated	22	mg
Dye black LB-1171	Oral; tablet	1.545	mg
Dye black LB-442	Oral; tablet	0.333	mg
Dye black LB-636	Oral-28; tablet	0.15	mg
Dye black LB-9972	Oral; tablet	0.19	mg
Dye blue #1	Oral; tablet	0.36	mg
Dye blue #1 Lake	Oral; tablet	15.4	mg
Dye blue #2	Oral; tablet, delayed action, enteric coated	0.0003	mg
Dye blue lake blend LB-1245	Oral; tablet	0.26	mg
Dye blue lake blend LB-332	Oral; tablet	0.11	mg
Dye blue lakolene	Oral; tablet	0.12	mg
Dye blue LB-781	Oral; tablet	2	mg
Dye brown lake	Oral; tablet	0.17	mg
Dye brown lake blend	Oral; tablet	0.258	mg
Dye brown lake blend LB-1685	Oral; tablet	0.45	mg
Dye brown lake blend LB-1792	Oral; tablet	0.22	mg
Dye brown LB-292	Oral; tablet	0.825	mg
Dye brown LB-464	Oral; tablet	1.3	mg
Dye burnt umber	Oral; tablet, film coated	0.06	mg
Dye carmine 09349	Oral; tablet, film coated	0.54	mg
Dye chroma-teric DEB-5037-ORE	Oral; tablet, delayed action, enteric coated	10	mg
Dye chroma-teric Yellow T3277-YE	Oral; tablet, delayed action, enteric coated	30.54	mg
Dye chroma-tone	Oral; tablet, film coated	1.53	mg
Dye chroma-tone PDDB-8906W	Oral; tablet	6	mg
Dye chroma-tone-P DDB-8746-OR	Oral; tablet	11.9	mg
Dye DC green #1 lake	Oral; tablet	0.649	mg
Dye DC red #2 lake	Oral; tablet	0.722	mg
Dye DC red #27 lake	Oral; tablet, film coated	0.333	mg
Dye DC red #27 lake	Oral; tablet	0.69	mg
Dye DC red #27 lake	Oral; tablet (immed./comp. release), uncoated, chewable	1.25	mg
Dye DC red #28 lake	Oral-28; tablet	0.106	mg
Dye DC red #30 HT lake	Oral; tablet, extended release	0.1	mg
Dye DC red #33 lake	Oral; tablet	0.3	mg
Dye DC red #6 barium lake	Oral; tablet	0.38	mg
Dye DC red #7 calcium lake	Sublingual; tablet	0.005	mg
Dye DC red #7 calcium lake	Oral; tablet	0.5	mg
Dye DC red lake	Oral; tablet	2.4	mg
Dye DC red LB #9570	Oral; tablet	0.85	mg
Dye DC red LB WJ-9570	Oral; tablet	0.5605	mg
Dye DC yellow #10 HT lake	Oral; tablet, sustained action	1.32	mg

Ingredient	Dosage form	Quantity	Unit
Dye DC yellow #10 HT lake	Oral; tablet	1.4	mg
Dye diolack 00F32892 yellow	Oral; tablet	2.8	mg
Dye emerald green LB	Oral; tablet	0.05	mg
Dye emerald green LB-9207	Oral; tablet	0.44	mg
Dye FDC black LB260	Oral; tablet	3	mg
Dye FDC blue #1 H.T. aluminum lake	Oral; tablet	0.288	mg
Dye FDC blue #2 HT lake	Oral; tablet	0.2	mg
Dye FDC blue #40 HT lake	Oral; tablet	0.225	mg
Dye FDC brown R LB-56069	Buccal; gum, chewing	0.14	mg
Dye FDC brown R LB-56069	Oral; tablet	0.2	mg
Dye FDC green LB-1174	Oral-21; tablet	0.3	mg
Dye FDC green LB-1174	Oral-28; tablet	0.3	mg
Dye FDC green LB-3323	Oral; tablet	1.65	mg
Dye FDC green LB-9583	Oral; tablet	0.23	mg
Dye FDC LB483	Oral; tablet	0.28	mg
Dye FDC orange LB-452	Oral; tablet	0.54	mg
Dye FDC purple LB588	Oral; tablet	0.2	mg
Dye FDC purple LB-694	Oral; tablet	0.25	mg
Dye FDC red #2 lake	Oral; tablet	0.14	mg
Dye FDC red #27 lake	Oral; tablet	0.4	mg
Dye FDC red #30 lake	Oral-21; tablet	0.03	mg
Dye FDC red #30 lake	Oral; tablet, extended release	0.315	mg
Dye FDC red #30 lake	Oral; tablet	0.4	mg
Dye FDC red #7 lake	Oral; tablet	0.06	mg
Dye FDC violet #1 lake	Oral; tablet	0.1	mg
Dye FDC yellow #10 lake	Oral-21; tablet	0.096	mg
Dye FDC yellow #10 lake	Oral-28; tablet	0.15	mg
Dye FDC yellow #10 lake	Sublingual; tablet	0.151	mg
Dye FDC yellow #10 lake	Oral; tablet (immed./comp. release), uncoated, chewable	3	mg
Dye FDC yellow #10 lake	Oral; tablet	6.52	mg
Dye FDC yellow #6 HT lake	Oral; tablet, sustained action	0.2	mg
Dye FDC yellow #6 HT lake	Oral; tablet, extended release	0.4	mg
Dye FDC yellow #6 HT lake	Oral; tablet	0.45	mg
Dye ferric oxide orange	Oral; tablet	0.5	mg
Dye green 70363	Oral; tablet	1.05	mg
Dye green AL LB-265	Oral; tablet	0.64	mg
Dye green aluminum LB	Oral; tablet	8	mg
Dye green lake blend LB-1236	Oral; tablet	0.35	mg
Dye green lake blend LB-1441	Oral; tablet	1.32	mg
Dye green lake blend LB-1644	Oral; tablet	0.26	mg
Dye green lake blend LB-333	Oral; tablet	0.11	mg
Dye green LB	Oral; tablet	0.4	mg
Dye green LB-1594	Oral; tablet	0.75	mg

Ingredient	Dosage form	Quantity	Unit
Dye green LB-1616	Oral; tablet	0.94	mg
Dye green LB-279	Oral; tablet	2	mg
Dye green LB-482	Oral; tablet	1.27	mg
Dye green LB-555	Oral; tablet	0.44	mg
Dye green LB-603	Oral; tablet	0.7	mg
Dye green LB-820	Oral; tablet	0.6	mg
Dye green LB-883	Oral; tablet	0.6	mg
Dye green PB-1543	Oral; tablet	0.02	mg
Dye green PR-1333	Oral; tablet	0.0014	ml
Dye lavender lake blend LB-1603	Oral; tablet	0.66	mg
Dye lavender LB-1356	Oral; tablet	0.03	mg
Dye mint green	Oral; tablet	0.0055	mg
Dye mint green	Oral; tablet (immed./comp. release), uncoated, chewable	0.075	mg
Dye ochre 3506	Oral; tablet, coated	0.285	mg
Dye ochre 3506	Oral; tablet	0.76	mg
Dye orange 54172	Oral; tablet	6.6	mg
Dye orange lake blend 3810	Oral; tablet	0.45	mg
Dye orange lake blend LB-1439	Oral; tablet	0.22	mg
Dye orange LB-1387	Oral; tablet, sustained action	0.4	mg
Dye orange LB-1387	Oral; tablet	0.5	mg
Dye orange LB-715	Oral; tablet	4.8	mg
Dye peach LB-1576	Oral-21; tablet	0.3	mg
Dye peach LB-1576	Oral-28; tablet	0.3	mg
Dye pink	Oral; tablet	0.3	mg
Dye pink	Oral; tablet, delayed action	7.93	mg
Dye purple LB-1902	Oral; tablet, sustained action	0.8	mg
Dye purple LB-562	Oral; tablet	0.81	mg
Dye purple LB-639	Oral; tablet	0.084	mg
Dye purple LB-694	Oral; tablet	0.125	mg
Dye red #3 lake HT	Oral; tablet	0.03	mg
Dye red #33	Oral; tablet	0.292	mg
Dye red cotolene-P	Oral; tablet	20.7	mg
Dye red lake blend 6053-R	Oral; tablet	0.6	mg
Dye red PB-1595	Oral; tablet	0.8	mg
Dye salmon LB-1668	Oral; tablet	0.2	mg
Dye spectraspray blue 50726	Oral; tablet, extended release	3.66	mg
Dye tan PB-1388	Oral; tablet	0.05	mg
Dye tan PB-1388	Oral; tablet, film coated	0.75	mg
Dye turquoise LB-1430	Oral; tablet	0.035	mg
Dye white cotolene-P	Oral; tablet	10.35	mg
Dye yellow #10	Oral; tablet	1.31	mg
Dye yellow #5 lake	Oral-21; tablet	0.1	mg
Dye yellow #5 lake	Oral; tablet	0.15	mg

Ingredient	Dosage form	Quantity	Unit
Dye yellow 70362	Oral; tablet	2.8	mg
Dye yellow lake blend LB-1769	Oral; tablet	0.13	mg
Dye yellow LB 104	Oral; tablet	0.22	mg
Dye yellow LB 9706	Oral; tablet	0.44	mg
Dye yellow LB-111	Oral; tablet	0.6	mg
Dye yellow LB-1577	Oral; tablet	5	mg
Dye yellow LB-1637	Oral; tablet	0.2	mg
Dye yellow ochre	Oral; tablet	0.24	mg
Dye yellow PB1345	Oral; tablet	0.5	mg
Dye yellow PB-1381	Oral; tablet	0.2	mg
Dye yellow WD-2014	Oral; tablet	3.07	mg
Edetate calcium disodium	Oral; tablet, film coated	0.4	mg
Edetate calcium disodium	Oral; tablet, orally disintegrating	0.775	mg
Edetate calcium disodium	Oral; tablet	4	mg
Edetate disodium	Oral; tablet, coated	0.21	mg
Edetate disodium	Oral; tablet	4	mg
Edetate disodium	Oral; tablet, film coated	4	mg
Edetate disodium	Oral; tablet, extended release	5	mg
Edetate sodium	Oral; tablet	5	mg
Edetic acid	Oral; tablet, film coated	0.2	mg
Edetic acid	Oral; tablet	4	mg
Eiderdown soap	Oral; tablet, repeat action	0.39	mg
Ethyl vanillin	Oral; tablet (immed./comp. release), uncoated, chewable	0.143	mg
Ethylcellulose	Oral-28; tablet	1.05	mg
Ethylcellulose	Oral; tablet (immed./comp. release), uncoated, chewable	8.8	mg
Ethylcellulose	Oral; tablet, sustained action, coated	15.15	mg
Ethylcellulose	Oral; tablet, orally disintegrating	17.46	mg
Ethylcellulose	Oral; tablet, coated	20	mg
Ethylcellulose	Vaginal; tablet	50	mg
Ethylcellulose	Oral; tablet, sustained action, film coated	52.5	mg
Ethylcellulose	Oral; tablet, delayed action, enteric coated	53.8	mg
Ethylcellulose	Oral; tablet, extended release	80	mg
Ethylcellulose	Oral; tablet, film coated	83	mg
Ethylcellulose	Oral; tablet	120.8	mg
Ethylcellulose	Oral; tablet, sustained action	308.8	mg
Eudragit E 100	Oral; tablet	3.5	mg
Eudragit E 100	Oral; tablet, sustained action	3.96	mg
Eudragit E 100	Oral; tablet (immed./comp. release), uncoated, chewable	4.57	mg
Eudragit E 100	Oral; tablet, film coated	7.2	mg
Eudragit E 100	Oral; tablet, orally disintegrating	214.28	mg
Eudragit L 100 - 55	Oral; tablet, extended release	4.75	mg
Eudragit L 100 - 55	Oral; tablet, delayed action	15.86	mg
Eudragit L 100 - 55	Oral; tablet, delayed action, enteric coated	17	mg

Ingredient	Dosage form	Quantity	Unit
Eudragit L 30 D	Oral; tablet, repeat action	9.45	mg
Eudragit L 30 D	Oral; tablet, sustained action, coated	15.4	mg
Eudragit L 30 D	Oral; tablet, delayed action, enteric coated	25.5	mg
Eudragit L 30 D	Oral; tablet, enteric coated particles	27.9	mg
Eudragit L 30D - 55	Oral; tablet, extended release	6.86	mg
Eudragit L 30D - 55	Oral; tablet	13.56	mg
Eudragit L 30D - 55	Oral; tablet, sustained action, coated	15	mg
Eudragit L 30D - 55	Oral; tablet, delayed action, enteric coated	140	mg
Eudragit NE 30 D	Oral; tablet, sustained action	0.35	mg
Eudragit NE 30 D	Oral; tablet	6.63	mg
Eudragit NE 30 D	Oral; tablet, sustained action, coated	30	mg
Eudragit NE 30 D	Oral; tablet, extended release	54.7	mg
Eudragit NE 30 D	Oral; tablet, controlled release	56.2	mg
Eudragit NE 30 D	Oral; tablet, coated	66	mg
Eudragit NE 40 D	Oral; tablet, sustained action, film coated	10	mg
Eudragit RL 12.5	Oral; tablet, sustained action, coated	25	mg
Eudragit RS 30 D	Oral; tablet, film coated	8	mg
Eudragit RS 30 D	Oral; tablet, controlled release	14	mg
Eudragit RS 30 D	Oral; tablet (immed./comp. release), uncoated, chewable	16.67	mg
Eudragit RS 30 D	Oral; tablet	33.33	mg
Eudragit RS 30 D	Oral; tablet, sustained action	81.6	mg
Eudragit S 100	Oral; tablet	0.82	mg
FD&C blue no. 1	Oral; tablet, coated	0.0085	mg
FD&C blue no. 1	Oral; tablet, sustained action	0.03	mg
FD&C blue no. 1	Sublingual; tablet	0.03	mg
FD&C blue no. 1	Oral; tablet, film coated	0.0324	mg
FD&C blue no. 1	Oral-21; tablet	0.05	mg
FD&C blue no. 1	Oral-28; tablet	0.15	mg
FD&C blue no. 1	Oral; bar, chewable	2	mg
FD&C blue no. 1	Oral; tablet	3	mg
FD&C blue no. 1–aluminum lake	Oral; tablet, delayed action, enteric coated	0.03	mg
FD&C blue no. 1–aluminum lake	Oral-28; tablet	0.1	mg
FD&C blue no. 1–aluminum lake	Oral; tablet, coated	0.1375	mg
FD&C blue no. 1–aluminum lake	Oral; tablet (immed./comp. release), uncoated, chewable	0.18	mg
FD&C blue no. 1–aluminum lake	Oral; tablet, extended release	0.85	mg
FD&C blue no. 1–aluminum lake	Oral; tablet, controlled release	1.665	mg
FD&C blue no. 1–aluminum lake	Oral; tablet, sustained action	2	mg
FD&C blue no. 1–aluminum lake	Oral; tablet, film coated	8	mg
FD&C blue no. 1–aluminum lake	Oral; tablet	360	mg
FD&C blue no. 2	Buccal; tablet	0.008	mg
FD&C blue no. 2	Oral; tablet, delayed action, enteric coated	0.2018	mg
FD&C blue no. 2	Oral; tablet, sustained action	0.6	mg
FD&C blue no. 2	Oral; tablet, film coated	0.7	mg

Ingredient	Dosage form	Quantity	Unit
FD&C blue no. 2	Oral; tablet	21	mg
FD&C blue no. 2	Oral; tablet, coated	24.12	mg
FD&C blue no. 2–aluminum lake	Oral; tablet, orally disintegrating	0.005	mg
FD&C blue no. 2–aluminum lake	Oral; tablet, delayed action, enteric coated	0.05	mg
FD&C blue no. 2–aluminum lake	Oral-21; tablet	0.208	mg
FD&C blue no. 2–aluminum lake	Oral-28; tablet	0.25	mg
FD&C blue no. 2–aluminum lake	Oral; tablet, extended release	0.3	mg
FD&C blue no. 2–aluminum lake	Oral; tablet, controlled release	0.546	mg
FD&C blue no. 2–aluminum lake	Oral; tablet, coated	0.75	mg
FD&C blue no. 2–aluminum lake	Oral; tablet (immed./comp. release), uncoated, chewable	1.25	mg
FD&C blue no. 2–aluminum lake	Oral; tablet, film coated	1.25	mg
FD&C blue no. 2–aluminum lake	Oral; tablet	6.5	mg
FD&C blue no. 2–aluminum lake	Oral; tablet, sustained action	7	mg
FD&C green no. 1	Oral; tablet	0.124	mg
FD&C green no. 1–aluminum lake	Sublingual; tablet	0.25	mg
FD&C green no. 1–aluminum lake	Oral; tablet	4	mg
FD&C green no. 3	Oral; tablet, coated	0.005	mg
FD&C green no. 3	Oral; tablet	10	mg
FD&C orange no. 2	Oral; tablet, coated	0.07	mg
FD&C red no. 1	Oral; tablet	0.092	mg
FD&C red no. 1	Oral; tablet, coated	0.1944	mg
FD&C red no. 19	Oral; tablet	0.0032	mg
FD&C red no. 2	Oral; tablet	0.025	mg
FD&C red no. 3	Oral-21; tablet	0.0025	mg
FD&C red no. 3	Oral; tablet, film coated	0.0042	mg
FD&C red no. 3	Oral; tablet, delayed action, enteric coated	0.0048	mg
FD&C red no. 3	Oral; tablet, extended release	0.03	mg
FD&C red no. 3	Oral; tablet (immed./comp. release), uncoated, chewable	0.05	mg
FD&C red no. 3	Oral; tablet, coated	0.06	mg
FD&C red no. 3	Oral; tablet	2.2	mg
FD&C red no. 3–aluminum lake	Sublingual; tablet	0.01	mg
FD&C red no. 3–aluminum lake	Oral; tablet, sustained action	0.161	mg
FD&C red no. 3–aluminum lake	Oral; tablet, coated	0.541	mg
FD&C red no. 3–aluminum lake	Oral; tablet (immed./comp. release), uncoated, chewable	4.25	mg
FD&C red no. 3–aluminum lake	Oral; tablet	8	mg
FD&C red no. 4	Oral; tablet	0.091	mg
FD&C red no. 4	Oral; tablet, coated	0.35	mg
FD&C red no. 40	Sublingual; tablet	0.0036	mg
FD&C red no. 40	Buccal; tablet	0.006	mg
FD&C red no. 40	Oral-21; tablet	0.007	mg
FD&C red no. 40	Oral-28; tablet	0.007	mg
FD&C red no. 40	Oral; tablet, film coated	0.028	mg
FD&C red no. 40	Oral; tablet, delayed action, enteric coated	0.043	mg

Ingredient	Dosage form	Quantity	Unit
FD&C red no. 40	Oral; tablet	2	mg
FD&C red no. 40	Oral; bar, chewable	10	mg
FD&C red no. 40	Oral; tablet (immed./comp. release), uncoated, chewable	40	mg
FD&C red no. 40–aluminum lake	Sublingual; tablet	0.0005	mg
FD&C red no. 40–aluminum lake	Oral-28; tablet	0.12	mg
FD&C red no. 40–aluminum lake	Oral; tablet, extended release	0.4	mg
FD&C red no. 40–aluminum lake	Oral; tablet, sustained action	0.4	mg
FD&C red no. 40–aluminum lake	Oral; tablet, film coated	2.5	mg
FD&C red no. 40–aluminum lake	Oral; tablet (immed./comp. release), uncoated, chewable	3.5	mg
FD&C red no. 40–aluminum lake	Oral; tablet	21.25	mg
FD&C violet no. 1	Oral; tablet, coated	0.001	mg
FD&C violet no. 1	Oral; tablet	0.2	mg
FD&C yellow no. 1	Oral; tablet	0.025	mg
FD&C yellow no. 10	Oral; tablet, sustained action	0.015	mg
FD&C yellow no. 10	Oral; tablet	3.15	mg
FD&C yellow no. 3	Oral; tablet	0.2	mg
FD&C yellow no. 5	Oral-20; tablet	0.0056	mg
FD&C yellow no. 5	Oral; tablet, sustained action	0.032	mg
FD&C yellow no. 5	Buccal/sublingual; tablet	0.11	mg
FD&C yellow no. 5	Oral; tablet, sustained action, coated	0.7564	mg
FD&C yellow no. 5	Oral; tablet, film coated	1.68	mg
FD&C yellow no. 5	Oral; tablet, coated	7.93	mg
FD&C yellow no. 5	Oral; tablet	500	mg
FD&C yellow no. 5–aluminum lake	Sublingual; tablet	0.03	mg
FD&C yellow no. 5–aluminum lake	Oral; tablet, coated	0.135	mg
FD&C yellow no. 5–aluminum lake	Oral; tablet, film coated	0.6	mg
FD&C yellow no. 5–aluminum lake	Oral; tablet (immed./comp. release), uncoated, chewable	1	mg
FD&C yellow no. 5–aluminum lake	Oral; tablet	2.423	mg
FD&C yellow no. 6	Oral; tablet, delayed action, enteric coated	0.0192	mg
FD&C yellow no. 6	Oral; tablet, repeat action	0.02	mg
FD&C yellow no. 6	Oral-28; tablet	0.03	mg
FD&C yellow no. 6	Oral-21; tablet	0.14	mg
FD&C yellow no. 6	Oral; tablet (immed./comp. release), uncoated, chewable	0.3	mg
FD&C yellow no. 6	Sublingual; tablet	0.4	mg
FD&C yellow no. 6	Oral; tablet, film coated	0.9	mg
FD&C yellow no. 6	Oral; tablet, sustained action	1.06	mg
FD&C yellow no. 6	Oral; tablet, coated	3.17	mg
FD&C yellow no. 6	Oral; tablet	555	mg
FD&C yellow no. 6–aluminum lake	Oral-21; tablet	0.1	mg
FD&C yellow no. 6–aluminum lake	Oral; tablet, film coated	0.254	mg
FD&C yellow no. 6–aluminum lake	Oral; tablet, coated	0.343	mg
FD&C yellow no. 6–aluminum lake	Sublingual; tablet	0.4	mg
FD&C yellow no. 6–aluminum lake	Oral-28; tablet	0.75	mg

Ingredient	Dosage form	Quantity	Unit
FD&C yellow no. 6–aluminum lake	Buccal/sublingual; tablet	1	mg
FD&C yellow no. 6–aluminum lake	Oral; tablet, delayed action, enteric coated	1.4	mg
FD&C yellow no. 6–aluminum lake	Oral; tablet (immed./comp. release), uncoated, chewable	1.76	mg
FD&C yellow no. 6–aluminum lake	Oral; tablet, sustained action	2.8	mg
FD&C yellow no. 6–aluminum lake	Oral; tablet, extended release	3.3	mg
FD&C yellow no. 6–aluminum lake	Oral; tablet	6.97	mg
Ferric oxide	Oral; tablet, orally disintegrating	0.0125	mg
Ferric oxide	Oral; tablet (immed./comp. release), uncoated, chewable	0.1	mg
Ferric oxide	Oral; tablet, sustained action, film coated	0.112	mg
Ferric oxide	Oral; tablet, orally disintegrating, delayed release	0.15	mg
Ferric oxide	Oral; tablet, film coated	0.25	mg
Ferric oxide	Oral; tablet (immed./comp. release), film coated	0.961	mg
Ferric oxide	Oral; tablet, sustained action	1	mg
Ferric oxide	Oral; tablet	50	mg
Ferric oxide green	Oral; tablet, controlled release	1.8	mg
Ferric oxide pink	Oral; tablet, film coated	0.039	mg
Ferric oxide red	Oral-21; tablet	0.0019	mg
Ferric oxide red	Oral-21; tablet, coated	0.014	mg
Ferric oxide red	Oral-28; tablet, coated	0.014	mg
Ferric oxide red	Oral-28; tablet	0.0212	mg
Ferric oxide red	Oral; tablet, multilayer, extended release	0.11	mg
Ferric oxide red	Oral; tablet, controlled release	0.199	mg
Ferric oxide red	Buccal; tablet	0.4	mg
Ferric oxide red	Oral; tablet (immed./comp. release), film coated	0.86	mg
Ferric oxide red	Oral; tablet, extended release	1.01	mg
Ferric oxide red	Oral; tablet (immed./comp. release), uncoated, chewable	1.19	mg
Ferric oxide red	Oral; tablet, sustained action, film coated	1.8	mg
Ferric oxide red	Oral; tablet, delayed action, enteric coated	2.3	mg
Ferric oxide red	Oral; tablet, film coated	3	mg
Ferric oxide red	Oral; tablet, sustained action	3	mg
Ferric oxide red	Oral; tablet, sustained action, coated	3.6	mg
Ferric oxide red	Oral; tablet	13	mg
Ferric oxide red 30	Oral; tablet	0.4	mg
Ferric oxide red-brown	Oral; tablet, sustained action	0.04	mg
Ferric oxide red-brown	Oral; tablet	0.05	mg
Ferric oxide yellow	Oral-21; tablet, coated	0.008	mg
Ferric oxide yellow	Oral-28; tablet, coated	0.008	mg
Ferric oxide yellow	Oral-21; tablet	0.013	mg
Ferric oxide yellow	Oral-28; tablet	0.0275	mg
Ferric oxide yellow	Oral; tablet, extended release	0.03	mg
Ferric oxide yellow	Oral; tablet (immed./comp. release), film coated	0.18	mg
Ferric oxide yellow	Oral; tablet, controlled release	0.36	mg
Ferric oxide yellow	Oral; tablet, coated	0.38	mg

Ingredient	Dosage form	Quantity	Unit
Ferric oxide yellow	Oral; tablet, delayed action, enteric coated	0.43	mg
Ferric oxide yellow	Oral; tablet, orally disintegrating	0.93	mg
Ferric oxide yellow	Buccal; tablet	1	mg
Ferric oxide yellow	Oral; tablet, film coated	1.06	mg
Ferric oxide yellow	Oral; tablet, multilayer, extended release	1.96	mg
Ferric oxide yellow	Oral; tablet	2	mg
Ferric oxide yellow	Oral; tablet, sustained action	3	mg
Ferric oxide, brown	Oral; tablet	1.125	mg
Ferric oxide, hydrated	Oral; tablet, sustained action, film coated	0.0002	mg
Ferric oxide, hydrated	Oral; tablet (immed./comp. release), film coated	0.0653	mg
Ferrosoferric oxide	Oral; tablet (immed./comp. release), film coated	0.0003	mg
Ferrosoferric oxide	Oral; tablet, sustained action, film coated	0.002	mg
Ferrosoferric oxide	Oral; tablet, extended release	0.01	mg
Ferrosoferric oxide	Oral; tablet, film coated	0.2	mg
Ferrosoferric oxide	Oral; tablet, sustained action	1.23	mg
Ferrosoferric oxide	Oral; tablet	149	mg
Ferrous fumarate	Oral; tablet	75	mg
Ferrous fumarate	Oral-21; tablet	75	mg
Ferrous fumarate	Oral-28; tablet	75	mg
Film coating solution, aqueous im-163	Oral; tablet, film coated	6.3	mg
Film coating solution, aqueous im-163	Oral; tablet	20	mg
Flavor banana durarome 860.095 TD09.91	Oral; tablet (immed./comp. release), uncoated, chewable	10	mg
Flavor banana SA84	Oral; tablet	2.5	mg
Flavor butterscotch 61005-U	Oral; tablet (immed./comp. release), uncoated, chewable	12	mg
Flavor cherry 594 S.D.	Oral; tablet (immed./comp. release), uncoated, chewable	5	mg
Flavor cherry durarome 860.097 TD10.91	Oral; tablet (immed./comp. release), uncoated, chewable	45	mg
Flavor cherry FI-8568	Oral; tablet, orally disintegrating	1.63	mg
Flavor cherry NV-1489	Oral; tablet	9	mg
Flavor creme 46971	Oral; tablet (immed./comp. release), uncoated, chewable	2.5	mg
Flavor fruit 84.6422	Buccal; gum, chewing	11	mg
Flavor fruit gum 912	Oral; tablet (immed./comp. release), uncoated, chewable	25	mg
Flavor grape 054158	Oral; tablet, orally disintegrating	11.4	mg
Flavor grape 486939	Oral; tablet, film coated	1.35	mg
Flavor grape 59.145/APO5.51	Oral; tablet (immed./comp. release), uncoated, chewable	1.25	mg
Flavor haverstroo ZD 49284	Buccal; gum, chewing	11	mg
Flavor MCP lemon duramone 4409A	Oral; tablet (immed./comp. release), uncoated, chewable	44	mg
Flavor MCP lime duramone 6419	Oral; tablet (immed./comp. release), uncoated, chewable	2	mg
Flavor menthol mint PFC-9926	Oral; troche	1.2	mg
Flavor menthol veralock	Buccal; gum, chewing	3.84	mg
Flavor mint 287	Buccal; gum, chewing	25.92	mg
Flavor mint 51296 TP0551	Oral; tablet, orally disintegrating	0.15	mg
Flavor mint SN027513	Oral; tablet	1.5	mg

Ingredient	Dosage form	Quantity	Unit
Flavor mint SN027513	Oral; tablet, orally disintegrating	9.31	mg
Flavor peppermint seelock 34907	Oral; tablet (immed./comp. release), uncoated, chewable	11	mg
Flavor peppermint WL-6167	Oral; tablet	5	mg
Flavor peppermint, natural spraylene	Oral; tablet	4	mg
Flavor pharmasweet	Oral; tablet, film coated	0.225	mg
Flavor raspberry 954	Oral; tablet (immed./comp. release), uncoated, chewable	5	mg
Flavor strawberry 17.36.8509	Oral; tablet, orally disintegrating	12	mg
Flavor strawberry 17C56217	Oral; tablet, orally disintegrating	0.25	mg
Flavor strawberry guarana 586.997/AP05.51	Oral; tablet (immed./comp. release), uncoated, chewable	14.415	mg
Flavor strawberry guarana 586.997/AP05.51	Oral; tablet	20	mg
Flavor sweet 24052	Oral; tablet (immed./comp. release), uncoated, chewable	2.7	mg
Flavor sweet 604978	Oral; tablet, film coated	0.45	mg
Flavor tutti frutti 51.880/AP05.51	Oral; tablet	10	mg
Flour	Oral; tablet	1.16	mg
Flour	Oral; tablet, coated	11.25	mg
Fructose	Oral; bar, chewable	438	mg
Fumaric acid	Oral; tablet (immed./comp. release), uncoated, chewable	10	mg
Fumaric acid	Oral; tablet, extended release	10	mg
Fumaric acid	Oral; tablet	26	mg
Fumaric acid	Oral; tablet, controlled release	36.5	mg
Fumaric acid	Oral; tablet, sustained action	55.56	mg
Galactose	Oral; tablet	0.665	mg
Gelatin	Oral-21; tablet	1	mg
Gelatin	Oral-28; tablet	1	mg
Gelatin	Sublingual; tablet	1.485	mg
Gelatin	Oral; tablet, repeat action	1.608	mg
Gelatin	Oral; tablet (immed./comp. release), uncoated, chewable	2	mg
Gelatin	Oral; tablet, delayed action, enteric coated	15	mg
Gelatin	Oral; tablet, orally disintegrating	23.75	mg
Gelatin	Oral; tablet, film coated	28.35	mg
Gelatin	Oral; tablet, sustained action	40	mg
Gelatin	Oral; tablet, coated	42.12	mg
Gelatin	Oral; tablet	45.36	mg
Gelatin	Oral; pastille	143	mg
Gelatin	Oral; bar, chewable	1000	mg
Gelatin 200 bloom	Oral; tablet	18	mg
Gelatin, crosslinked	Dental; tablet	3.44	mg
Glucose, liquid	Oral; tablet, sustained action	2	mg
Glucose, liquid	Oral; tablet	10.37	mg
Glutamic acid hydrochloride	Oral; tablet	30	mg
Glycerin	Oral-21; tablet, coated	0.137	mg

Ingredient	Dosage form	Quantity	Unit
Glycerin	Oral-28; tablet, coated	0.137	mg
Glycerin	Oral-28; tablet	0.28	mg
Glycerin	Dental; tablet	0.53	mg
Glycerin	Oral; tablet, film coated	0.91	mg
Glycerin	Oral; tablet (immed./comp. release), uncoated, chewable	1	mg
Glycerin	Oral; tablet, sustained action	3.45	mg
Glycerin	Oral; tablet	16	mg
Glycerin	Buccal; gum, chewing	28.8	mg
Glycerin	Oral; bar, chewable	48	mg
Glycerin	Buccal; patch, controlled release	66	mg
Glycerin polymer solution I-137	Oral; tablet	0.5	mg
Glyceryl behenate	Oral; tablet	14	mg
Glyceryl behenate	Oral; tablet, controlled release	15.04	mg
Glyceryl behenate	Oral; tablet, extended release	33	mg
Glyceryl behenate	Oral; tablet, sustained action	50.6	mg
Glyceryl distearate	Oral; tablet, orally disintegrating	4	mg
Glyceryl oleate	Oral; tablet	0.15	mg
Glyceryl oleate	Oral-28; tablet	0.15	mg
Glyceryl palmitostearate	Oral; tablet	18	mg
Glyceryl stearate	Oral; tablet, delayed action, enteric coated	0.005	mg
Glyceryl stearate	Oral; tablet (immed./comp. release), uncoated, chewable	0.253	mg
Glyceryl stearate	Sublingual; tablet	1.231	mg
Glyceryl stearate	Oral; tablet	6	mg
Glyceryl stearate	Oral; tablet, orally disintegrating, delayed release	7.5	mg
Glyceryl stearate	Oral; tablet, sustained action	154	mg
Glyceryl stearate	Oral; tablet, sustained action, film coated	264.3	mg
Glyceryl stearate/PEG stearate	Oral; tablet	1.8	mg
Glyceryl stearate/PEG stearate	Oral; tablet, coated	1.8	mg
Glycine	Oral; tablet, orally disintegrating	12	mg
Glycine	Oral; tablet	163.31	mg
Glycine	Oral; tablet (immed./comp. release), uncoated, chewable	200	mg
Glycine hydrochloride	Oral; tablet	6	mg
Glycyrrhizin, ammoniated	Oral; tablet (immed./comp. release), uncoated, chewable	0.5	mg
Green starch blend	Oral; tablet	2	mg
Guar gum	Buccal/sublingual; tablet	1.1	mg
Guar gum	Vaginal; tablet	2.76	mg
Guar gum	Oral; tablet, sustained action	5.04	mg
Guar gum	Oral; tablet	12.9597	mg
Guar gum	Oral; tablet, film coated	35.4	mg
Guar gum	Oral; bar, chewable	40	mg
Gum base, chewing	Buccal; gum, chewing	729.6	mg
Gum rosin	Oral; tablet, repeat action	8.987	mg
Gum rosin	Oral; tablet, sustained action	9	mg

Ingredient	Dosage form	Quantity	Unit
Hydrogel polymer	Vaginal; insert, extended release	236	mg
Hydroxyethyl cellulose	Oral; tablet, extended release	10.45	mg
Hydroxyethyl cellulose	Oral; tablet (immed./comp. release), uncoated, chewable	11.8	mg
Hydroxyethyl cellulose	Oral; tablet	12	mg
Hydroxyethyl cellulose	Oral; tablet, delayed action, enteric coated	45	mg
Hydroxyethyl cellulose	Oral; tablet, sustained action, film coated	47.99	mg
Hydroxyethyl cellulose	Oral; tablet, sustained action, coated	140	mg
Hydroxyethyl cellulose	Oral; tablet, sustained action	150	mg
Hydroxyethyl cellulose 250L	Oral; tablet	2	mg
Hydroxymethyl cellulose	Oral; tablet, film coated	30	mg
Hydroxypropyl cellulose	Sublingual; tablet	1	mg
Hydroxypropyl cellulose	Oral; tablet (immed./comp. release), uncoated, chewable	2.85	mg
Hydroxypropyl cellulose	Oral; tablet, coated	8.36	mg
Hydroxypropyl cellulose	Oral; tablet, enteric coated particles	9	mg
Hydroxypropyl cellulose	Oral; tablet, orally disintegrating, delayed release	10	mg
Hydroxypropyl cellulose	Oral; tablet (immed./comp. release), film coated	12	mg
Hydroxypropyl cellulose	Oral; tablet, delayed action, enteric coated	15	mg
Hydroxypropyl cellulose	Oral; tablet, sustained action, coated	15	mg
Hydroxypropyl cellulose	Oral; tablet, extended release	16.92	mg
Hydroxypropyl cellulose	Oral; tablet, controlled release	43.8	mg
Hydroxypropyl cellulose	Oral; tablet	46	mg
Hydroxypropyl cellulose	Oral; tablet, multilayer, extended release	107	mg
Hydroxypropyl cellulose	Oral; tablet, film coated	131.67	mg
Hydroxypropyl cellulose	Oral; tablet, sustained action, film coated	187.6	mg
Hydroxypropyl cellulose	Oral; tablet, sustained action	240	mg
Hydroxypropyl cellulose LF	Oral; tablet	16	mg
Hydroxypropyl cellulose, low substituted	Oral; tablet, sustained action	11.66	mg
Hydroxypropyl cellulose, low substituted	Oral; tablet (immed./comp. release), uncoated, chewable	25	mg
Hydroxypropyl cellulose, low substituted	Oral; tablet, delayed action, enteric coated	26.3	mg
Hydroxypropyl cellulose, low substituted	Oral; tablet, film coated	40	mg
Hydroxypropyl cellulose, low substituted	Oral; tablet, orally disintegrating, delayed release	40	mg
Hydroxypropyl cellulose, low substituted	Oral; tablet, multilayer, extended release	63	mg
Hydroxypropyl cellulose, low substituted	Oral; tablet	80	mg
Hydroxypropyl ethylcellulose 250L	Oral; tablet, film coated	1	mg
Hydroxypropyl methylcellulose 2208	Oral; tablet, coated	33	mg
Hydroxypropyl methylcellulose 2208	Oral; tablet	86	mg
Hydroxypropyl methylcellulose 2208	Oral; tablet, sustained action, coated	94	mg
Hydroxypropyl methylcellulose 2208	Oral; tablet, controlled release	105	mg
Hydroxypropyl methylcellulose 2208	Oral; tablet, sustained action, film coated	200	mg
Hydroxypropyl methylcellulose 2208	Oral; tablet, extended release	320	mg
Hydroxypropyl methylcellulose 2208	Oral; tablet, sustained action	480	mg
Hydroxypropyl methylcellulose 2906	Buccal; tablet	2.25	mg
Hydroxypropyl methylcellulose 2906	Oral; tablet, extended release	17	mg

Ingredient	Dosage form	Quantity	Unit
Hydroxypropyl methylcellulose 2906	Oral; tablet	50	mg
Hydroxypropyl methylcellulose 2910	Oral-21; tablet	0.75	mg
Hydroxypropyl methylcellulose 2910	Oral-28; tablet	0.75	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet, sustained action, coated	6	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet, orally disintegrating, delayed release	7	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet (immed./comp. release), uncoated, chewable	11.8	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet (immed./comp. release), film coated	16.76	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet, delayed action, enteric coated	19	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet, controlled release	20	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet, multilayer, coated	22	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet, coated	29.25	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet	54	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet, sustained action, film coated	54	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet, film coated	60	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet, extended release	150	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet, sustained action	250	mg
Hydroxypropyl methylcellulose 2910	Oral; tablet, enteric coated particles	445	mg
Hydroxypropyl methylcellulose 4000	Oral; tablet, controlled release	31.25	mg
Hydroxypropyl methylcellulose phthalate	Oral; tablet, delayed action, enteric coated	44.57	mg
Hydroxypropyl methylcellulose phthalate	Oral; tablet	65	mg
Hydroxypropyl methylcellulose phthalate	Oral; tablet, enteric coated particles	119.4	mg
Illicium anisatum	Oral; tablet	50	mg
Ink black A-10527	Oral; tablet, repeat action	0.185	mg
Ink black SW-9007	Oral; tablet	0.09	mg
Ink black SW-9007	Oral; tablet, film coated	0.09	mg
Ink blue TEK print SB-6029	Oral; tablet, sustained action	0.2	mg
Ink edible black	Oral; tablet, coated	0.1	mg
Ink edible black	Oral-28; tablet	0.2	mg
Ink edible black	Oral; tablet, sustained action	1	mg
Ink edible white	Oral; tablet, repeat action	0.185	mg
Ink fine black 2202C	Oral; tablet	0.0011	ml
Ink green A-10454	Oral; tablet, sustained action	0.125	mg
Ink thinner	Oral; tablet, sustained action	0.018	mg
Iron subcarbonate	Oral; tablet, film coated	0.2	mg
Iron subcarbonate	Oral; tablet	0.7875	mg
Isooctyl acrylate/acrylamide/vinyl acetate copolymer, kollidon VA 64 polymer	Oral; tablet, film coated	53	mg
Isopropyl alcohol	Oral; tablet, delayed action, enteric coated	0.2	mg
Isopropyl alcohol	Oral; tablet, sustained action	0.5	ml
Isopropyl alcohol	Oral-21; tablet	2	mg
Isopropyl alcohol	Oral; tablet	5.21	mg
Kaolin	Oral; tablet, coated	8	mg
Kaolin	Oral; tablet, delayed action, enteric coated	18.5	mg

Ingredient	Dosage form	Quantity	Unit
Kaolin	Oral; tablet	30.4	mg
Kaolin	Oral; tablet, sustained action	66	mg
Karaya gum	Buccal; patch, controlled release	68.1	mg
Lactic acid	Vaginal; tablet	70	mg
Lactoferrin, bovine	Oral; tablet	28.6	mg
Lactose	Oral; tablet, sustained release, film coated	38.75	mg
Lactose	Oral; tablet, sustained action, film coated	51.1	mg
Lactose	Rectal; tablet	65.3816	mg
Lactose	Oral; tablet, controlled release	69.25	mg
Lactose	Oral-20; tablet	70.7	mg
Lactose	Oral-21; tablet	89.275	mg
Lactose	Oral; tablet, delayed action	92.02	mg
Lactose	Oral; tablet (immed./comp. release), uncoated, chewable	117.7	mg
Lactose	Oral; tablet, multilayer, extended release	122	mg
Lactose	Oral; tablet, repeat action	153.2	mg
Lactose	Oral-28; tablet	179.2	mg
Lactose	Buccal; tablet	183.3	mg
Lactose	Sublingual; tablet	191.76	mg
Lactose	Oral; tablet, delayed action, enteric coated	209	mg
Lactose	Buccal/sublingual; tablet	296.7	mg
Lactose	Oral; tablet, coated	332.05	mg
Lactose	Oral; tablet, sustained action	400	mg
Lactose	Oral; tablet, film coated	590	mg
Lactose	Vaginal; tablet	1013	mg
Lactose	Oral; tablet	1020	mg
Lactose monohydrate	Vaginal; tablet, film coated	17.9	mg
Lactose monohydrate	Buccal; tablet	21.375	mg
Lactose monohydrate	Oral; tablet, multilayer, coated	22.7	mg
Lactose monohydrate	Oral; tablet, repeat action	25	mg
Lactose monohydrate	Oral; tablet, orally disintegrating	29.75	mg
Lactose monohydrate	Sublingual; tablet	33.874	mg
Lactose monohydrate	Oral-21; tablet, coated	35.19	mg
Lactose monohydrate	Oral; tablet, delayed action	50	mg
Lactose monohydrate	Oral; tablet (immed./comp. release), uncoated, chewable	62.3	mg
Lactose monohydrate	Oral; tablet, sustained release, film coated	81.9	mg
Lactose monohydrate	Oral-28; tablet, coated	82.89	mg
Lactose monohydrate	Oral-21; tablet	83.645	mg
Lactose monohydrate	Oral-28; tablet	93.865	mg
Lactose monohydrate	Oral; tablet, controlled release	138.913	mg
Lactose monohydrate	Oral; tablet, enteric coated particles	150	mg
Lactose monohydrate	Oral; tablet, delayed action, enteric coated	157.95	mg
Lactose monohydrate	Oral; tablet (immed./comp. release), film coated	182.6	mg
Lactose monohydrate	Oral; tablet, sustained action, coated	215	mg

Ingredient	Dosage form	Quantity	Unit
Lactose monohydrate	Oral; tablet, extended release	258.25	mg
Lactose monohydrate	Oral; tablet, sustained action, film coated	260	mg
Lactose monohydrate	Oral; tablet, sustained action	299.2	mg
Lactose monohydrate	Oral; tablet, coated	346.5	mg
Lactose monohydrate	Oral; tablet, sustained action, multilayer, film coated	374.5	mg
Lactose monohydrate	Oral; tablet, film coated	587.44	mg
Lactose monohydrate	Vaginal; insert	760.5	mg
Lactose monohydrate	Oral; tablet	889.42	mg
Lactose monohydrate - cellulose, microcrystalline	Oral; tablet	211.26	mg
Lactose, anhydrous	Buccal; tablet	23.75	mg
Lactose, anhydrous	Oral; tablet, controlled release	29.99	mg
Lactose, anhydrous	Oral-21; tablet, coated	58	mg
Lactose, anhydrous	Oral-28; tablet, coated	58	mg
Lactose, anhydrous	Oral; tablet, coated	69.94	mg
Lactose, anhydrous	Oral-21; tablet	75.687	mg
Lactose, anhydrous	Oral-28; tablet	79.335	mg
Lactose, anhydrous	Oral; tablet, delayed action, enteric coated	90	mg
Lactose, anhydrous	Oral; tablet (immed./comp. release), uncoated, chewable	108	mg
Lactose, anhydrous	Sublingual; tablet	128	mg
Lactose, anhydrous	Oral; tablet, sustained action, coated	130.7	mg
Lactose, anhydrous	Oral; tablet, sustained action, film coated	157.95	mg
Lactose, anhydrous	Oral; tablet, sustained action	180.9	mg
Lactose, anhydrous	Oral; tablet, film coated	453.6	mg
Lactose, anhydrous	Vaginal; tablet	605	mg
Lactose, anhydrous	Oral; tablet	613.6	mg
Lactose, hydrous	Oral-28; tablet	39.62	mg
Lactose, hydrous	Oral; tablet, extended release	43.23	mg
Lactose, hydrous	Oral-21; tablet	48	mg
Lactose, hydrous	Oral; tablet, sustained action, coated	83.3	mg
Lactose, hydrous	Oral; tablet, delayed action, enteric coated	88.5	mg
Lactose, hydrous	Oral; tablet (immed./comp. release), uncoated, chewable	100	mg
Lactose, hydrous	Oral; tablet, repeat action	155.28	mg
Lactose, hydrous	Oral; tablet, sustained action	156.8	mg
Lactose, hydrous	Sublingual; tablet	164.38	mg
Lactose, hydrous	Oral; tablet, coated	186	mg
Lactose, hydrous	Oral; tablet, film coated	556	mg
Lactose, hydrous	Vaginal; tablet	596	mg
Lactose, hydrous	Oral; tablet	708.9	mg
Landalgene	Oral; tablet, coated	5	mg
Landalgine P	Oral; tablet, coated	5	mg
Lecithin	Oral; bar, chewable	54	mg
Lecithin, egg	Oral; tablet	48	mg
Lemon oil	Oral; tablet	0.0007	ml

Ingredient	Dosage form	Quantity	Unit
Leucine	Oral; tablet	3.6	mg
Levomenthol	Buccal; inhalation	0.1	%
Levomenthol	Buccal; gum, chewing	3.84	mg
Light mineral oil	Oral; tablet, sustained action	0.2	mg
Light mineral oil	Oral; tablet, film coated	2.494	mg
Light mineral oil	Oral; pastille	3.6	mg
Light mineral oil	Oral; tablet, coated	4.8	mg
Light mineral oil	Oral; tablet	1474	mg
Locust bean gum	Oral; bar, chewable	40	mg
Locust bean gum	Oral; tablet, sustained action, coated	74.25	mg
Lubritab	Oral; tablet	10	mg
Lubritab	Oral; tablet, sustained action	35	mg
Magnasweet 100	Oral; tablet	0.75	mg
Magnasweet 135	Oral; tablet (immed./comp. release), uncoated, chewable	11.5	mg
Magnesium aluminum silicate	Oral; tablet (immed./comp. release), uncoated, chewable	8	mg
Magnesium aluminum silicate	Oral; tablet	24	mg
Magnesium aluminum silicate hydrate	Oral; tablet (immed./comp. release), uncoated, chewable	12	mg
Magnesium aluminum silicate hydrate	Oral; tablet	60	mg
Magnesium aspartate	Oral; tablet	1.5	mg
Magnesium carbonate	Oral; tablet, coated	1.157	mg
Magnesium carbonate	Oral; tablet, orally disintegrating, delayed release	10	mg
Magnesium carbonate	Oral; tablet (immed./comp. release), uncoated, chewable	100	mg
Magnesium carbonate	Oral; tablet	175	mg
Magnesium carbonate	Oral; tablet, delayed action, enteric coated	250	mg
Magnesium carbonate	Oral; tablet, film coated	250	mg
Magnesium hydroxide	Oral; tablet	40	mg
Magnesium hydroxide	Oral; tablet, film coated	43.4	mg
Magnesium hydroxide	Oral; tablet, delayed action, enteric coated	60	mg
Magnesium hydroxide	Oral; tablet (immed./comp. release), uncoated, chewable	450	mg
Magnesium oxide	Buccal; gum, chewing	7.2	mg
Magnesium oxide	Oral; tablet, sustained action	25.74	mg
Magnesium oxide	Oral; tablet	26.4	mg
Magnesium oxide	Oral; tablet, film coated	40	mg
Magnesium oxide	Oral; tablet, delayed action, enteric coated	63	mg
Magnesium phosphate	Oral; tablet	0.85	mg
Magnesium silicate	Oral; tablet	10	mg
Magnesium silicate	Oral; tablet, film coated	14.3	mg
Magnesium silicate	Oral; tablet, coated	29.03	mg
Magnesium silicate	Oral; tablet, enteric coated particles	30	mg
Magnesium stearate	Vaginal; tablet, film coated	0.4	mg
Magnesium stearate	Oral-21; tablet, coated	0.88	mg
Magnesium stearate	Oral-28; tablet, coated	0.88	mg
Magnesium stearate	Oral; tablet, multilayer, extended release	1.2	mg

Ingredient	Dosage form	Quantity	Unit
Magnesium stearate	Oral; tablet, repeat action	1.5	mg
Magnesium stearate	Oral-20; tablet	1.5	mg
Magnesium stearate	Oral-21; tablet	1.5	mg
Magnesium stearate	Oral; tablet, delayed action	3	mg
Magnesium stearate	Oral; tablet, multilayer, coated	3	mg
Magnesium stearate	Sublingual; tablet	3	mg
Magnesium stearate	Buccal; tablet	4	mg
Magnesium stearate	Oral; tablet, orally disintegrating, delayed release	6	mg
Magnesium stearate	Oral; tablet, enteric coated particles	7	mg
Magnesium stearate	Oral; tablet, controlled release	7.2	mg
Magnesium stearate	Oral; tablet, uncoated, troche	9	mg
Magnesium stearate	Oral; tablet (immed./comp. release), film coated	10	mg
Magnesium stearate	Oral; tablet, sustained action, coated	10	mg
Magnesium stearate	Oral; tablet, extended release	15	mg
Magnesium stearate	Oral; tablet, sustained action, film coated	15.8	mg
Magnesium stearate	Vaginal; tablet	17	mg
Magnesium stearate	Buccal/sublingual; tablet	17.5	mg
Magnesium stearate	Oral; troche	21	mg
Magnesium stearate	Vaginal; insert	23	mg
Magnesium stearate	Oral; tablet, film coated	28.31	mg
Magnesium stearate	Oral; tablet, coated	40	mg
Magnesium stearate	Oral; tablet (immed./comp. release), uncoated, chewable	50	mg
Magnesium stearate	Oral; tablet, delayed action, enteric coated	53.8	mg
Magnesium stearate	Oral; tablet, orally disintegrating	71.43	mg
Magnesium stearate	Oral-28; tablet	75	mg
Magnesium stearate	Oral; tablet, sustained action	150	mg
Magnesium stearate	Oral; tablet	400.748	mg
Magnesium sulfate	Oral; tablet	2.9	mg
Magnesium sulfate	Oral; tablet, extended release	4	mg
Magnesium sulfate	Oral; tablet, film coated	14	mg
Magnesium tartrate	Oral; tablet	3.24	mg
Magnesium trisilicate	Oral; tablet (immed./comp. release), uncoated, chewable	15	mg
Magnesium trisilicate	Oral; tablet, coated	20	mg
Magnesium trisilicate	Oral; tablet	76.89	mg
Maleic acid	Oral; tablet	4	mg
Maltodextrin	Oral-28; tablet	0.158	mg
Maltodextrin	Oral; tablet, coated	5.6	mg
Maltodextrin	Oral; tablet, sustained action	72.5	mg
Maltodextrin	Oral; tablet	80	mg
Maltodextrin	Oral; tablet, extended release	150	mg
Maltodextrin	Oral; tablet (immed./comp. release), uncoated, chewable	292	mg
Maltose	Oral; tablet	473	mg
Mannitol	Oral; tablet, delayed action, enteric coated	42.7	mg

Ingredient	Dosage form	Quantity	Unit
Mannitol	Oral; tablet (immed./comp. release), film coated	48.88	mg
Mannitol	Buccal/sublingual; tablet	52.5	mg
Mannitol	Oral; tablet, dispersible	90	mg
Mannitol	Buccal; tablet	97.685	mg
Mannitol	Sublingual; tablet	158.45	mg
Mannitol	Oral; tablet, coated	177.7	mg
Mannitol	Oral; tablet, orally disintegrating, delayed release	221	mg
Mannitol	Oral; tablet, film coated	241.21	mg
Mannitol	Oral; tablet, sustained action, film coated	274.972	mg
Mannitol	Oral; tablet, sustained action	392.2	mg
Mannitol	Oral; tablet	454.2	mg
Mannitol	Oral; tablet (immed./comp. release), uncoated, chewable	600	mg
Mannitol	Oral; tablet, orally disintegrating	606.72	mg
Mannitol	Oral; troche	1035.175	mg
Mannitol 2080	Oral; tablet (immed./comp. release), film coated	32.58	mg
Mannitol 60	Oral; tablet, orally disintegrating	174.78	mg
Mannitol M300	Oral; tablet, orally disintegrating	174.76	mg
Mannose, D-	Oral; tablet	1.197	mg
Medical antifoam emulsion C	Oral; tablet	1	mg
Meglumine	Oral; tablet	24	mg
Melojel	Oral; tablet	35	mg
Menthol	Oral; tablet	0.58	mg
Menthol	Buccal; gum, chewing	10	mg
Methacrylic acid copolymer	Oral; tablet	5.8	mg
Methacrylic acid copolymer	Oral; tablet, sustained action, coated	24.6	mg
Methacrylic acid copolymer	Oral; tablet, sustained action	35	mg
Methacrylic acid copolymer	Oral; tablet, delayed action, enteric coated	54	mg
Methacrylic acid copolymer	Oral; tablet, delayed action	58.362	mg
Methacrylic acid copolymer	Oral; tablet, orally disintegrating, delayed release	106.89	mg
Methacrylic acid copolymer type A	Oral; tablet, sustained action	6	mg
Methacrylic acid copolymer type A	Oral; tablet, sustained action, coated	10.5	mg
Methacrylic acid copolymer type A	Oral; tablet, film coated	16	mg
Methacrylic acid copolymer type B	Oral; tablet	0.83	mg
Methacrylic acid copolymer type B	Oral; tablet, sustained action	5.6	mg
Methacrylic acid copolymer type B	Oral; tablet, sustained action, coated	10.5	mg
Methacrylic acid copolymer type B	Oral; tablet, film coated	16	mg
Methacrylic acid copolymer type C	Oral; tablet, sustained action	7.2	mg
Methacrylic acid copolymer type C	Oral; tablet	7.8	mg
Methacrylic acid copolymer type C	Oral; tablet, extended release	66.7	mg
Methyl alcohol	Oral; tablet, film coated	10.36	mg
Methyl alcohol	Oral; tablet, coated	15.7	mg
Methyl alcohol	Oral; tablet	210	mg
Methyl chloride	Oral; tablet	69.82	mg

Ingredient	Dosage form	Quantity	Unit
Methyl ethyl ketone	Oral; tablet, delayed action, enteric coated	61	mg
Methyl hydroxyethyl cellulose	Oral; tablet	24	mg
Methylcellulose	Buccal/sublingual; tablet	4	mg
Methylcellulose	Oral-28; tablet	15	mg
Methylcellulose	Oral; tablet, film coated	21	mg
Methylcellulose	Oral; tablet (immed./comp. release), uncoated, chewable	50	mg
Methylcellulose	Oral; tablet, sustained action	96	mg
Methylcellulose	Oral; tablet, coated	138.3	mg
Methylcellulose	Oral; tablet	183.6	mg
Methylcellulose 1500	Oral; tablet	2.75	mg
Methylcellulose 400	Oral; tablet	33	mg
Methylene chloride	Oral; tablet, film coated	103.6	mg
Methylene chloride	Oral; tablet, coated	157	mg
Methylene chloride	Oral; tablet	209	mg
Methylparaben	Oral; tablet, coated	0.016	mg
Methylparaben	Oral; tablet, controlled release	0.0814	mg
Methylparaben	Oral; tablet, sustained action, multilayer, film coated	0.09	mg
Methylparaben	Oral; tablet, sustained action	0.17	mg
Methylparaben	Oral; tablet, film coated	0.23	mg
Methylparaben	Oral; tablet (immed./comp. release), uncoated, chewable	1.27	mg
Methylparaben	Oral; tablet	1.8	mg
Methylparaben sodium	Oral; tablet	0.1875	mg
Methylparaben sodium	Oral; tablet, orally disintegrating	0.3	mg
Mineral oil	Oral; tablet, coated	1.3	mg
Mineral oil	Oral; tablet, delayed action, enteric coated	5.67	mg
Mineral oil	Oral; tablet	50	mg
Monoglycerides	Oral; tablet	33.33	mg
Monosodium citrate	Oral; tablet	50	mg
Montan wax	Oral; tablet, film coated	0.03	mg
Montan wax	Oral-21; tablet	0.03	mg
Montan wax	Oral-21; tablet, coated	0.05	mg
Montan wax	Oral-28; tablet	0.05	mg
Montan wax	Oral-28; tablet, coated	0.05	mg
Montan wax	Oral; tablet	0.06	mg
Myristyl alcohol	Oral; tablet, sustained action	2	mg
Naphtha	Oral; tablet	0.9934	mg
Nonpareil seeds	Oral; tablet, sustained action	157.5	mg
Nonpareil seeds	Oral; tablet	166.36	mg
N-propyl orthosilicate	Vaginal; intrauterine device	0.7	mg
Oleic acid	Oral; tablet, coated	0.72	mg
Oleic acid	Oral; tablet, repeat action	1.854	mg
Oleic acid	Oral; tablet, sustained action	2	mg
Opacoat NA7013 clear	Oral; tablet, sustained action	4	mg

Ingredient	Dosage form	Quantity	Unit
Opacode NS-78-10013-N	Oral; tablet	0.03	mg
Opacode NS-78-8000 black	Oral; tablet, coated	0.1	mg
Opacode NS-78-8000 black	Oral; tablet, film coated	0.1	mg
Opacode NS-78-8000 black	Oral; tablet, sustained action	0.2	mg
Opacode NS-78-8000 black	Oral; tablet	0.3	mg
Opacode S-1-13001 orange	Oral; tablet	0.03	mg
Opacode S-1-15038 red	Oral; tablet	0.2	mg
Opacode S-1-26514 brown	Oral; tablet, delayed action, enteric coated	0.06	mg
Opacode S-1-4172 blue	Oral; tablet, film coated	1	mg
Opacode S-1-4172M blue	Oral; tablet, film coated	1	mg
Opacode S-1-8090 black	Oral; tablet	0.6	mg
Opacode S-1-8090 black	Oral; tablet, film coated	0.7	mg
Opacode S-1-8090 black	Oral; tablet, coated	2.4	mg
Opacode S-1-8095	Oral; tablet, film coated	0.7	mg
Opacode S-1-8100-HV black	Oral; tablet, sugar coated	0.09	mg
Opacode S-1-8100-HV black	Oral; tablet	0.5	mg
Opacode WB NS-78-10521 blue	Oral; tablet	0.09	mg
Opacode WB NS-78-17715 black	Oral; tablet	0.09	mg
Opacode WB NS-78-18001 white	Oral; tablet, coated	0.2	mg
Opadry 00A28646	Oral; tablet, film coated	3.4	mg
Opadry 02B14941 pink	Oral; tablet	6	mg
Opadry 02B22429 yellow	Oral; tablet	30	mg
Opadry 02B94016 pink	Oral; tablet	1.75	mg
Opadry 02G22555 yellow	Oral; tablet, film coated	5	mg
Opadry 02G24523 pink	Oral; tablet, film coated	8	mg
Opadry 02G26637 brown	Oral; tablet, film coated	8	mg
Opadry 02G28619 white	Oral; tablet, film coated	2.5	mg
Opadry 02-H-22703 yellow	Oral; tablet, sustained action	9	mg
Opadry 03A 58900 white	Oral; tablet	4.46	mg
Opadry 03A14309 pink	Oral; tablet	11.9	mg
Opadry 03B11434 green	Oral; tablet	32.38	mg
Opadry 03B12878 yellow	Oral; tablet, extended release	12	mg
Opadry 03B12896 yellow	Oral; tablet	24	mg
Opadry 03B12914 yellow	Oral; tablet, film coated	2.38	mg
Opadry 03B14424 pink	Oral; tablet, extended release	15	mg
Opadry 03B14436 pink	Oral; tablet	8	mg
Opadry 03B16083 maroon	Oral; tablet, coated	5	mg
Opadry 03B17426 beige	Oral; tablet, extended release	18	mg
Opadry 03B17495 beige	Oral; tablet	8	mg
Opadry 03B22426 yellow	Oral; tablet	15	mg
Opadry 03B24562 peach	Oral; tablet, film coated	18	mg
Opadry 03B50899 blue	Oral; tablet, film coated	5.97	mg
Opadry 03B54504 pink	Oral; tablet, film coated	27	mg

Ingredient	Dosage form	Quantity	Unit
Opadry 03B54573 pink	Oral; tablet	4	mg
Opadry 03B54588 pink	Oral; tablet	2	mg
Opadry 03B54955 pink	Oral; tablet	18.5	mg
Opadry 03B56518 brown	Oral; tablet	3	mg
Opadry 03B57631 grey	Oral; tablet, film coated	2.99	mg
Opadry 03B58902 white	Oral; tablet	10.5	mg
Opadry 03B58930 white	Oral; tablet	13.4	mg
Opadry 03B58965 white	Oral; tablet	24.05	mg
Opadry 03B86636 brown	Oral; tablet, delayed action	9	mg
Opadry 03F12967 yellow	Oral; tablet, film coated	4	mg
Opadry 03F13325 orange	Oral; tablet	12	mg
Opadry 03F14895 pink	Oral; tablet, film coated	4	mg
Opadry 03F54568 pink	Oral; tablet	7	mg
Opadry 03J18312 white	Oral; tablet	30	mg
Opadry 03K14881 pink	Oral; tablet	34.2	mg
Opadry 03K50891 blue	Oral; tablet	3.75	mg
Opadry 03K51211 green	Oral; tablet	2.25	mg
Opadry 03K52543 yellow	Oral; tablet	5	mg
Opadry 03K54121 pink	Oral; tablet	10	mg
Opadry 04F50702 blue	Oral; tablet	5	mg
Opadry 04F58804 white	Oral; tablet	10	mg
Opadry 05B10446 purple	Oral; tablet	16	mg
Opadry 05B10446 purple	Oral; tablet, coated	23	mg
Opadry 05B10457 purple	Oral; tablet	16	mg
Opadry 05B11552 green	Oral; tablet, sustained action	3.642	mg
Opadry 05B11781 green	Oral; tablet	7	mg
Opadry 05B12337 yellow	Oral; tablet	8.5	mg
Opadry 05B15325 red	Oral; tablet	5	mg
Opadry 05B17055 tan	Oral; tablet	4	mg
Opadry 05B17055 tan	Oral; tablet, film coated	5	mg
Opadry 12B58900 white	Oral; tablet	20	mg
Opadry 12F20984 blue	Oral; tablet, film coated	4	mg
Opadry 12F21129 green	Oral; tablet, film coated	2	mg
Opadry 12F22609 yellow	Oral; tablet, film coated	8	mg
Opadry 13B50780 blue	Oral; tablet	4.5	mg
Opadry 13B51260 green	Oral; tablet	2.25	mg
Opadry 13B52329 yellow	Oral; tablet	9	mg
Opadry 13B58802 white	Oral; tablet	9.6	mg
Opadry 15B11947 green	Oral; tablet	2.5	mg
Opadry 15B13335 orange	Oral; tablet, extended release	20	mg
Opadry 15B20780 blue	Oral; tablet	9	mg
Opadry 15B21340 green	Oral; tablet	12	mg
Opadry 15B22275 yellow	Oral; tablet	3	mg

Ingredient	Dosage form	Quantity	Unit
Opadry 15B24473 pink	Oral; tablet	6	mg
Opadry 15B24879 pink	Oral; tablet, film coated	4	mg
Opadry 15B28665 white	Oral; tablet, film coated	8	mg
Opadry 15B53449 orange	Oral; tablet	12.5	mg
Opadry 16B38982 white	Oral; tablet	2	mg
Opadry 16B5900 yellow	Oral; tablet, film coated	7.5	mg
Opadry 20014832 pink	Oral; tablet, film coated	3.745	mg
Opadry 20A52229 yellow	Oral; tablet	5.6	mg
Opadry 20A52560 yellow	Oral; tablet, film coated	4.5	mg
Opadry 20A52900 yellow	Oral; tablet	2.5	mg
Opadry 20A54211 pink	Oral; tablet	22.4	mg
Opadry 20A54239 pink	Oral; tablet	2.8	mg
Opadry 20A54614 pink	Oral; tablet, film coated	16	mg
Opadry 20A54616 pink	Oral; tablet, film coated	2	mg
Opadry 20A54900 pink	Oral; tablet	2.5	mg
Opadry 20A54901 pink	Oral; tablet	20	mg
Opadry 20A56500 brown	Oral; tablet	5	mg
Opadry 20A56694 brown	Oral; tablet, film coated	4	mg
Opadry 20A56788 brown	Oral; tablet, film coated	9	mg
Opadry 20A58806 white	Oral; tablet, film coated	13.5	mg
Opadry 20A58916 white	Oral; tablet, film coated	13.5	mg
Opadry 20A59015 clear	Oral; tablet, film coated	30	mg
Opadry 20B11521 green	Oral; tablet, film coated	28	mg
Opadry 20B17583 gray	Oral; tablet, film coated	21	mg
Opadry 20B97160 beige	Oral; tablet, film coated	12	mg
Opadry 20C15347 red	Oral; tablet, film coated	22	mg
Opadry 20H58983 white	Oral; tablet	8.7	mg
Opadry 31F20963 blue	Oral; tablet, sustained action	23	mg
Opadry 31F32870 yellow	Oral; tablet, sustained action, film coated	21	mg
Opadry 32K14834 pink	Oral; tablet, film coated	16.8	mg
Opadry 32K23123 orange	Oral; tablet, sustained action	7	mg
Opadry 33G12976 yellow	Oral; tablet, film coated	4.5	mg
Opadry 33G25171 brick red	Oral; tablet, film coated	28	mg
Opadry 40L14278 pink	Oral; tablet, film coated	33.6	mg
Opadry 80W 12319 yellow	Oral; tablet	9.7	mg
Opadry 80W22657 AMB yellow	Oral; tablet	7.5	mg
Opadry 80W-93032 AMB orange	Oral; tablet, film coated	9.967	mg
Opadry 85F14999 pink	Oral; tablet	8	mg
Opadry 85G93096 orange	Oral; tablet	4.53	mg
Opadry AMB 80W52110 yellow	Oral; tablet	16	mg
Opadry I 03B22409 yellow	Oral; tablet, multilayer, coated	17	mg
Opadry I 03B23197 orange	Oral; tablet, multilayer, coated	18	mg
Opadry I 03B24658 pink	Oral; tablet, multilayer, coated	17	mg

Ingredient	Dosage form	Quantity	Unit
Opadry II 03B10903 blue	Oral; tablet, sustained action	20.82	mg
Opadry II 31F22071 yellow	Oral; tablet, delayed action, enteric coated	2	mg
Opadry II 31F22088 yellow	Oral; tablet	6	mg
Opadry II 31F23111 orange	Oral; tablet, sustained action	16	mg
Opadry II 31F24239 pink	Oral; tablet	20	mg
Opadry II 31F27625 gray	Oral; tablet, sustained action	19	mg
Opadry II 31F32090 yellow	Oral; tablet	1	mg
Opadry II 31F58914 white	Oral; tablet	3	mg
Opadry II 31K52633 yellow	Oral; tablet	6	mg
Opadry II 32B10817 blue	Oral; tablet	6	mg
Opadry II 32K10054 purple	Oral; tablet	13.1	mg
Opadry II 32K12160 yellow	Oral; tablet, film coated	32.28	mg
Opadry II 32K12884 yellow	Oral; tablet	14	mg
Opadry II 32K12942 yellow	Oral; tablet	38.85	mg
Opadry II 32K12968 yellow	Oral; tablet, controlled release	8.88	mg
Opadry II 32K13357 orange	Oral-21; tablet	5	mg
Opadry II 32K13357 orange	Oral-28; tablet	5	mg
Opadry II 32K13699 orange	Oral; tablet, film coated	9	mg
Opadry II 32K14826 pink	Oral; tablet	7.2	mg
Opadry II 32K14833 pink	Oral; tablet, film coated	5	mg
Opadry II 32K14833 pink	Oral; tablet	21	mg
Opadry II 32K16706 brown	Oral; tablet, film coated	14	mg
Opadry II 32K17089 tan	Oral; tablet	3.75	mg
Opadry II 32K17573 gray	Oral; tablet	7.5	mg
Opadry II 33G10907 blue	Oral; tablet	4.5	mg
Opadry II 33G11635 green	Oral; tablet, sustained action	11.2	mg
Opadry II 33G28707 white	Oral; tablet	31.25	mg
Opadry II 40 L14235 pink	Oral; tablet, sustained action, film coated	22	mg
Opadry II 40 L17589 gray	Oral; tablet, sustained action	26	mg
Opadry II 40014876 pink	Oral; tablet, film coated	4.93	mg
Opadry II 40B12994 beige	Oral; tablet	10	mg
Opadry II 40B97172 yellow	Oral; tablet	5	mg
Opadry II 40C10881 blue	Oral; tablet, film coated	6	mg
Opadry II 40C13396 orange	Oral; tablet, film coated	6	mg
Opadry II 40C18303 white	Oral; tablet, film coated	6	mg
Opadry II 40L10412 purple	Oral; tablet, sustained action	5.25	mg
Opadry II 40L10884 blue	Oral; tablet, film coated	18	mg
Opadry II 40L11438 green	Oral; tablet, sustained action	-40	mg
Opadry II 40L11588 green	Oral; tablet, sustained action, film coated	22	mg
Opadry II 40L11588 green	Oral; tablet	26.25	mg
Opadry II 40L12917 yellow	Oral; tablet, film coated	18	mg
Opadry II 40L12979 yellow	Oral; tablet, sustained action, coated	30	mg
Opadry II 40L13950 orange	Oral; tablet	9	mg

Ingredient	Dosage form	Quantity	Unit
Opadry II 40L14190 pink	Oral; tablet	24.5	mg
Opadry II 40L14336 pink	Oral; tablet	9	mg
Opadry II 40L14836 pink	Oral; tablet, film coated	4.75	mg
Opadry II 40L17427 beige	Oral; tablet	9	mg
Opadry II 40L17587 gray	Oral; tablet	6.2	mg
Opadry II 40L92058 yellow	Oral; tablet, sustained action, film coated	12.9	mg
Opadry II 40093122 orange	Oral; tablet	9	mg
Opadry II 49B10882 blue	Oral; tablet	26.9	mg
Opadry II 49B13460 orange	Oral; tablet	19	mg
Opadry II 49B16716 brown	Oral; tablet	9.57	mg
Opadry II 85F10919 blue	Oral; tablet	24	mg
Opadry II 85F12345 yellow	Oral; tablet	6	mg
Opadry II 85F12372 yellow	Oral; tablet	4.5	mg
Opadry II 85F13980 orange	Oral; tablet	4.5	mg
Opadry II 85F16876 brown	Oral; tablet	24	mg
Opadry II 85F18378 white	Oral; tablet	40	mg
Opadry II 85F18422 white	Oral; tablet	35.4	mg
Opadry II 85F22055 yellow	Oral; tablet	10	mg
Opadry II 85F23470 pink	Oral; tablet	7.5	mg
Opadry II 85F24033 pink	Oral; tablet	7.5	mg
Opadry II 85F24307 pink	Oral; tablet	35	mg
Opadry II 85F28751 white	Oral; tablet	24	mg
Opadry II 85F288751 white	Oral; tablet	30	mg
Opadry II 85F94172 pink	Oral; tablet	46.5	mg
Opadry II 85G20583 blue	Oral; tablet	48	mg
Opadry II OY-L-22903	Oral; tablet, film coated	6	mg
Opadry II OY-L-23028 orange	Oral; tablet, film coated	4.5	mg
Opadry II OY-L-24802 pink	Oral; tablet, film coated	4.5	mg
Opadry II OY-L-24803 pink	Oral; tablet, film coated	9	mg
Opadry II OY-L-24808	Oral; tablet, film coated	12	mg
Opadry II OY-L-32920	Oral; tablet, film coated	12	mg
Opadry II pink 85G94027	Oral; tablet	16.2	mg
Opadry II pink 85G94065	Oral; tablet (immed./comp. release), film coated	7	mg
Opadry II red 85G94101	Oral; tablet (immed./comp. release), film coated	7	mg
Opadry II Y-19-7483 clear	Oral; tablet	5.6	mg
Opadry II Y-19-7483 clear	Oral; tablet, sustained action, coated	9.8	mg
Opadry II Y-19-7483 clear	Oral; tablet, film coated	34	mg
Opadry II Y-19-7483 clear	Oral; tablet, sustained action	35	mg
Opadry II Y-22-10274 lavender	Oral; tablet, film coated	8	mg
Opadry II Y-22-10274 lavender	Oral; tablet, sustained action	14.95	mg
Opadry II Y-22-10508 blue	Oral; tablet	14.83	mg
Opadry II Y-22-10519 blue	Oral; tablet	29.66	mg
Opadry II Y-22-10538 blue	Oral; tablet	90	mg

Ingredient	Dosage form	Quantity	Unit
Opadry II Y-22-10702 blue	Oral; tablet, sustained action	5.25	mg
Opadry II Y-22-10702 blue	Oral; tablet	6.2	mg
Opadry II Y-22-10764 blue	Oral; tablet	15	mg
Opadry II Y-22-11184 green	Oral; tablet	8	mg
Opadry II Y-22-11210 green	Oral; tablet	3	mg
Opadry II Y-22-11251 green	Oral; tablet	2	mg
Opadry II Y-22-12098 yellow	Oral; tablet	9	mg
Opadry II Y-22-12664 yellow	Oral; tablet, delayed action, enteric coated	12	mg
Opadry II Y-22-12664 yellow	Oral; tablet	86.4	mg
Opadry II Y-22-12718 yellow	Oral; tablet, sustained action	15	mg
Opadry II Y2212720 pale yellow	Oral; tablet, film coated	2.375	mg
Opadry II Y-22-12780 yellow	Oral; tablet, film coated	10.85	mg
Opadry II Y-22-13034 orange	Oral; tablet	4.2	mg
Opadry II Y-22-13061 orange	Oral; tablet, sustained action	-40	mg
Opadry II Y-22-13061 orange	Oral; tablet, film coated	6.5	mg
Opadry II Y-22-13061 orange	Oral; tablet, coated	13	mg
Opadry II Y-22-13061 orange	Oral; tablet	24	mg
Opadry II Y-22-13083 orange	Oral; tablet	15	mg
Opadry II Y-22-13089 orange	Oral; tablet	4.9	mg
Opadry II Y-22-13167 orange	Oral; tablet, controlled release	6	mg
Opadry II Y-22-13167 orange	Oral; tablet, sustained action, film coated	17.19	mg
Opadry II Y-22-13167 orange	Oral; tablet	25	mg
Opadry II Y-22-13577 flesh	Oral; tablet	4	mg
Opadry II Y-22-13577 flesh	Oral; tablet, film coated	9.3	mg
Opadry II Y-22-13577 flesh	Oral; tablet, sustained action	15	mg
Opadry II Y-22-13603 orange	Oral; tablet	67.5	mg
Opadry II Y-22-13663 orange	Oral; tablet, sustained action	5.25	mg
Opadry II Y-22-14001 pink	Oral; tablet	6	mg
Opadry II Y2214701 pink	Oral; tablet, film coated	19	mg
Opadry II Y-22-15061	Oral; tablet, sustained action, coated	17.1	mg
Opadry II Y-22-16562 brown	Oral; tablet	15	mg
Opadry II Y-22-16577 brown	Oral; tablet, sustained action, coated	12	mg
Opadry II Y-22-17025 beige	Oral; tablet, film coated	15	mg
Opadry II Y-22-17165 beige	Oral; tablet	20	mg
Opadry II Y-22-17221 beige	Oral; tablet, film coated	12	mg
Opadry II Y2217279 beige	Oral; tablet, film coated	9.5	mg
Opadry II Y-22-17515 gray	Oral; tablet, sustained release, film coated	40	mg
Opadry II Y-22-18238 white	Oral; tablet	3	mg
Opadry II Y-22-18238 white	Oral; tablet, controlled release	5.85	mg
Opadry II Y-22-7719 white	Oral; tablet, sustained action	9	mg
Opadry II Y-22-7719 white	Oral; tablet, sustained action, multilayer, film coated	17.91	mg
Opadry II Y-22-7719 white	Oral; tablet, sustained action, coated	18.15	mg
Opadry II Y-22-7719 white	Oral; tablet, film coated	40	mg

Ingredient	Dosage form	Quantity	Unit
Opadry II Y-22-7719 white	Oral; tablet	42.42	mg
Opadry II Y-30-10701 blue	Oral; tablet	40	mg
Opadry II Y-30-12705 yellow	Oral; tablet, sustained action	20	mg
Opadry II Y-30-12736A yellow	Oral; tablet, sustained action, film coated	7	mg
Opadry II Y-30-12736A yellow	Oral; tablet, film coated	18	mg
Opadry II Y-30-12737A yellow	Oral; tablet, film coated	5	mg
Opadry II Y-30-12737A yellow	Oral; tablet	6	mg
Opadry II Y-30-12842A yellow	Oral; tablet	2	mg
Opadry II Y-30-12863A yellow	Oral; tablet, film coated	4.5	mg
Opadry II Y-30-13091 orange	Oral-21; tablet	3	mg
Opadry II Y-30-13091 orange	Oral-28; tablet	3	mg
Opadry II Y-30-13616 orange	Oral; tablet	6	mg
Opadry II Y-30-13642A orange	Oral; tablet, sustained action	24.5	mg
Opadry II Y-30-14700A pink	Oral; tablet, film coated	7	mg
Opadry II Y-30-14758 pink	Oral; tablet, sustained action, film coated	7.99	mg
Opadry II Y-30-17295A tan	Oral; tablet	6	mg
Opadry II Y-30-17296A beige	Oral; tablet	6	mg
Opadry II Y-30-17340A beige	Oral; tablet, film coated	6	mg
Opadry II Y-30-17528 gray	Oral; tablet, sustained action	5.6	mg
Opadry II Y-30-17528 gray	Oral; tablet	25	mg
Opadry II Y-30-18037 white	Oral; tablet	16	mg
Opadry II Y-30-18037 white	Oral; tablet, sustained release, film coated	26	mg
Opadry II Y-30-18037 white	Oral; tablet, extended release	33	mg
Opadry II Y-30-18037 white	Oral; tablet, controlled release	38	mg
Opadry II Y-30-18037 white	Oral; tablet, film coated	43.2	mg
Opadry II YS-1-12524A	Oral; tablet, film coated	16	mg
Opadry II YS-1-19025A clear	Oral; tablet, coated	9.9	mg
Opadry II YS-1-7006 clear	Oral; tablet	4.8	mg
Opadry II YS-1-7006 clear	Oral; tablet, coated	4.8	mg
Opadry II YS-1-7006 clear	Oral; tablet, sustained action	13	mg
Opadry II YS-22-13571 orange	Oral; tablet, film coated	7.5	mg
Opadry II YS-22-17227A beige	Oral; tablet, film coated	5.25	mg
Opadry II YS-22-18096 white	Oral; tablet	28.5	mg
Opadry II YS-30-12788A yellow	Oral; tablet, controlled release	18	mg
Opadry II YS-30-13641A orange	Oral; tablet	15	mg
Opadry II YS-30-14743A pink	Oral; tablet, film coated	5.1	mg
Opadry II YS-30-14777A pink	Oral; tablet, film coated	5	mg
Opadry II YS-30-17265A beige	Oral; tablet	6	mg
Opadry II YS-30-17265A beige	Oral; tablet, sustained action	9	mg
Opadry II YS-30-17271A beige	Oral; tablet, film coated	15.46	mg
Opadry II YS-30-18105 white	Oral; tablet, sustained action	9	mg
Opadry II YS-30-18105 white	Oral; tablet, film coated	13.2	mg
Opadry OS-F-32867 yellow	Oral; tablet	20	mg

Ingredient	Dosage form	Quantity	Unit
opadry OY-27301 butterscotch	Oral; tablet, delayed action, enteric coated	6	mg
Opadry OY-3736 butterscotch	Oral; tablet	29.2	mg
Opadry OY-38924 white	Oral; tablet	39	mg
Opadry OY-52945 yellow	Oral; tablet, film coated	11.95	mg
Opadry OY-52945 yellow	Oral; tablet	23.16	mg
Opadry OY-54937 pink	Oral; tablet, film coated	3	mg
Opadry OY-58900 white	Oral; tablet	31.8	mg
Opadry OY-7240 clear	Oral; tablet	24	mg
Opadry OY-7300 white	Oral; tablet	35	mg
Opadry OY-8764H orange	Oral; tablet, film coated	25.2	mg
Opadry OY-B-28920 white	Oral; tablet, film coated	14	mg
Opadry OY-B-28920 white	Oral; tablet	28	mg
Opadry OY-B-32830	Oral; tablet	28	mg
Opadry OY-GM-28900	Oral; tablet, film coated	26	mg
Opadry OY-L-27204 tan	Oral; tablet	4	mg
Opadry OY-L-27205 beige	Oral; tablet	4	mg
Opadry OY-L-28906	Oral; tablet	4.5	mg
Opadry OY-L-34836 pink	Oral; tablet	4	mg
Opadry OY-LS-20921 blue	Oral; tablet	15	mg
Opadry OY-LS-23016 orange	Oral; tablet, film coated	6	mg
Opadry OY-LS-23018 orange	Oral; tablet, delayed action, enteric coated	6	mg
Opadry OY-LS-28908 white	Oral; tablet	7.5	mg
Opadry OY-LS-28908 white	Oral; tablet, film coated	13.5	mg
Opadry OY-LS-28914 white	Oral; tablet, sustained action	7	mg
Opadry OY-LS-28914 white	Oral; tablet, film coated	15	mg
Opadry OY-LS-33111 orange	Oral; tablet	7	mg
Opadry OY-LS-37200 buff	Oral; tablet, film coated	9	mg
Opadry OY-S-1387 pink	Oral; tablet, sustained action, film coated	0.25	mg
Opadry OY-S-20007 purple	Oral; tablet, sustained action, coated	13	mg
Opadry OY-S-20900 blue	Oral; tablet, film coated	4.5	mg
Opadry OY-S-20901 blue	Oral; tablet	8	mg
Opadry OY-S-21001 green	Oral; tablet, film coated	4.5	mg
Opadry OY-S-21027 green	Oral; tablet	9	mg
Opadry OY-S-22802 yellow	Oral; tablet	5	mg
Opadry OY-S-22815 yellow	Oral-28; tablet	1.22	mg
Opadry OY-S-22907 yellow	Oral; tablet, film coated	4.5	mg
Opadry OY-S-23049 orange	Oral-28; tablet	1.21	mg
Opadry OY-S-24900 pink	Oral; tablet, film coated	4.5	mg
Opadry OY-S-24972 pink	Oral; tablet	8.6	mg
Opadry OY-S-26530 red	Oral-28; tablet	1.21	mg
Opadry OY-S-28849 white	Oral; tablet	5	mg
Opadry OY-S-28924 white	Oral; tablet	13	mg
Opadry OY-S-28924 white	Oral; tablet, film coated	16.52	mg

Ingredient	Dosage form	Quantity	Unit
Opadry OY-S-29019 clear	Oral; tablet, sustained action	30	mg
Opadry OY-S-30013 purple	Oral; tablet	17	mg
Opadry OY-S-30913 blue	Oral; tablet	10	mg
Opadry OY-S-30953 blue	Oral; tablet	6	mg
Opadry OY-S-32921 yellow	Oral; tablet	4	mg
Opadry OY-S-32921 yellow	Oral; tablet, film coated	4	mg
Opadry OY-S-32986 yellow	Oral; tablet	10.35	mg
Opadry OY-S-33016	Oral; tablet	30	mg
Opadry OY-S-34800 pink	Oral; tablet	6	mg
Opadry OY-S-34817 pink	Oral; tablet, film coated	18	mg
Opadry OY-S-34923 pink	Oral; tablet	8	mg
Opadry OY-S-34995 pink	Oral; tablet	13.8	mg
Opadry OY-S-38928	Oral; tablet, film coated	20	mg
Opadry OY-S-38944 white	Oral; tablet	11	mg
Opadry OY-S-52902 yellow	Oral; tablet	16.656	mg
Opadry OY-S-53010 orange	Oral; tablet	8.328	mg
Opadry OY-S-54902 pink	Oral; tablet, film coated	5.24	mg
Opadry OY-S-54904 pink	Oral; tablet, film coated	3.6	mg
Opadry OY-S-6937 pink	Oral; tablet, film coated	6	mg
Opadry OY-S-7322 white	Oral; tablet, film coated	9	mg
Opadry OY-S-7399 white	Oral; tablet, film coated	10	mg
Opadry OY-S-7399 white	Oral; tablet	19	mg
Opadry OY-S-9476 brown	Oral; tablet, sustained action	28.26	mg
Opadry OY-S-9603 white	Oral; tablet	24	mg
Opadry OY-S-9603 white	Oral; tablet, film coated	38.5	mg
Opadry OY-SR-34907	Oral; tablet	12.25	mg
Opadry Y-1-17272A beige	Oral; tablet	12	mg
Opadry Y-1-2102 yellow	Oral; tablet, coated	10.87	mg
Opadry Y-1-2132 yellow	Oral; tablet	28	mg
Opadry Y-1-2516 orange	Oral; tablet, sustained action	5	mg
Opadry Y-1-2553 orange	Oral; tablet	10.5	mg
Opadry Y-1-4205 blue	Oral; tablet, film coated	12.2	mg
Opadry Y-1-4206 blue	Oral; tablet, sustained action	5.7	mg
Opadry Y-1-4234 blue	Oral; tablet	3.055	mg
Opadry Y-1-7000 white	Oral; tablet, coated	3	mg
Opadry Y-1-7000 white	Oral; tablet, extended release	11.1	mg
Opadry Y-1-7000 white	Oral; tablet, film coated	27	mg
Opadry Y-1-7000 white	Oral; tablet	30	mg
Opadry Y-1-7000B white	Oral; tablet	10	mg
Opadry Y-1-7000H white	Oral; tablet	15	mg
Opadry Y-1-7000H white	Oral; tablet, film coated	28	mg
Opadry Y-1-7006 blue	Oral; tablet	3.232	mg
Opadry Y-1-7503 gray	Oral; tablet, sustained action	5	mg

Ingredient	Dosage form	Quantity	Unit
Opadry Y-22-12720 pale yellow	Oral; tablet, film coated	4.2	mg
Opadry Y-22-12751 yellow	Oral; tablet	25.8	mg
Opadry Y-22-13558 orange	Oral; tablet	12.8	mg
Opadry Y-22-14525 pink	Oral; tablet	4.8	mg
Opadry Y-22-15008 red	Oral; tablet, film coated	3.83	mg
Opadry Y-22-15119 red	Oral; tablet, sustained action, coated	18	mg
Opadry Y-22-18238 white	Oral; tablet, film coated	6	mg
Opadry Y-30-13168A orange	Oral; tablet	7	mg
Opadry Y-30-14565 pink	Oral; tablet (immed./comp. release), film coated	18	mg
Opadry Y-30-14565 pink	Oral; tablet, film coated	36	mg
Opadry Y-5-10300 lavender	Oral; tablet, film coated	2	mg
Opadry Y-5-10670 blue	Oral; tablet	18	mg
Opadry Y-5-1244 pink	Oral; tablet	2	mg
Opadry Y-5-12539 yellow	Oral; tablet	12.6	mg
Opadry Y-5-12544A yellow	Oral; tablet, film coated	6	mg
Opadry Y-5-12584 yellow	Oral; tablet, delayed action, enteric coated	11.55	mg
Opadry Y-5-13512 orange	Oral; tablet	25.2	mg
Opadry Y-5-13513 orange	Oral; tablet, sustained action	5	mg
Opadry Y-5-14530A pink	Oral; tablet, delayed action, enteric coated	11.55	mg
Opadry Y-5-1727 red	Oral; tablet	7	mg
Opadry Y-5-2042 yellow	Oral; tablet, sustained action	18.3	mg
Opadry Y-5-2086 yellow	Oral; tablet	26	mg
Opadry Y-5-2328 orange	Oral; tablet	24.6	mg
Opadry Y-5-2371 orange	Oral; tablet	28.875	mg
Opadry Y-5-2394 orange	Oral; tablet	31.5	mg
Opadry Y-5-2450 orange	Oral; tablet, film coated	7.875	mg
Opadry Y-5-2450 orange	Oral; tablet	20.895	mg
Opadry Y-5-2451 orange	Oral; tablet	6	mg
Opadry Y-5-2646 beige	Oral; tablet	14	mg
Opadry Y-5-3171 green	Oral; tablet, sustained action	10	mg
Opadry Y-5-3296 green	Oral; tablet	36.4	mg
Opadry Y-5-4129 blue	Oral; tablet	7	mg
Opadry Y-5-4270 blue	Oral; tablet	14	mg
Opadry Y-5-4295 blue	Oral; tablet, sustained action, coated	17.11	mg
Opadry Y-5-6233 light orange	Oral; tablet, film coated	6	mg
Opadry Y-5-6301 yellow	Oral; tablet, film coated	5.25	mg
Opadry Y-5-7058 white	Oral; tablet, coated	3	mg
Opadry Y-5-7058 white	Oral; tablet	6	mg
Opadry Y-5-7068 white	Oral; tablet, controlled release	5	mg
Opadry Y-5-7068 white	Oral; tablet, sustained action	6	mg
Opadry Y-5-7068 white	Oral; tablet, coated	21	mg
Opadry Y-5-7068 white	Oral; tablet, film coated	22.5	mg
Opadry Y-5-7068 white	Oral; tablet	120	mg

Ingredient	Dosage form	Quantity	Unit
Opadry Y-5-7411 purple	Oral; tablet	12	mg
Opadry Y-5-7524 grey	Oral; tablet, sustained action, film coated	31.5	mg
Opadry Y-5-8050 black	Oral; tablet	7	mg
Opadry Y-5-9006 brown	Oral; tablet	8	mg
Opadry Y-5-9006 brown	Oral; tablet, extended release	15	mg
Opadry Y-5-9006 brown	Oral; tablet, sustained action	15	mg
Opadry Y-5-9020 brown	Oral; tablet, film coated	12	mg
Opadry yellow	Oral; tablet, film coated	1.89	mg
Opadry yellow	Oral; tablet	12.75	mg
Opadry YPS-7-2127	Oral; tablet, delayed action, enteric coated	54	mg
Opadry YS-1-003 white	Oral; tablet	7	mg
Opadry YS-1-10010 purple	Oral; tablet	18	mg
Opadry YS-1-10291 lavender	Oral; tablet, sustained action	5	mg
Opadry YS-1-10523A blue	Oral; tablet, film coated	12	mg
Opadry YS-1-10525 blue	Oral; tablet	23	mg
Opadry YS-1-10533A	Oral; tablet	8.16	mg
Opadry YS-1-10542A blue	Oral; tablet, sustained action	5	mg
Opadry YS-1-10547A blue	Oral; tablet, film coated	35	mg
Opadry YS-1-10563 blue	Oral; tablet	4.2	mg
Opadry YS-1-10618	Oral; tablet, film coated	3.75	mg
Opadry YS-1-10629	Oral; tablet	9.12	mg
Opadry YS-1-10654A blue	Oral; tablet	2.17	mg
Opadry YS-1-10682 blue	Oral; tablet, film coated	24	mg
Opadry YS-1-10699 blue	Oral; tablet, extended release	19.59	mg
Opadry YS-1-10748A light blue	Oral; tablet	4.5	mg
Opadry YS-1-10755 blue	Oral; tablet	8.4	mg
Opadry YS-1-10783A blue	Oral; tablet	2.17	mg
Opadry YS-1-11000 pink	Oral; tablet, film coated	3.75	mg
Opadry YS-1-11051 green	Oral; tablet, coated	16	mg
Opadry YS-1-11051 green	Oral; tablet	17.56	mg
Opadry YS-1-11060 green	Oral; tablet, film coated	10	mg
Opadry YS-1-1107 green	Oral; tablet, film coated	12	mg
Opadry YS-1-11075A green	Oral; tablet, sustained action	8	mg
Opadry YS-1-11113 green	Oral; tablet, sustained action	30	mg
Opadry YS-1-11171 green	Oral; tablet	6.3	mg
Opadry YS-1-11234 green	Oral; tablet	5.89	mg
Opadry YS-1-11305 green	Oral; tablet	7.2	mg
Opadry YS-1-11369 green	Oral; tablet, sustained action	21	mg
Opadry YS-1-1246 pink	Oral; tablet	4.3	mg
Opadry YS-1-1252 pink	Oral; tablet, film coated	4.5	mg
Opadry YS-1-12524A yellow	Oral; tablet	9	mg
Opadry YS-1-12525A yellow	Oral; tablet, controlled release	5	mg
Opadry YS-1-12525A yellow	Oral; tablet, film coated	5	mg

Ingredient	Dosage form	Quantity	Unit
Opadry YS-1-12525A yellow	Oral; tablet	7	mg
Opadry YS-1-12526A yellow	Oral; tablet, film coated	5	mg
Opadry YS-1-12526A yellow	Oral; tablet	15	mg
Opadry YS-1-12529 yellow	Oral; tablet, film coated	3.75	mg
Opadry YS-1-12541 yellow	Oral; tablet, coated	12	mg
Opadry YS-1-12541 yellow	Oral; tablet	22	mg
Opadry YS-1-1256-A yellow	Oral; tablet	7.5	mg
Opadry YS-1-12573 yellow	Oral; tablet, film coated	20	mg
Opadry YS-1-12581 yellow	Oral; tablet	8.4	mg
Opadry YS-1-1262 pink	Oral; tablet, film coated	10.5	mg
Opadry YS-1-12625 yellow	Oral; tablet	10	mg
Opadry YS-1-12702A yellow	Oral; tablet (immed./comp. release), film coated	12.5	mg
Opadry YS-1-12732 yellow	Oral; tablet, film coated	20.96	mg
Opadry YS-1-1277 pink	Oral; tablet	2.4	mg
Opadry YS-1-12826 yellow	Oral; tablet	8.1	mg
Opadry YS-1-12844 yellow	Oral; tablet, film coated	10	mg
Opadry YS-1-12847 yellow	Oral; tablet, sustained action	9.66	mg
Opadry YS-1-1298 pink	Oral; tablet	4.4	mg
Opadry YS-1-13013 peach	Oral; tablet	10.3	mg
Opadry YS-1-13065A orange	Oral; tablet	41	mg
Opadry YS-1-13119 orange	Oral; tablet	4.2	mg
Opadry YS-1-13121 yellow	Oral; tablet, film coated	11.25	mg
Opadry YS-1-13148A orange	Oral; tablet, film coated	5	mg
Opadry YS-1-13148A orange	Oral; tablet	10	mg
Opadry YS-1-13214 orange	Oral; tablet, controlled release	7.68	mg
Opadry YS-1-13269 orange	Oral; tablet, film coated	5	mg
Opadry YS-1-13271 orange	Oral; tablet, film coated	20	mg
Opadry YS-1-13555 orange	Oral; tablet	6	mg
Opadry YS-1-13591A orange	Oral; tablet, film coated	9	mg
Opadry YS-1-13664A orange	Oral; tablet	10.11	mg
Opadry YS-1-13673A orange	Oral; tablet	5.09	mg
Opadry YS-1-13675A orange	Oral; tablet	5.09	mg
Opadry YS-1-14012 pink	Oral; tablet	5	mg
Opadry YS-1-14129 pink	Oral; tablet, film coated	19	mg
Opadry YS-1-14130 pink	Oral-21; tablet, coated	5	mg
Opadry YS-1-14130 pink	Oral-28; tablet, coated	5	mg
Opadry YS-1-14130 pink	Oral; tablet	12	mg
Opadry YS-1-1418 pink	Oral; tablet	2.4	mg
Opadry YS-1-1441G	Oral; tablet, film coated	8	mg
Opadry YS-1-1448G pink	Oral; tablet, sustained action	11	mg
Opadry YS-1-14518A pink	Oral; tablet	4.5	mg
Opadry YS-1-14518A pink	Oral; tablet, controlled release	5	mg
Opadry YS-1-14518A pink	Oral; tablet, film coated	8	mg

Ingredient	Dosage form	Quantity	Unit
Opadry YS-1-14518A pink	Oral; tablet, sustained action	12	mg
Opadry YS-1-14519A pink	Oral; tablet	18	mg
Opadry YS-1-14532 pink	Oral; tablet, sustained action	15	mg
Opadry YS-1-1454 pink	Oral; tablet, film coated	15	mg
Opadry YS-1-14555A pink	Oral; tablet, film coated	4	mg
Opadry YS-1-1456G pink	Oral; tablet, coated	10.9	mg
Opadry YS-1-14587A pink	Oral-21; tablet	2.38	mg
Opadry YS-1-14587A pink	Oral-28; tablet	2.38	mg
Opadry YS-1-14593A pink	Oral; tablet, film coated	12	mg
Opadry YS-1-14595 pink	Oral; tablet	10	mg
Opadry YS-1-14608A	Oral; tablet	10.18	mg
Opadry YS-1-14643A pink	Oral; tablet	32	mg
Opadry YS-1-14725 pink	Oral; tablet	39	mg
Opadry YS-1-14756A pink	Oral; tablet	8	mg
Opadry YS-1-14779A pink	Oral; tablet, controlled release	7.48	mg
Opadry YS-1-15050 red	Oral; tablet	6	mg
Opadry YS-1-1510 pink	Oral; tablet	4.2	mg
Opadry YS-1-1528 pink	Oral; tablet	15	mg
Opadry YS-1-1543 pink	Oral; tablet, film coated	4.8	mg
Opadry YS-1-1543 pink	Oral; tablet	6	mg
Opadry YS-1-15585A red	Oral; tablet	15	mg
Opadry YS-1-16002 maroon	Oral-21; tablet	4	mg
Opadry YS-1-16002 maroon	Oral-28; tablet	4	mg
Opadry YS-1-16518A brown	Oral; tablet	16.2	mg
Opadry YS-1-17180A beige	Oral; tablet	15	mg
Opadry YS-1-17181A beige	Oral; tablet	34.5	mg
Opadry YS-1-17192A	Oral; tablet	20.36	mg
Opadry YS-1-17209 beige	Oral; tablet	30	mg
Opadry YS-1-17220	Oral; tablet, film coated	7.5	mg
Opadry YS-1-17222A tan	Oral; tablet (immed./comp. release), film coated	20	mg
Opadry YS-1-17235A peach	Oral; tablet	18	mg
Opadry YS-1-1724 red	Oral; tablet	18.566	mg
Opadry YS-1-17277A beige	Oral; tablet	3.75	mg
Opadry YS-1-17307A butterscotch	Oral; tablet, film coated	5	mg
Opadry YS-1-17307A butterscotch	Oral; tablet	5.6	mg
Opadry YS-1-17505A gray	Oral; tablet, sustained action	20	mg
Opadry YS-1-17506A gray	Oral; tablet, film coated	15	mg
Opadry YS-1-17506A gray	Oral; tablet	15.75	mg
Opadry YS-1-1751G red	Oral; tablet, coated	13.6	mg
Opadry YS-1-1755 gray	Oral; tablet	4.5	mg
Opadry YS-1-18005 white	Oral; tablet	5.89	mg
Opadry YS-1-18022 white	Oral; tablet	30.54	mg
Opadry YS-1-18027 white	Oral; tablet	12.6	mg

Ingredient	Dosage form	Quantity	Unit
Opadry YS-1-18027 white	Oral; tablet, film coated	16.32	mg
Opadry YS-1-18027A white	Oral; tablet, film coated	5.5	mg
Opadry YS-1-18027A white	Oral; tablet	21	mg
Opadry YS-1-18028 white	Oral; tablet	18.8	mg
Opadry YS-1-1811 red	Oral; tablet, sustained action	43.35	mg
Opadry YS-1-18111 white	Oral; tablet, film coated	32	mg
Opadry YS-1-18130A white	Oral; tablet	2.17	mg
Opadry YS-1-18177A white	Oral; tablet, film coated	8.4	mg
Opadry YS-1-18177A white	Oral; tablet	18	mg
Opadry YS-1-18202A white	Oral; tablet	21	mg
Opadry YS-1-18229 white	Oral; tablet, sustained action	18.09	mg
Opadry YS-1-1847 red	Oral; tablet	25	mg
Opadry YS-1-19025-A clear	Oral; tablet, sustained action, film coated	0.8	mg
Opadry YS-1-19025-A clear	Oral; tablet, film coated	1.1	mg
Opadry YS-1-19025-A clear	Oral; tablet, coated	4.45	mg
Opadry YS-1-19025-A clear	Oral; tablet	6	mg
Opadry YS-1-19025-A clear	Oral; tablet, controlled release	6	mg
Opadry YS-1-19025-A clear	Oral; tablet, sustained release, film coated	10	mg
Opadry YS-1-2007 yellow	Oral; tablet, film coated	5.25	mg
Opadry YS-1-2013 yellow	Oral; tablet	8	mg
Opadry YS-1-2063 yellow	Oral; tablet, film coated	30	mg
Opadry YS-1-2074 yellow	Oral; tablet, film coated	4.8	mg
Opadry YS-1-2074 yellow	Oral; tablet	19.25	mg
Opadry YS-1-2083 yellow	Oral; tablet, sustained action	27.1	mg
Opadry YS-1-2115 yellow	Oral; tablet	14.144	mg
Opadry YS-1-2134 yellow	Oral; tablet	147.8	mg
Opadry YS-1-2136 yellow	Oral; tablet	3.75	mg
Opadry YS-1-2167 yellow	Oral; tablet, sustained action	25.32	mg
Opadry YS-1-2181 yellow	Oral; tablet	15	mg
Opadry YS-1-2184 gold	Oral; tablet	15.52	mg
Opadry YS-1-2192 yellow	Oral-21; tablet	1.9	mg
Opadry YS-1-2305 orange	Oral; tablet, film coated	1.2	mg
Opadry YS-1-2308 dark orange	Oral; tablet, film coated	3	mg
Opadry YS-1-2383 orange	Oral; tablet	12.755	mg
Opadry YS-1-2398 orange	Oral; tablet	25.3	mg
Opadry YS-1-2449 orange	Oral; tablet, extended release	15	mg
Opadry YS-1-2522 orange	Oral; tablet	22.5	mg
Opadry YS-1-2527 orange	Oral; tablet	20	mg
Opadry YS-1-2534	Oral; tablet, film coated	20	mg
Opadry YS-1-2534	Oral; tablet	147.8	mg
Opadry YS-1-2546 orange	Oral; tablet	11.7	mg
Opadry YS-1-2546 orange	Oral; tablet, film coated	14	mg
Opadry YS-1-2548 orange	Oral; tablet	6.9	mg

Ingredient	Dosage form	Quantity	Unit
Opadry YS-1-2548 orange	Oral; tablet, film coated	13	mg
Opadry YS-1-2549 orange	Oral; tablet	120	mg
Opadry YS-1-2558 orange	Oral; tablet, film coated	14	mg
Opadry YS-1-2558 orange	Oral; tablet	25	mg
Opadry YS-1-2563 orange	Oral; tablet	11.25	mg
Opadry YS-1-2564	Oral; tablet	7.5	mg
Opadry YS-1-2578 orange	Oral; tablet, sustained action	21	mg
Opadry YS-1-2596 orange	Oral; tablet, film coated	20	mg
Opadry YS-1-2604 beige	Oral; tablet	7.5	mg
Opadry YS-1-2612 beige	Oral; tablet, sustained action	34.5	mg
Opadry YS-1-2619	Oral; tablet	23	mg
Opadry YS-1-2621 rust	Oral; tablet, film coated	17	mg
Opadry YS-1-2621 rust	Oral; tablet	20	mg
Opadry YS-1-2623 brown	Oral; tablet, film coated	34	mg
Opadry YS-12630 yellow	Oral; tablet	4	mg
Opadry YS-1-2635 tan	Oral; tablet, sustained action	13	mg
Opadry YS-1-2660 salmon	Oral; tablet	7.5	mg
Opadry YS-1-2665 beige	Oral; tablet	9	mg
Opadry YS-1-2669 rust	Oral; tablet	24	mg
Opadry YS-1-2671 beige	Oral; tablet	16	mg
Opadry YS-1-3105 green	Oral; tablet	15	mg
Opadry YS-1-3130 green	Oral; tablet, controlled release	8.08	mg
Opadry YS-1-3130 green	Oral; tablet, coated	20	mg
Opadry YS-1-3130 green	Oral; tablet	36	mg
Opadry YS-1-3134 green	Oral; tablet, film coated	16	mg
Opadry YS-1-3146 green	Oral; tablet	10	mg
Opadry YS-1-3147	Oral; tablet	0.8	mg
Opadry YS-1-3166 green	Oral; tablet	12	mg
Opadry YS-1-3256 green	Oral; tablet	12	mg
Opadry YS-1-3288 green	Oral; tablet	4.05	mg
Opadry YS-1-4014 blue	Oral; tablet	7.8	mg
Opadry YS-1-4018 blue	Oral; tablet	28	mg
Opadry YS-1-4112 blue	Oral; tablet	147.8	mg
Opadry YS-1-4137 blue	Oral; tablet	11.5	mg
Opadry YS-1-4228 blue	Oral; tablet	19.94	mg
Opadry YS-1-4229 blue	Oral; tablet	22.5	mg
Opadry YS-1-4234 blue	Oral; tablet, sustained action	2.5	mg
Opadry YS-1-4235 blue	Oral; tablet	20.25	mg
Opadry YS-1-4236 blue	Oral; tablet	4.4	mg
Opadry YS-1-4236 blue	Oral; tablet, sustained action	5	mg
Opadry YS-1-4236 blue	Oral; tablet, film coated	12.5	mg
Opadry YS-1-4240 blue	Oral; tablet	11.34	mg
Opadry YS-1-4241 blue	Oral; tablet, film coated	6	mg

Ingredient	Dosage form	Quantity	Unit
Opadry YS-1-4245 blue	Oral; tablet	6	mg
Opadry YS-1-4249 blue	Oral; tablet	22.68	mg
Opadry YS-1-4251 blue	Oral; tablet, film coated	2.52	mg
Opadry YS-1-4255	Oral; tablet, film coated	22.5	mg
Opadry YS-1-4256 blue	Oral; tablet, film coated	15.7	mg
Opadry YS-1-4256 blue	Oral; tablet, sustained action, coated	35.4	mg
Opadry YS-1-4282 blue	Oral; tablet, sustained action, film coated	10	mg
Opadry YS-1-4298 blue	Oral; tablet, film coated	20	mg
Opadry YS-14644 pink	Oral; tablet, sustained action	7.95	mg
Opadry YS-1-4700 purple	Oral; tablet	0.0064	mg
Opadry YS-1-4710	Oral; tablet	4	mg
Opadry YS-1-4739 lavender	Oral; tablet, sustained action	25	mg
Opadry YS-1-4812 lavender	Oral; tablet, sustained action	5	mg
Opadry YS-1-4845 purple	Oral; tablet, sustained action, film coated	16	mg
Opadry YS-1-6275 orange	Oral; tablet	3	mg
Opadry YS-1-6300	Oral; tablet, film coated	20	mg
Opadry YS-1-6312 yellow	Oral; tablet, film coated	17.45	mg
Opadry YS-1-6318 yellow	Oral; tablet	6	mg
Opadry YS-1-6320 yellow	Oral; tablet	4.8	mg
Opadry YS-1-6357 yellow	Oral; tablet	6	mg
Opadry YS-1-6370G yellow	Oral; tablet, coated	10	mg
Opadry YS-1-6378G yellow	Oral; tablet	13.4	mg
Opadry YS-1-6381 yellow	Oral; tablet, coated	3	mg
Opadry YS-1-6382G yellow	Oral; tablet, coated	6	mg
Opadry YS-1-6382G yellow	Oral; tablet	11	mg
Opadry YS-1-7000E white	Oral; tablet, film coated	40	mg
Opadry YS-1-7002 white	Oral; tablet, film coated	11.7	mg
Opadry YS-1-7003 white	Oral; tablet, sustained action, coated	6.24	mg
Opadry YS-1-7003 white	Oral; tablet, delayed action, enteric coated	9	mg
Opadry YS-1-7003 white	Oral; tablet, coated	14	mg
opadry YS-1-7003 white	Oral; tablet, controlled release	23.7	mg
Opadry YS-1-7003 white	Oral; tablet, extended release	24.39	mg
Opadry YS-1-7003 white	Oral; tablet, film coated	36	mg
Opadry YS-1-7003 white	Oral; tablet, sustained action	42.97	mg
Opadry YS-1-7003 white	Oral; tablet	147.8	mg
Opadry YS-1-7003H white	Oral; tablet, film coated	4	mg
Opadry YS-1-7006 clear	Oral-28; tablet	1.5	mg
Opadry YS-1-7006 clear	Oral; tablet, sustained action, film coated	2.625	mg
Opadry YS-1-7006 clear	Oral; tablet, delayed action, enteric coated	9	mg
Opadry YS-1-7006 clear	Oral; tablet, film coated	11	mg
Opadry YS-1-7006 clear	Oral; tablet, coated	11.16	mg
Opadry YS-1-7006 clear	Oral; tablet, controlled release	14.9	mg
Opadry YS-1-7006 clear	Oral; tablet, sustained action	38.4	mg

Ingredient	Dosage form	Quantity	Unit
Opadry YS-1-7006 clear	Oral; tablet, extended release	47.05	mg
Opadry YS-1-7006 clear	Oral; tablet	50	mg
Opadry YS-1-7022 off-white	Oral; tablet	4	mg
Opadry YS-1-7027 white	Oral; tablet, sustained action, coated	16	mg
Opadry YS-1-7027 white	Oral; tablet	37	mg
Opadry YS-1-7040 white	Oral; tablet (immed./comp. release), film coated	17.88	mg
Opadry YS-1-7040 white	Oral; tablet	35.76	mg
Opadry YS-1-7059 white	Oral; tablet, sustained action, film coated	5	mg
Opadry YS-1-7059 white	Oral; tablet, sustained action	30	mg
Opadry YS-1-7060 white	Oral-21; tablet	1.9	mg
Opadry YS-1-7086 white	Oral; tablet, sustained action, coated	10	mg
Opadry YS-1-7086 white	Oral; tablet	12	mg
Opadry Y-S-17191 brown	Oral; tablet, delayed action, enteric coated	11.55	mg
Opadry YS-1-7444G white	Oral; tablet, coated	22	mg
Opadry YS-1-7449 white	Oral; tablet, film coated	12	mg
Opadry YS-1-7472 clear	Oral-21; tablet	1.5	mg
Opadry YS-1-7472 clear	Oral-28; tablet	1.5	mg
Opadry YS-1-7472 clear	Oral; tablet	2.18	mg
Opadry YS-1-7472 clear	Oral; tablet, sustained action, coated	2.9	mg
Opadry YS-1-7507 grey	Oral; tablet, film coated	6	mg
Opadry YS-1-7507 grey	Oral; tablet	19.057	mg
Opadry YS-1-7507 grey	Oral; tablet, sustained action, coated	34.23	mg
Opadry YS-1-7552 grey	Oral; tablet	7.5	mg
Opadry YS-1-7700 white	Oral; tablet	35.2	mg
Opadry YS-1-7706G white	Oral; tablet, coated	18.1	mg
Opadry YS-1-8325 beige	Oral; tablet	15	mg
Opadry YS-1-8343G beige	Oral; tablet, sustained action	19	mg
Opadry YS-1-8345G beige	Oral; tablet, film coated	6	mg
Opadry YS-1-8608 orange	Oral; tablet, film coated	10	mg
Opadry YS-1-8619 orange	Oral; tablet, film coated	11	mg
Opadry YS-1-89193 clear	Oral; tablet	13	mg
Opadry YS-1-9011 brown	Oral-21; tablet	1.9	mg
Opadry YS-1-9012 brown	Oral; tablet	13.4	mg
Opadry YS-1-9012 brown	Oral; tablet, sustained action, film coated	15.5	mg
Opadry YS1R1418 pink	Oral; tablet, film coated	8	mg
Opadry YS-1R-7006 clear	Oral; tablet	26.25	mg
Opadry YS-2-10657 blue	Oral; tablet	9.75	mg
Opadry YS-2-19071A clear	Oral; tablet, film coated	4.4	mg
Opadry YS-2-19114A clear	Oral; tablet, controlled release	1.11	mg
Opadry YS-2-19114A clear	Oral; tablet, sustained action	1.5	mg
Opadry YS-2-19114A clear	Oral; tablet	4.5	mg
Opadry YS-2-19114A clear	Oral; tablet, film coated	23.5	mg
Opadry YS-22-16576 brown	Oral; tablet	10	mg

Ingredient	Dosage form	Quantity	Unit
Opadry YS-22-18119 white	Oral; tablet	10	mg
Opadry YS-2-7013 clear	Oral; tablet, film coated	1.2	mg
Opadry YS-2-7013 clear	Oral; tablet, coated	2.7	mg
Opadry YS-2-7013 clear	Oral; tablet	4.44	mg
Opadry YS-2-7063 white	Oral; tablet, film coated	2.5	mg
Opadry YS-2-7063 white	Oral; tablet, sustained action	24	mg
Opadry YS-3-7011 clear	Oral; tablet, film coated	1	mg
Opadry YS-3-7011 clear	Oral; tablet	17.2	mg
Opadry YS-3-7031 clear	Oral; tablet	8	mg
Opadry YS-3-7413 clear	Oral; tablet, film coated	1.5	mg
Opadry YS-3-7413 clear	Oral; tablet, coated	2.4	mg
Opadry YS-3-7413 clear	Oral; tablet	4	mg
Opadry YS-3-7413 clear	Oral; tablet, extended release	4	mg
Opadry YS-5-12575 yellow	Oral; tablet, film coated	7.5	mg
Opadry YS-5-12576 yellow	Oral; tablet, film coated	15	mg
Opadry YS-5-1260 pink	Oral; tablet, sustained action	150	mg
Opadry YS-5-1296 pink	Oral; tablet	7.455	mg
Opadry YS-5-17266 tan	Oral; tablet, film coated	3.91	mg
Opadry YS-5-18068 white	Oral; tablet	12.25	mg
Opadry YS-5-18074 white	Oral; tablet	24	mg
Opadry YS-5-4277 blue	Oral; tablet, film coated	0.9	mg
Opadry YS-5-4278 blue	Oral; tablet, film coated	2.16	mg
Opadry YS-5-7017	Oral; tablet, sustained action, coated	32.3	mg
Opadry YS-5-7042 clear	Oral; tablet	22	mg
Opadry YS-5-7068	Oral; tablet	1.5	mg
Opadry YS-5-7099 white	Oral; tablet, extended release	11	mg
Opaglos GS 2-0310	Oral; tablet, sugar coated	0.76	mg
Opaglos GS 2-0310	Oral; tablet	3.5	mg
Opaglos S 0750	Oral; tablet	0.028	mg
Opalux AS 1406 pink	Oral; tablet	1	mg
Opalux AS 1537 pink	Oral; tablet, coated	9.1	mg
Opalux AS 1589 pink	Oral; tablet, coated	0.07	mg
Opalux AS 2006 yellow	Oral; tablet	0.6	mg
Opalux AS 2007 yellow	Oral; tablet	0.02	mg
Opalux AS 2052 yellow	Oral-28; tablet	2.7	mg
Opalux AS 2062 yellow	Oral; tablet	1.4	mg
Opalux AS 2086 chartreuse	Oral; tablet	3.6	mg
Opalux AS 2094	Oral; tablet, delayed action, enteric coated	2.4	mg
Opalux AS 2167 yellow	Oral; tablet, coated	4	mg
Opalux AS 2236	Oral; tablet	10.2	mg
Opalux AS 2236	Oral; tablet, sustained action	11.8	mg
Opalux AS 2236	Oral; tablet, coated	22.125	mg
Opalux AS 2269 yellow	Oral; tablet	1.424	mg

Ingredient	Dosage form	Quantity	Unit
Opalux AS 2324 orange	Oral; tablet, coated	10.6	mg
Opalux AS 2336 orange	Oral; tablet	0.972	mg
Opalux AS 2395 peach	Oral; tablet	0.6	mg
Opalux AS 2433 orange	Oral; tablet	0.8	mg
Opalux AS 2498 orange	Oral; tablet	0.2	mg
Opalux AS 2498 orange	Oral; tablet, coated	3	mg
Opalux AS 2613 tan	Oral; tablet, sugar coated	2.18	mg
Opalux AS 2620-B tan	Oral; tablet	2.62	mg
Opalux AS 2676 salmon jasper red	Oral; tablet	1.4	mg
Opalux AS 2768	Oral; tablet	0.082	mg
Opalux AS 2787 butterscotch	Oral; tablet	4.47	mg
Opalux AS 3288 green	Oral; tablet, repeat action	8.605	mg
Opalux AS 3308 green	Oral; tablet, coated	6	mg
Opalux AS 3348-C green	Oral; tablet, sustained action	6	mg
Opalux AS 3381	Oral; tablet	0.01	mg
Opalux AS 3391 green	Oral; tablet	0.2	mg
Opalux AS 3391 green	Oral; tablet, coated	1.184	mg
Opalux AS 3942 maroon	Oral; tablet	17.6	mg
Opalux AS 4025	Oral; tablet	0.0082	mg
Opalux AS 4151 blue	Oral; tablet, repeat action	8.429	mg
Opalux AS 4188 blue	Oral; tablet, sustained action	0.2	mg
Opalux AS 4258 blue	Oral; tablet	0.0047	ml
Opalux AS 4270 blue	Oral; tablet, coated	12.632	mg
Opalux AS 4855 purple	Oral; tablet	0.02	mg
Opalux AS 5034 red	Oral; tablet, coated	0.02	mg
Opalux AS 5107	Oral; tablet, sustained action	17.6	mg
Opalux AS 5162 green	Oral; tablet	4.4	mg
Opalux AS 5178 green	Oral; tablet	20	mg
Opalux AS 5203 green	Oral; tablet	9.6	mg
Opalux AS 7000-B	Oral; tablet, coated	4.95	mg
Opalux AS 7000-P white	Oral; tablet	3.81	mg
Opalux AS 7001	Oral; tablet	0.0082	mg
Opalux AS 9010 brown	Oral; tablet, coated	0.45	mg
Opalux AS 9050 brown	Oral-28; tablet	2.76	mg
Opalux AS-9030 brown	Oral; tablet	2.5	mg
Opalux blue	Oral; tablet	0.0021	ml
Opalux green	Oral; tablet	0.8	mg
Opaspray 3-1700	Oral; tablet	2.17	mg
Opaspray 3-1810	Oral; tablet	2.43	mg
Opaspray IM-176	Oral; tablet	23.5	mg
Opaspray K-1-1243	Oral; tablet, sustained action	7.6	mg
Opaspray K-1-1254	Oral; tablet, film coated	4.5	mg
Opaspray K-1-1279	Oral; tablet	21.13	mg

Ingredient	Dosage form	Quantity	Unit
Opaspray K-1-1289 pink	Oral; tablet	21.13	mg
Opaspray K-1-14016 pink	Oral; tablet, film coated	3.75	mg
Opaspray K-1-1413 pink	Oral; tablet	1.818	mg
Opaspray K-1-1414 pink	Oral; tablet	11.4	mg
Opaspray K-1-1455 pink	Oral; tablet	0.56	mg
Opaspray K-1-1526 pink	Oral; tablet	2	mg
Opaspray K-1-1563 pink	Oral; tablet, film coated	3.1	mg
Opaspray K-1-1573 lavender	Oral; tablet	12	mg
Opaspray K-1-1574	Oral; tablet, coated	2.5	mg
Opaspray K-1-1719 red	Oral; tablet, film coated	1.67	mg
Opaspray K-1-2004 yellow	Oral; tablet	1.06	mg
Opaspray K-1-2013 yellow	Oral; tablet	8	mg
Opaspray K-1-2043 yellow	Oral; tablet	0.263	mg
Opaspray K-1-2182 yellow	Oral; tablet, film coated	1	mg
Opaspray K-1-2182 yellow	Oral; tablet	3	mg
Opaspray K-1-2186 yellow	Oral; tablet	6.4	mg
Opaspray K-1-2216-A yellow	Oral; tablet, coated	0.5	mg
Opaspray K-1-2216-A yellow	Oral; tablet	3	mg
Opaspray K-1-2216-A yellow	Oral; tablet, film coated	3	mg
Opaspray K-1-2216-A yellow	Oral; tablet, sustained action	6.8	mg
Opaspray K-1-2227 yellow	Oral; tablet, film coated	1.69	mg
Opaspray K-1-2227 yellow	Oral; tablet	6	mg
Opaspray K-1-2228 yellow	Oral; tablet, sustained action	17.8	mg
Opaspray K-1-2239	Oral; tablet	10	mg
Opaspray K-1-2240 yellow	Oral; tablet	2.2	mg
Opaspray K-1-2256 yellow	Oral; tablet	6.586	mg
Opaspray K-1-2300 peach	Oral; tablet	3.001	mg
Opaspray K-1-2301 peach	Oral; tablet	4.7	mg
Opaspray K-1-2303 orange	Oral; tablet	0.35	mg
Opaspray K-1-2304 orange	Oral; tablet	1.8	mg
Opaspray K-1-2314 orange	Oral; tablet	3.74	mg
Opaspray K-1-2327 orange	Oral; tablet, sustained action	6	mg
Opaspray K-1-2330 orange	Oral; tablet	11.1	mg
Opaspray K-1-2335 orange	Oral; tablet, film coated	0.525	mg
Opaspray K-1-2406 orange	Oral; tablet, film coated	2.1	mg
Opaspray K-1-2406 orange	Oral; tablet	4.42	mg
Opaspray K-1-2417 orange	Oral; tablet, coated	9	mg
Opaspray K-1-2430	Oral; tablet	13.5	mg
Opaspray K-1-2441 orange	Oral; tablet	4.48	mg
Opaspray K-1-2471 orange	Oral; tablet	6.02	mg
Opaspray K-1-2473	Oral; tablet, film coated	2.5	mg
Opaspray K-1-2473	Oral; tablet	22.5	mg
Opaspray K-1-2492	Oral; tablet	36	mg

Ingredient	Dosage form	Quantity	Unit
Opaspray K-1-2531	Oral; tablet, coated	2.25	mg
Opaspray K-1-2554	Oral; tablet, coated	1.8	mg
Opaspray K-1-2568 orange	Oral; tablet	1.2	mg
Opaspray K-1-2570 orange	Oral; tablet	5.25	mg
Opaspray K-1-2588 orange	Oral; tablet	5.44	mg
Opaspray K-1-2614 beige	Oral; tablet	6	mg
Opaspray K-1-2614 beige	Oral; tablet, film coated	6	mg
Opaspray K-1-2621 brown	Oral; tablet, film coated	1.49	mg
Opaspray K-1-2626 orange	Oral; tablet	4	mg
Opaspray K-1-2656 beige	Oral; tablet, film coated	9.08	mg
Opaspray K-1-2674 beige	Oral; tablet	0.35	mg
Opaspray K-1-2685	Oral; tablet	3	mg
Opaspray K-1-2711	Oral; tablet	12.6	mg
Opaspray K-1-2723 butterscotch	Oral; tablet	7.5	mg
Opaspray K-1-2837	Oral; tablet, film coated	5.8	mg
Opaspray K-1-3000	Oral; tablet	0.6	mg
Opaspray K-1-3000	Oral; tablet, coated	0.6	mg
Opaspray K-1-3142 green	Oral; tablet, sustained action	5.1	mg
Opaspray K-1-3144 green	Oral; tablet	5.214	mg
Opaspray K-1-3147	Oral; tablet, film coated	0.6	mg
Opaspray K-1-3147	Oral; tablet, sustained action	2	mg
Opaspray K-1-3147	Oral; tablet	3	mg
Opaspray K-1-3148 green	Oral; tablet, film coated	0.737	mg
Opaspray K-1-3148 green	Oral; tablet	1.35	mg
Opaspray K-1-3156	Oral; tablet	1.683	mg
Opaspray K-1-3173 green	Oral; tablet	1.188	mg
Opaspray K-1-3178 green	Oral; tablet	1.6	mg
Opaspray K-1-3197 green	Oral; tablet	1.12	mg
Opaspray K-1-3209 green	Oral; tablet	3.476	mg
Opaspray K-1-3220 green	Oral; tablet	1.798	mg
Opaspray K-1-3227	Oral; tablet, coated	3.2	mg
Opaspray K-1-3227	Oral; tablet	4	mg
Opaspray K-1-3300-A green	Oral; tablet	1.188	mg
Opaspray K-1-3300-C green	Oral; tablet	2.1	mg
Opaspray K-1-4108 blue	Oral; tablet	1.5	mg
Opaspray K-1-4108 blue	Oral; tablet, film coated	1.5	mg
Opaspray K-1-4119	Oral; tablet	0.6	mg
Opaspray K-1-4119	Oral; tablet, coated	0.6	mg
Opaspray K-1-4122 blue	Oral; tablet	2.2	mg
Opaspray K-1-4122 blue	Oral; tablet, film coated	4.5	mg
Opaspray K-1-4136 blue	Oral; tablet, coated	0.6	mg
Opaspray K-1-4136 blue	Oral; tablet, film coated	3	mg
Opaspray K-1-4205 blue	Oral; tablet, coated	3	mg

Ingredient	Dosage form	Quantity	Unit
Opaspray K-1-4210-A	Oral; tablet	3.26	mg
Opaspray K-1-4213 blue	Oral; tablet, film coated	1.75	mg
Opaspray K-1-4214	Oral; tablet	2.7	mg
Opaspray K-1-4214	Oral; tablet, coated	2.7	mg
Opaspray K-1-4234 blue	Oral; tablet	1.528	mg
Opaspray K-1-4235 blue	Oral; tablet	15.567	mg
Opaspray K-1-4728	Oral; tablet	4.677	mg
Opaspray K-1-4731 purple	Oral; tablet	0.5	ml
Opaspray K-1-4743 lavender	Oral; tablet	2.2	mg
Opaspray K-1-4786	Oral; tablet	2.1	mg
Opaspray K-1-4786	Oral; tablet, coated	2.1	mg
Opaspray K-1-7000 white	Oral; tablet, coated	0.9	mg
Opaspray K-1-7000 white	Oral; tablet, sustained action	6.25	mg
Opaspray K-1-7000 white	Oral; tablet, film coated	7.5	mg
Opaspray K-1-7000 white	Oral; tablet	22.5	mg
Opaspray K-1-70008 white	Oral; tablet	22.4	mg
Opaspray K-1-7000B	Oral; tablet	15	mg
Opaspray K-1-7076	Oral; tablet, film coated	1.5	mg
Opaspray K-1-9027 brown	Oral; tablet	1.2	mg
Opaspray K-1-9039-L brown	Oral; tablet, film coated	4.65	mg
Opaspray K-1-9039-L brown	Oral; tablet	12.2	mg
Opaspray K-1-9060 red	Oral; tablet	2.9	mg
Opaspray K-1-9080 brown	Oral; tablet	3.275	mg
Opaspray K-1-9112 brown	Oral; tablet	2.7	mg
Opaspray L-2113	Oral; tablet	2.92	mg
Opaspray L-3305 green	Oral; tablet	6.34	mg
Opaspray L-3306 green	Oral; tablet	4.12	mg
Opaspray L-7000 white	Oral; tablet	3.69	mg
Opaspray M-1-2042	Oral; tablet, film coated	1.11	mg
Opaspray M-1-3459 B orange	Oral; tablet	4	mg
Opaspray M-1-4395B blue	Oral; tablet	2.63	mg
Opaspray M-1-7111-B	Oral; tablet, film coated	2.9	mg
Opaspray M-1-7111-B	Oral; tablet	40	mg
Opaspray M-1-711B white	Oral; tablet	27.78	mg
Opaspray M-1-7120 white	Oral; tablet, film coated	1.52	mg
Opaspray M-1-7120 white	Oral; tablet	4.57	mg
Opaspray WD-1270 pink	Oral; tablet, delayed action, enteric coated	6.7	mg
Opatint AD-25000 red	Oral; tablet, orally disintegrating	2.5	mg
Opatint DD-13009 orange	Oral; tablet	1.52	mg
Opatint DD-14000 pink	Oral; tablet, film coated	0.94	mg
Opatint DD-1800 white	Oral; tablet	84	mg
Opatint DD-18000 white	Oral; tablet, film coated	0.68	mg
Orange oil	Oral; tablet (immed./comp. release), uncoated, chewable	0.002	mg

Ingredient	Dosage form	Quantity	Unit
Palmitic acid	Oral; tablet	6	mg
Paraffin	Oral; tablet, extended release	0.06	mg
Paraffin	Oral; tablet, coated	0.07	mg
Paraffin	Oral; tablet, sustained action	150.2	mg
Pectin	Oral; bar, chewable	1400	mg
Pentasodium triphosphate	Oral; tablet	4	mg
Peppermint	Oral; tablet, orally disintegrating	2	mg
Peppermint	Oral; tablet, film coated	5	mg
Peppermint OIL	Sublingual; tablet	0.15	mg
Peppermint oil	Oral; tablet, orally disintegrating	0.6	mg
Peppermint oil	Oral; tablet	3.5	mg
Pharmaburst B1	Oral; tablet, orally disintegrating	671.13	mg
Pharmaburst B2	Oral; tablet, orally disintegrating	91.187	mg
Pharmaceutical glaze	Oral; tablet, film coated	0.74	mg
Pharmaceutical glaze	Oral; tablet, coated	3.4	mg
Pharmaceutical glaze	Oral; tablet	18	mg
Pharmaceutical glaze	Oral; tablet, delayed action, enteric coated	21.44	mg
Pharmaceutical glaze	Oral; tablet, sustained action	213.24	mg
Pharmacoat 606	Oral; tablet, delayed action, enteric coated	5.25	mg
Pharmacoat 606	Oral; tablet	6.25	mg
Pharmatose DCL II	Oral; tablet	455	mg
Phosphoric acid	Oral; tablet, sustained action, film coated	2.975	mg
Piperazine	Oral; tablet	0.4	mg
Placebo	Oral; tablet	305.04	mg
Plusweet	Sublingual; tablet	0.25	mg
Polacrilin	Oral-21; tablet	3	mg
Polacrilin	Oral-28; tablet	3	mg
Polacrilin potassium	Oral-21; tablet	3	mg
Polacrilin potassium	Oral; tablet, coated	5	mg
Polacrilin potassium	Oral-28; tablet	8	mg
Polacrilin potassium	Oral; tablet, sustained action	10	mg
Polacrilin potassium	Oral; tablet (immed./comp. release), uncoated, chewable	21	mg
Polacrilin potassium	Oral; tablet, film coated	40	mg
Polacrilin potassium	Oral; tablet	45.8	mg
Polish wax 7625 P 100	Oral; tablet	0.05	mg
Polishing solution IM-182	Oral; tablet	0.7	mg
Poloxamer 188	Oral; tablet, controlled release	5.61	mg
Poloxamer 188	Oral; tablet	66.9	mg
Poloxamer 407	Oral; tablet	100	mg
Poloxamer 407	Oral; tablet, film coated	106.7	mg
Polycarbophil	buccal; tablet	3.125	mg
Polycarbophil, calcium	Oral; troche	32.039	mg
Polydextrose	Oral; tablet, film coated	3.83	mg

Ingredient	Dosage form	Quantity	Unit
Polydextrose	Oral; tablet	3.84	mg
Polydextrose	Oral; tablet, coated	7.67	mg
Polydextrose K	Oral; tablet, film coated	8.125	mg
Polyethylene	Oral; tablet, sustained action	0.64	mg
Polyethylene	Buccal/sublingual; tablet	70	mg
Polyethylene glycol 1000	Oral; tablet, film coated	1.5197	mg
Polyethylene glycol 1450	Oral; tablet, film coated	0.125	mg
Polyethylene glycol 1450	Oral-28; tablet	0.125	mg
Polyethylene glycol 1450	Oral-21; tablet	0.6	mg
Polyethylene glycol 1450	Oral; tablet, extended release	4.24	mg
Polyethylene glycol 1500	Oral; tablet	1.2	mg
Polyethylene glycol 20000	Oral; tablet, delayed action, enteric coated	0.008	mg
Polyethylene glycol 20000	Oral; tablet	0.3	mg
Polyethylene glycol 20000	Oral-28; tablet	0.3	mg
Polyethylene glycol 300	Oral; tablet	1	mg
Polyethylene glycol 300	Oral; tablet, film coated	1.5	mg
Polyethylene glycol 3350	Oral; tablet, coated	0.5	mg
Polyethylene glycol 3350	Oral; tablet, controlled release	0.72	mg
Polyethylene glycol 3350	Oral; tablet, extended release	1	mg
Polyethylene glycol 3350	Oral; tablet, sustained action, coated	4.2	mg
Polyethylene glycol 3350	Oral; tablet, sustained action	8.5	mg
Polyethylene glycol 3350	Oral; tablet, film coated	13	mg
Polyethylene glycol 3350	Oral; tablet (immed./comp. release), uncoated, chewable	15	mg
Polyethylene glycol 3350	Oral; tablet	25	mg
Polyethylene glycol 3500	Oral; tablet	3.048	mg
Polyethylene glycol 400	Oral-21; tablet	0.15	mg
Polyethylene glycol 400	Oral-28; tablet	0.15	mg
Polyethylene glycol 400	Oral; tablet, sustained action, film coated	1.8	mg
Polyethylene glycol 400	Oral; tablet, coated	3.15	mg
Polyethylene glycol 400	Oral; tablet, film coated	5.91	mg
Polyethylene glycol 400	Oral; tablet, enteric coated particles	12.5	mg
Polyethylene glycol 400	Oral; tablet (immed./comp. release), film coated	20	mg
Polyethylene glycol 400	Oral; tablet, extended release	45	mg
Polyethylene glycol 400	Oral; tablet, sustained action	45	mg
Polyethylene glycol 400	Oral; tablet	105.065	mg
Polyethylene glycol 4000	Oral; tablet, delayed action, enteric coated	0.96	mg
Polyethylene glycol 4000	Oral; tablet, sustained action, film coated	1.8	mg
Polyethylene glycol 4000	Oral; tablet, film coated	1.859	mg
Polyethylene glycol 4000	Oral; tablet, coated	2	mg
Polyethylene glycol 4000	Sublingual; tablet	2.5	mg
Polyethylene glycol 4000	Oral; tablet, multilayer, extended release	2.8	mg
Polyethylene glycol 4000	Oral; tablet	15	mg
Polyethylene glycol 4000	Oral; tablet, extended release	45	mg

Ingredient	Dosage form	Quantity	Unit
Polyethylene glycol 4000	Oral; tablet, sustained action	454	mg
Polyethylene glycol 4500	Oral; tablet, film coated	0.386	mg
Polyethylene glycol 600	Oral; tablet, sustained action	1.2	mg
Polyethylene glycol 600	Oral; tablet	6	mg
Polyethylene glycol 6000	Vaginal; tablet, film coated	0.064	mg
Polyethylene glycol 6000	Oral-28; tablet	0.2024	mg
Polyethylene glycol 6000	Oral; tablet (immed./comp. release), film coated	0.322	mg
Polyethylene glycol 6000	Oral; tablet, sustained action, film coated	0.322	mg
Polyethylene glycol 6000	Oral; tablet, sustained action, coated	0.5	mg
Polyethylene glycol 6000	Oral; tablet, delayed action, enteric coated	0.6	mg
Polyethylene glycol 6000	Oral; tablet, extended release	1.4	mg
Polyethylene glycol 6000	Oral; tablet, delayed action	1.713	mg
Polyethylene glycol 6000	Oral-21; tablet, coated	2.148	mg
Polyethylene glycol 6000	Oral-28; tablet, coated	2.148	mg
Polyethylene glycol 6000	Vaginal; tablet	3	mg
Polyethylene glycol 6000	Oral; tablet, sustained action	12.5	mg
Polyethylene glycol 6000	Oral; tablet, film coated	30	mg
Polyethylene glycol 6000	Oral; tablet, coated	40	mg
Polyethylene glycol 6000	Oral; tablet	375	mg
Polyethylene glycol 7000K	Oral; tablet, controlled release	132.66	mg
Polyethylene glycol 800	Oral; tablet	0.9	mg
Polyethylene glycol 8000	Oral; tablet, sustained action, film coated	0.18	mg
Polyethylene glycol 8000	Oral; tablet, coated	0.21	mg
Polyethylene glycol 8000	Oral; tablet, delayed action, enteric coated	0.75	mg
Polyethylene glycol 8000	Oral-28; tablet	2.05	mg
Polyethylene glycol 8000	Oral; tablet, extended release	2.52	mg
Polyethylene glycol 8000	Oral; tablet, orally disintegrating, delayed release	2.55	mg
Polyethylene glycol 8000	Vaginal; tablet	3	mg
Polyethylene glycol 8000	Oral; tablet (immed./comp. release), uncoated, chewable	6.5	mg
Polyethylene glycol 8000	Oral; tablet, sustained action, coated	14	mg
Polyethylene glycol 8000	Oral; tablet, film coated	49	mg
Polyethylene glycol 8000	Oral; tablet, sustained action	100	mg
Polyethylene glycol 8000	Oral; tablet	167.6	mg
Polyethylene oxide	Oral; tablet	57.86	mg
Polyethylene oxide	Oral; tablet, sustained action, film coated	180	mg
Polyethylene oxide	Oral; tablet, controlled release	252.14	mg
Polyethylene oxide	Oral; tablet, extended release	335.79	mg
Polyethylene oxide	Oral; tablet, sustained action	543.9	mg
Polyethylene oxide 200K	Oral; tablet, extended release	81.43	mg
Polyethylene oxide 7000K	Oral; tablet, extended release	73.7	mg
Polyoxyl 20 stearate	Oral; tablet, sustained action	0.08	mg
Polyoxyl 40 hydrogenated castor oil	Oral; tablet, sustained action	25	mg
Polyoxyl 40 stearate	Oral; tablet, film coated	2	mg

Ingredient	Dosage form	Quantity	Unit
Polyoxyl 40 stearate	Oral; tablet	8.48	mg
Polyoxyl glyceryl stearate	Oral; tablet	23.33	mg
Polyoxylethylene isononylphenyl ester	Oral; tablet, sustained action, coated	1.54	mg
Polypropylene glycol	Oral; tablet	1.26	mg
Polysaccharides	Oral; tablet, delayed action, enteric coated	80.4	mg
Polysaccharides soy	Oral; tablet, delayed action, enteric coated	53.5	mg
Polysorbate 20	Oral; tablet, extended release	2.8	mg
Polysorbate 20	Oral; tablet	6	mg
Polysorbate 20	Vaginal; tampon	64.8	mg
Polysorbate 80	Sublingual; tablet	0.075	mg
Polysorbate 80	Oral; tablet, extended release	0.12	mg
Polysorbate 80	Oral; tablet, sustained action	0.12	mg
Polysorbate 80	Oral; tablet, sustained action, film coated	0.2	mg
Polysorbate 80	Oral; tablet, coated	2.2	mg
Polysorbate 80	Oral; tablet, orally disintegrating, delayed release	2.25	mg
Polysorbate 80	Oral; tablet, sustained action, coated	8	mg
Polysorbate 80	Oral; tablet, film coated	14.8	mg
Polysorbate 80	Oral; tablet	21.25	mg
Polysorbate 80	Oral; tablet (immed./comp. release), film coated	24	mg
Polyvinyl acetate	Oral; tablet	7	mg
Polyvinyl acetate	Oral; tablet, sustained action	46	mg
Polyvinyl alcohol	Oral; tablet, coated	0.697	mg
Polyvinyl alcohol	Oral; tablet, orally disintegrating	2	mg
Polyvinyl alcohol	Oral; tablet	14.4	mg
Polyvinyl alcohol	Oral; tablet, film coated	20	mg
Polyvinyl alcohol	Oral; tablet, extended release	34.1	mg
Polyvinylacetal	Oral; tablet	41.85	mg
Polyvinylpyrrolidone ethylcellulose	Oral; tablet	1.71	mg
Potassium bicarbonate	Oral; troche	4	mg
Potassium bicarbonate	Oral; tablet	12.2	mg
Potassium bitartrate	Oral; tablet, controlled release	10	mg
Potassium carbonate	Oral; tablet	25	mg
Potassium chloride	Oral; tablet	40	mg
Potassium phosphate, monobasic	Oral; tablet, sustained action	4	mg
Potassium phosphate, monobasic	Oral; tablet	25	mg
Potassium sorbate	Oral; tablet, sustained release, film coated	0.2	mg
Potassium sorbate	Oral; tablet	0.8	mg
Povidone K25	Oral; tablet, multilayer, extended release	1.8	mg
Povidone K25	Oral; tablet, delayed action, enteric coated	20	mg
Povidone K25	Oral; tablet, film coated	22.5	mg
Povidone K25	Oral; tablet	52	mg
Povidone K26/28	Oral; tablet	26.6	mg
Povidone K29-32	Oral-21; tablet	4.5	mg

Ingredient	Dosage form	Quantity	Unit
Povidone K29-32	Oral-28; tablet	4.51	mg
Povidone K29-32	Oral-28; tablet, coated	4.51	mg
Povidone K29-32	Sublingual; tablet	6	mg
Povidone K29-32	Oral; tablet (immed./comp. release), uncoated, chewable	10	mg
Povidone K29-32	Oral; tablet, delayed action, enteric coated	13	mg
Povidone K29-32	Oral; tablet, multilayer, coated	15	mg
Povidone K29-32	Oral; tablet, enteric coated particles	18.6	mg
Povidone K29-32	Oral; tablet, coated	21	mg
Povidone K29-32	Oral; tablet, extended release	40	mg
Povidone K29-32	Oral; tablet, sustained action	45	mg
Povidone K29-32	Oral; tablet	49.55	mg
Povidone K29-32	Vaginal; tablet	50	mg
Povidone K29-32	Oral; tablet, film coated	75	mg
Povidone K30	Oral-21; tablet	5	mg
Povidone K30	Oral-28; tablet	5	mg
Povidone K30	sublingual; tablet	8	mg
Povidone K30	Oral; tablet (immed./comp. release), uncoated, chewable	18	mg
Povidone K30	Oral; tablet, delayed action, enteric coated	27.2	mg
Povidone K30	Oral; tablet, orally disintegrating	35.71	mg
Povidone K30	Oral; tablet (immed./comp. release), uncoated, effervescent	40	mg
Povidone K30	Oral; tablet, film coated	42	mg
Povidone K30	Oral; tablet, extended release	50	mg
Povidone K30	Oral; tablet, sustained action	55	mg
Povidone K30	Oral; tablet	75	mg
Povidone K90	Oral-28; tablet	0.174	mg
Povidone K90	Oral; tablet, delayed action, enteric coated	4	mg
Povidone K90	Oral; tablet, coated	9.767	mg
Povidone K90	Oral; tablet, enteric coated particles	27.6	mg
Povidone K90	Oral; tablet, controlled release	35	mg
Povidone K90	Oral; tablet, sustained action	40.8	mg
Povidone K90	Oral; tablet, film coated	44	mg
Povidone K90	Oral; tablet	55	mg
Povidone K90	Oral; tablet, extended release	78	mg
Povidone K90F	Oral; tablet, sustained action	60	mg
Primajel	Oral; tablet	33.75	mg
Propyl gallate	Oral; tablet	0.04	mg
Propyl gallate	Oral; tablet, sustained action, coated	0.04	mg
Propyl gallate	Oral; tablet, sustained action	0.06	mg
Propylene glycol	Oral; tablet, coated	1.5	mg
Propylene glycol	Oral; tablet, enteric coated particles	4.3	mg
Propylene glycol	Oral; tablet, delayed action, enteric coated	6.95	mg
Propylene glycol	Oral; tablet, sustained action	9	mg
Propylene glycol	Oral; tablet, sustained action, film coated	12.8	mg

Ingredient	Dosage form	Quantity	Unit
Propylene glycol	Oral; tablet, film coated	14.4	mg
Propylene glycol	Oral; tablet	14.7	mg
Propylene glycol	Vaginal; tampon	62.1	mg
Propylene glycol–lecithin	Buccal; patch, controlled release	49.4	mg
Propylparaben	Oral; tablet, coated	0.002	mg
Propylparaben	Oral; tablet, film coated	0.04	mg
Propylparaben	Oral; tablet, sustained action	0.12	mg
Propylparaben	Oral; tablet (immed./comp. release), uncoated, chewable	0.142	mg
Propylparaben	Oral; tablet	0.2	mg
Propylparaben sodium	Oral; tablet	0.0625	mg
Propylparaben sodium	Oral; tablet, orally disintegrating	0.1	mg
Prosolv 50	Oral; tablet	11.4286	mg
Prosolv 50	Oral; tablet, controlled release	24	mg
Prosolv 50	Oral; tablet, sustained action	217.5	mg
Prosolv 50	Oral; tablet, extended release	315	mg
Prosolv 90	Oral; tablet, controlled release	-22.07	mg
Prosolv 90	Oral; tablet	104.307	mg
Prosolv SMCC 50	Oral; tablet	194	mg
Prosolv SMCC 90	Oral; tablet, controlled release	20	mg
Prosolv SMCC 90	Oral; tablet	199	mg
Prosweet	Oral; tablet (immed./comp. release), uncoated, chewable	5	mg
QUSO F-22	Oral; tablet	0.6	mg
Rosin	Oral; tablet, coated	3.44	mg
Saccharin	Sublingual; tablet	0.2	mg
Saccharin sodium	Buccal/sublingual; tablet	0.4	mg
Saccharin sodium	Rectal; tablet	0.6	mg
Saccharin sodium	Oral; tablet, film coated	1	mg
Saccharin sodium	Sublingual; tablet	1	mg
Saccharin sodium	Oral; tablet (immed./comp. release), uncoated, chewable	9	mg
Saccharin sodium	Oral; tablet	20	mg
Saccharin sodium, anhydrous	Oral; tablet	2.08	mg
Saccharin sodium, anhydrous	Oral; tablet (immed./comp. release), uncoated, chewable	7.5	mg
Satialgine H	Oral; tablet	20	mg
SD alcohol 3A	Oral; tablet	0.11	ml
SEPIFILM LP-761 blanc	Oral; tablet	5	mg
SEPIFILM LP-761 blanc	Oral; tablet, delayed action, enteric coated	10	mg
Shellac	Oral; tablet, delayed action, enteric coated	3.314	mg
Shellac	Oral; tablet, film coated	4.4	mg
Shellac	Oral; tablet, coated	5	mg
Shellac	Oral; tablet, sustained action	7.3	mg
Shellac	Oral; tablet	24.04	mg
Shellac P.V.P. solution no. 4	Oral-28; tablet	5.62	mg
Silica, diatomaceous	Oral; tablet (immed./comp. release), uncoated, chewable	2	mg

Ingredient	Dosage form	Quantity	Unit
Silica, diatomaceous	Oral; tablet	5	mg
Silica, diatomaceous	Oral; tablet, coated	7.2	mg
Silicon dioxide	Sublingual; tablet	1.2	mg
Silicon dioxide	Oral; tablet, coated	5	mg
Silicon dioxide	Oral; tablet, sustained action, coated	7	mg
Silicon dioxide	Oral; tablet, orally disintegrating	7.1	mg
Silicon dioxide	Oral; tablet, film coated	8	mg
Silicon dioxide	Oral; tablet, extended release	15	mg
Silicon dioxide	Oral; tablet	19.8	mg
Silicon dioxide	Oral; tablet, sustained release, film coated	26	mg
Silicon dioxide	Oral; tablet (immed./comp. release), uncoated, chewable	33	mg
Silicon dioxide	Oral; tablet, sustained action	40	mg
Silicon dioxide	Oral; tablet, sustained action, film coated	60	mg
Silicon dioxide	Oral; tablet, delayed action, enteric coated	85	mg
Silicon dioxide	Oral; tablet, delayed action	170	mg
Silicon dioxide, colloidal	Oral; tablet, repeat action	0.5	mg
Silicon dioxide, colloidal	Oral-21; tablet	0.65	mg
Silicon dioxide, colloidal	Oral-28; tablet	0.65	mg
Silicon dioxide, colloidal	Oral; tablet, for solution	0.75	mg
Silicon dioxide, colloidal	Oral; tablet, sugar coated	0.8	mg
Silicon dioxide, colloidal	Sublingual; tablet	1	mg
Silicon dioxide, colloidal	Buccal; tablet	1.25	mg
Silicon dioxide, colloidal	Oral; tablet, sustained action, multilayer, film coated	1.55	mg
Silicon dioxide, colloidal	Vaginal; insert	2.5	mg
Silicon dioxide, colloidal	Oral; tablet, enteric coated particles	3	mg
Silicon dioxide, colloidal	Oral; tablet, sustained action, coated	5	mg
Silicon dioxide, colloidal	Oral; tablet, controlled release	5.6	mg
Silicon dioxide, colloidal	Oral; tablet, delayed action, enteric coated	6	mg
Silicon dioxide, colloidal	Oral; tablet, dispersible	6	mg
Silicon dioxide, colloidal	Oral; tablet, sustained action, film coated	6.1	mg
Silicon dioxide, colloidal	Oral; tablet, orally disintegrating	7.8	mg
Silicon dioxide, colloidal	Vaginal; tablet	8	mg
Silicon dioxide, colloidal	Oral; tablet (immed./comp. release), film coated	8.5	mg
Silicon dioxide, colloidal	Oral; tablet, coated	16	mg
Silicon dioxide, colloidal	Oral; tablet, extended release	24.8	mg
Silicon dioxide, colloidal	Oral; tablet, sustained release, film coated	30	mg
Silicon dioxide, colloidal	Oral; tablet, film coated	33	mg
Silicon dioxide, colloidal	Oral; tablet, sustained action	48	mg
Silicon dioxide, colloidal	Oral; tablet (immed./comp. release), uncoated, chewable	84.8	mg
Silicon dioxide, colloidal	Oral; tablet	99	mg
Silicone	Vaginal; intrauterine device	27.48	mg
Simethicone	Oral; tablet, coated	0.0004	mg
Simethicone	Oral; tablet, orally disintegrating	0.04	mg

Ingredient	Dosage form	Quantity	Unit
Simethicone	Oral; tablet, film coated	0.18	mg
Simethicone	Oral; pastille	0.4	mg
Simethicone	Oral; tablet, delayed action, enteric coated	0.56	mg
Simethicone	Oral; tablet, extended release	0.61	mg
Simethicone	Oral; tablet	1.5	mg
Simethicone	Oral; tablet, sustained action	7.5	mg
Simethicone C	Oral; tablet, extended release	0.08	mg
Simethicone emulsion	Oral; tablet, coated	0.009	mg
Simethicone emulsion	Oral; tablet, delayed action, enteric coated	0.04	mg
Simethicone emulsion	Oral; tablet, sustained action	0.07	mg
Simethicone emulsion	Oral; tablet (immed./comp. release), film coated	0.12	mg
Simethicone emulsion	Oral; tablet	0.35	mg
Simethicone emulsion	Oral; tablet, sustained action, coated	1.41	mg
Simethicone MDX4-4036	Oral; tablet, sustained action	1.14	mg
Soap	Oral; tablet, sustained action	0.4	mg
Sodium alginate	Oral; tablet	20	mg
Sodium alginate	Oral; troche	64.309	mg
Sodium alginate	Oral; tablet, sustained action, film coated	240	mg
Sodium alginate	Oral; tablet, controlled release	262	mg
Sodium alginate	Oral; tablet (immed./comp. release), film coated	320	mg
Sodium alginate	Oral; tablet, sustained action	350	mg
Sodium aminobenzoate	Oral; tablet	0.001	mg
Sodium ascorbate	Oral; tablet	5	mg
Sodium benzoate	Oral; tablet, film coated	0.02	mg
Sodium benzoate	Oral; tablet, delayed action, enteric coated	0.34	mg
Sodium benzoate	Oral; tablet	0.75	mg
Sodium benzoate	Oral; tablet, for solution	5	mg
Sodium benzoate	Oral; tablet, coated	9	mg
Sodium benzoate	Oral; tablet (immed./comp. release), uncoated, effervescent	60	mg
Sodium bicarbonate	Oral; tablet, sustained action	2.56	mg
Sodium bicarbonate	Oral; tablet, sustained action, coated	2.56	mg
Sodium bicarbonate	Oral; tablet (immed./comp. release), film coated	4.24	mg
Sodium bicarbonate	Oral; tablet, coated	9	mg
Sodium bicarbonate	Buccal; gum, chewing	10	mg
Sodium bicarbonate	Oral; tablet, delayed action, enteric coated	15	mg
Sodium bicarbonate	Oral; tablet, orally disintegrating	26.97	mg
Sodium bicarbonate	Oral; tablet, film coated	40	mg
Sodium bicarbonate	Buccal; tablet	42	mg
Sodium bicarbonate	Vaginal; insert	43	mg
Sodium bicarbonate	Oral; tablet	125	mg
Sodium bicarbonate	Oral; tablet (immed./comp. release), uncoated, chewable	140	mg
Sodium bicarbonate	Oral; tablet (immed./comp. release), uncoated, effervescent	267	mg
Sodium bisulfite	Sublingual; tablet	0.5	mg

Ingredient	Dosage form	Quantity	Unit
Sodium bisulfite	Oral; tablet	0.65	mg
Sodium bitartrate	Oral; tablet, sustained action	306	mg
Sodium carbonate	Oral; tablet, delayed action, enteric coated	10	mg
Sodium carbonate	Oral; tablet	10.4	mg
Sodium carbonate	Buccal; tablet	20	mg
Sodium carbonate	Oral; tablet, film coated	25	mg
Sodium carbonate	Oral; troche	25	mg
Sodium carbonate	Buccal; gum, chewing	30	mg
Sodium carbonate	Oral; tablet, extended release	30	mg
Sodium carbonate hydrate	Oral; tablet	4.92	mg
Sodium carboxymethyl betaglucan	Oral-21; tablet	4	mg
Sodium caseinate	Oral; tablet	100	mg
Sodium chloride	Oral; tablet (immed./comp. release), uncoated, chewable	7.5	mg
Sodium chloride	Oral; tablet, controlled release	36	mg
Sodium chloride	Oral; tablet, sustained action	143.26	mg
Sodium chloride	Oral; tablet	148	mg
Sodium chloride	Oral; tablet, extended release	223.4	mg
Sodium citrate	Sublingual; tablet	2.68	mg
Sodium citrate	Oral; tablet, coated	18.34	mg
Sodium citrate	Oral; tablet, delayed action, enteric coated	82	mg
Sodium citrate	Oral; tablet, film coated	200	mg
Sodium citrate	Oral; tablet	275	mg
Sodium citrate	Oral; tablet (immed./comp. release), uncoated, chewable	300	mg
Sodium citrate, anhydrous	Oral; tablet, delayed action, enteric coated	15	mg
Sodium citrate, anhydrous	Oral; tablet	28	mg
Sodium citrate, anhydrous	Oral; tablet (immed./comp. release), uncoated, effervescent	935	mg
Sodium cyclamate	Oral; tablet (immed./comp. release), uncoated, chewable	75	mg
Sodium hydroxide	Oral; tablet, sustained action, coated	0.04	mg
Sodium hydroxide	Oral; tablet, orally disintegrating	0.156	mg
Sodium hydroxide	Oral; tablet, delayed action	0.211	mg
Sodium hydroxide	Oral; tablet, delayed action, enteric coated	0.32	mg
Sodium hydroxide	Oral; tablet, sustained action	0.4	mg
Sodium hydroxide	Oral; tablet, extended release	2.7	mg
Sodium hydroxide	Oral; tablet	6.72	mg
Sodium laureth sulfate	Oral; tablet	0.91	mg
Sodium lauryl sulfate	Sublingual; tablet	0.02	mg
Sodium lauryl sulfate	Oral; tablet, orally disintegrating	0.1	mg
Sodium lauryl sulfate	Oral-28; tablet	0.65	mg
Sodium lauryl sulfate	Oral; tablet (immed./comp. release), film coated	0.7	mg
Sodium lauryl sulfate	Oral; tablet, multilayer, extended release	0.8	mg
Sodium lauryl sulfate	Buccal/sublingual; tablet	1.1	mg
Sodium lauryl sulfate	Oral; tablet (immed./comp. release), uncoated, chewable	5	mg
Sodium lauryl sulfate	Vaginal; insert	5	mg

Ingredient	Dosage form	Quantity	Unit
Sodium lauryl sulfate	Oral; tablet, coated	5.2	mg
Sodium lauryl sulfate	Oral; tablet, delayed action, enteric coated	8.09	mg
Sodium lauryl sulfate	Oral; tablet, sustained action, coated	10.5	mg
Sodium lauryl sulfate	Oral; tablet, film coated	11.25	mg
Sodium lauryl sulfate	Oral; tablet, sustained action	20.62	mg
Sodium lauryl sulfate	Oral; tablet	50	mg
Sodium lauryl sulfate	Oral; tablet, extended release	51.69	mg
Sodium metabisulfite	Rectal; tablet	2	mg
Sodium metabisulfite	Sublingual; tablet	2	mg
Sodium metabisulfite	Oral; tablet	8	mg
Sodium phosphate	Oral-21; tablet	0.75	mg
Sodium phosphate	Oral; tablet	16	mg
Sodium phosphate, dibasic, anhydrous	Oral; tablet	48	mg
Sodium phosphate, dibasic, anhydrous	Oral; tablet, sustained action	110	mg
Sodium phosphate, dibasic, heptahydrate	Oral-20; tablet	0.0008	mg
Sodium phosphate, dibasic, heptahydrate	Oral; tablet, coated	0.22	mg
Sodium phosphate, dibasic, heptahydrate	Oral; tablet, delayed action, enteric coated	4	mg
Sodium phosphate, dibasic, heptahydrate	Oral; tablet, sustained action	70	mg
Sodium phosphate, dibasic, heptahydrate	Oral; tablet	80	mg
Sodium phosphate, dibasic, heptahydrate	Oral; tablet, sustained action, film coated	105	mg
Sodium phosphate, monobasic	Oral; tablet	1.376	mg
Sodium phosphate, monobasic, anhydrous	Oral-20; tablet	0.075	mg
Sodium phosphate, monobasic, anhydrous	Oral-21; tablet	0.075	mg
Sodium phosphate, monobasic, anhydrous	Oral; tablet	4.18	mg
Sodium phosphate, monobasic, anhydrous	Oral; tablet, delayed action, enteric coated	23.4	mg
Sodium phosphate, monobasic, anhydrous	Oral; tablet, sustained action, film coated	30.97	mg
Sodium phosphate, monobasic, monohydrate	Oral; tablet	31.72	mg
Sodium phosphate, monobasic, monohydrate	Oral; tablet, delayed action, enteric coated	35	mg
Sodium phosphate, tribasic, hydrate	Oral; tablet, delayed action, enteric coated	11	mg
Sodium starch glycolate	Oral; tablet, multilayer, coated	2	mg
Sodium starch glycolate	Oral-28; tablet	3.999	mg
Sodium starch glycolate	Oral-21; tablet	4	mg
Sodium starch glycolate	Sublingual; tablet	5.5	mg
Sodium starch glycolate	Buccal; tablet	8.3	mg
Sodium starch glycolate	Oral; tablet, delayed action	9	mg
Sodium starch glycolate	Oral; tablet, sustained action, film coated	10	mg
Sodium starch glycolate	Oral; tablet, enteric coated particles	12	mg
Sodium starch glycolate	Oral; tablet, controlled release	15	mg
Sodium starch glycolate	Oral; tablet, sustained action	15	mg
Sodium starch glycolate	Oral; tablet, delayed action, enteric coated	21	mg
Sodium starch glycolate	Oral; tablet, extended release	30	mg
Sodium starch glycolate	Oral; tablet (immed./comp. release), uncoated, chewable	50	mg

Ingredient	Dosage form	Quantity	Unit
Sodium starch glycolate	Oral; tablet, orally disintegrating	71.43	mg
Sodium starch glycolate	Oral; tablet, coated	73	mg
Sodium starch glycolate	Oral; tablet, film coated	85.5	mg
Sodium starch glycolate	Oral; tablet	876	mg
Sodium stearate	Oral; tablet, orally disintegrating	0.85	mg
Sodium stearate	Oral; tablet	9.48	mg
Sodium stearyl fumarate	Oral; tablet, coated	1.18	mg
Sodium stearyl fumarate	Oral; tablet (immed./comp. release), film coated	2	mg
Sodium stearyl fumarate	Oral; tablet (immed./comp. release), uncoated, chewable	2	mg
Sodium stearyl fumarate	Oral; tablet, controlled release	2	mg
Sodium stearyl fumarate	Oral; tablet, sustained action, coated	4	mg
Sodium stearyl fumarate	Oral; tablet, orally disintegrating	6	mg
Sodium stearyl fumarate	Oral; tablet, sustained action	8.9	mg
Sodium stearyl fumarate	Oral; tablet, sustained action, film coated	16	mg
Sodium stearyl fumarate	Oral; tablet, extended release	20	mg
Sodium stearyl fumarate	Oral; tablet	24.4	mg
Sodium stearyl fumarate	Oral; tablet, film coated	26	mg
Sodium stearyl fumarate	Oral; tablet, delayed action, enteric coated	27	mg
Sodium sulfate	Oral; tablet	7.37	mg
Sodium sulfate	Oral-20; tablet	120	mg
Sodium sulfate, anhydrous	Oral-21; tablet	96	mg
Sodium sulfate, anhydrous	Oral; tablet	105.1	mg
Sodium thiosulfate	Oral; tablet	3	mg
Sodium thiosulfate, anhydrous	Oral; tablet	0.6	mg
Sorbic acid	Oral; tablet, delayed action, enteric coated	0.0285	mg
Sorbic acid	Sublingual; tablet	0.16	mg
Sorbic acid	Oral; tablet, sustained action, film coated	0.4	mg
Sorbic acid	Oral; tablet	0.935	mg
Sorbitan monolaurate	Oral; tablet, film coated	83.9	mg
Sorbitan monooleate	Oral; tablet, coated	0.108	mg
Sorbitan monooleate	Oral; tablet, film coated	0.69	mg
Sorbitan monooleate	Oral; tablet, sustained action, film coated	1	mg
Sorbitan monooleate	Oral; tablet	1.7	mg
Sorbitan monooleate	Oral; tablet, delayed action, enteric coated	1.89	mg
Sorbitan monooleate	Oral; tablet, sustained action	7.8	mg
Sorbitol	Oral; tablet, film coated	5	mg
Sorbitol	Oral; tablet, coated	12.96	mg
Sorbitol	Sublingual; tablet	50.5	mg
Sorbitol	Oral; tablet, sustained action	53.75	mg
Sorbitol	Oral; bar, chewable	144	mg
Sorbitol	Buccal; gum, chewing	212.9	mg
Sorbitol	Oral; tablet (immed./comp. release), uncoated, chewable	300	mg
Sorbitol	Oral; tablet	337.28	mg

Ingredient	Dosage form	Quantity	Unit
Sorbitol solution	Oral; tablet	14	mg
Sorbitol solution	Buccal; gum, chewing	38.1	mg
Soybean oil	Oral; tablet (immed./comp. release), uncoated, chewable	0.14	mg
Soybean oil, hydrogenated	Oral; tablet, coated	3	mg
Soybean oil, hydrogenated	Oral; tablet	13.5	mg
Spearmint	Oral; tablet, orally disintegrating	0.0625	mg
Spectrablend CSL-15764 (blue)	Oral; tablet	5.91	mg
Stannous octoate	Vaginal; intrauterine device	0.14	mg
Starch	Buccal/sublingual; tablet	14.19	mg
Starch	Oral-20; tablet	22.25	mg
Starch	Buccal; tablet	22.5	mg
Starch	Oral; tablet (immed./comp. release), uncoated, chewable	25.75	mg
Starch	Oral; tablet, sustained action, coated	27	mg
Starch	Oral-21; tablet	34.465	mg
Starch	Oral-28; tablet	35.46	mg
Starch	Oral; tablet, sugar coated	43.25	mg
Starch	Oral; tablet, sustained action	48.6	mg
Starch	Rectal; tablet	55	mg
Starch	Sublingual; tablet	55	mg
Starch	Oral; tablet (immed./comp. release), film coated	74.3	mg
Starch	Oral; tablet, delayed action, enteric coated	76	mg
Starch	Oral; tablet, film coated	100	mg
Starch	Oral; tablet, coated	210	mg
Starch	Vaginal; tablet	260	mg
Starch	Oral; tablet	615.6	mg
Starch 1500 pregelatinized	Oral; tablet	50	mg
Starch 1500, pregelatinized	Oral; tablet, coated	22	mg
Starch 1500, pregelatinized	Oral; tablet, sustained action, multilayer, film coated	35	mg
Starch 1500, pregelatinized	Sublingual; tablet	43	mg
Starch 1500, pregelatinized	Oral; tablet (immed./comp. release), uncoated, chewable	50	mg
Starch 1500, pregelatinized	Oral; tablet, delayed action, enteric coated	51.5	mg
Starch 1500, pregelatinized	Vaginal; tablet	165	mg
Starch 1500, pregelatinized	Oral; tablet, film coated	180	mg
Starch 1500, pregelatinized	Oral; tablet	435.8	mg
Starch 1551	Sublingual; tablet	11	mg
Starch 1551	Oral; tablet (immed./comp. release), uncoated, chewable	25	mg
Starch 1551	Oral; tablet, film coated	90	mg
Starch 1551	Oral; tablet	100	mg
Starch 21	Oral; tablet, delayed action, enteric coated	20	mg
Starch 21	Oral; tablet	100	mg
Starch 7150	Oral; tablet	50	mg
Starch 826	Oral; tablet, film coated	10	mg
Starch 826	Sublingual; tablet	12	mg

Ingredient	Dosage form	Quantity	Unit
Starch 826	Oral; tablet	138	mg
Starch, corn	Vaginal; tablet, film coated	8	mg
Starch, corn	Oral-21; tablet, coated	9.9	mg
Starch, corn	Oral-28; tablet, coated	9.9	mg
Starch, corn	Oral; tablet, multilayer, extended release	10	mg
Starch, corn	Buccal; tablet	16.6	mg
Starch, corn	Oral; tablet, extended release	18	mg
Starch, corn	Oral-28; tablet	30.1	mg
Starch, corn	Oral; tablet, repeat action	32	mg
Starch, corn	Oral-21; tablet	33	mg
Starch, corn	Oral; tablet, delayed action, enteric coated	54	mg
Starch, corn	Oral-20; tablet	57	mg
Starch, corn	Sublingual; tablet	60	mg
Starch, corn	Oral; tablet, sustained action, film coated	74.3	mg
Starch, corn	Oral; tablet, sustained action	92	mg
Starch, corn	Vaginal; tablet	150	mg
Starch, corn	Oral; tablet, film coated	158	mg
Starch, corn	Oral; tablet (immed./comp. release), uncoated, chewable	170	mg
Starch, corn	Oral; tablet, coated	285	mg
Starch, corn	Oral; tablet	433.32	mg
Starch, corn 21	Oral; tablet	110.4	mg
Starch, modified	Oral; tablet	50	mg
Starch, potato	Oral; tablet, coated	2.1	mg
Starch, potato	Oral; tablet	80.5895	mg
Starch, pregelatinized	Oral-21; tablet, coated	6.6	mg
Starch, pregelatinized	Oral-28; tablet, coated	6.6	mg
Starch, pregelatinized	Oral; tablet, sugar coated	9.4	mg
Starch, pregelatinized	Oral-21; tablet	22.25	mg
Starch, pregelatinized	Oral-28; tablet	26.35	mg
Starch, pregelatinized	Oral; tablet (immed./comp. release), uncoated, chewable	32	mg
Starch, pregelatinized	Oral; tablet, sustained action, coated	33.75	mg
Starch, pregelatinized	Sublingual; tablet	43	mg
Starch, pregelatinized	Oral; tablet, sustained action	60	mg
Starch, pregelatinized	Oral; tablet, delayed action, enteric coated	64.8	mg
Starch, pregelatinized	Oral; tablet (immed./comp. release), film coated	71.35	mg
Starch, pregelatinized	Oral; tablet, coated	73	mg
Starch, pregelatinized	Oral; tablet, sustained action, film coated	75	mg
Starch, pregelatinized	Oral; tablet, film coated	240	mg
Starch, pregelatinized	Oral; tablet	345.95	mg
Starch, pregelatinized corn	Oral; tablet, coated	26.4	mg
Starch, pregelatinized corn	Oral; tablet, film coated	70	mg
Starch, pregelatinized corn	Vaginal; insert	210	mg
Starch, pregelatinized corn	Oral; tablet	482	mg

Ingredient	Dosage form	Quantity	Unit
Starch, pregelatinized tapioca	Oral; tablet	5	mg
Starch, rice	Oral; tablet, sustained action	301	mg
Starch, wheat	Oral; tablet	65.5895	mg
Stearic acid	Oral; tablet, sugar coated	0.9	mg
Stearic acid	Oral-21; tablet	1	mg
Stearic acid	Oral-28; tablet	1	mg
Stearic acid	Buccal; tablet	5	mg
Stearic acid	Oral; tablet, enteric coated particles	5	mg
Stearic acid	Sublingual; tablet	5.049	mg
Stearic acid	Buccal/sublingual; tablet	6	mg
Stearic acid	Oral; tablet, delayed action, enteric coated	8	mg
Stearic acid	Oral; tablet, sustained release, film coated	9	mg
Stearic acid	Oral; tablet (immed./comp. release), uncoated, chewable	15	mg
Stearic acid	Oral; tablet, film coated	22	mg
Stearic acid	Oral; tablet, sustained action, multilayer, film coated	26.48	mg
Stearic acid	Oral; tablet, coated	42.4	mg
Stearic acid	Vaginal; tablet	60	mg
Stearic acid	Oral; tablet	72	mg
Stearic acid	Oral; tablet, extended release	180	mg
Stearic acid	Oral; tablet, sustained action	187.5	mg
Stear-O-wet C	Oral; tablet, sustained action	10	mg
Stear-O-wet C	Oral; tablet	12	mg
Stear-O-wet M	Oral; tablet, extended release	1.2	mg
Stear-O-wet M	Oral; tablet, delayed action, enteric coated	4	mg
Stear-O-wet M	Oral; tablet, coated	5.5	mg
Stear-O-wet M	Oral; tablet, controlled release	11	mg
Stear-O-wet M	Oral; tablet (immed./comp. release), film coated	13.11	mg
Stear-O-wet M	Oral; tablet, film coated	18	mg
Stear-O-wet M	Oral; tablet	860	mg
Stearyl alcohol	Oral; tablet, controlled release	25	mg
Stearyl alcohol	Oral; tablet, sustained action, film coated	60	mg
Stearyl alcohol	Oral; tablet, sustained action	244	mg
Strawberry	Oral; tablet, orally disintegrating	1	mg
Strawberry	Oral; tablet, orally disintegrating, delayed release	3	mg
Succinic acid	Oral; tablet (immed./comp. release), uncoated, chewable	2.857	mg
Succinic acid	Oral; tablet, controlled release	4	mg
Succinic acid	Oral; tablet	65.1	mg
Sucralose	Oral-28; tablet	0.018	mg
Sucralose	Oral; tablet (immed./comp. release), uncoated, chewable	1.88	mg
Sucralose	Oral; tablet, orally disintegrating	5.75	mg
Sucrose	Sublingual; tablet	8.415	mg
Sucrose	Oral-20; tablet	12	mg
Sucrose	Oral-21; tablet	12	mg

Ingredient	Dosage form	Quantity	Unit
Sucrose	Buccal; tablet	16.6	mg
Sucrose	Oral-21; tablet, coated	19.374	mg
Sucrose	Oral-28; tablet, coated	19.374	mg
Sucrose	Oral; tablet, sugar coated	73.18	mg
Sucrose	Oral; tablet, film coated	84.2	mg
Sucrose	Buccal/sublingual; tablet	91	mg
Sucrose	Oral; tablet, sustained action, film coated	119.12	mg
Sucrose	Oral; tablet, repeat action	152.664	mg
Sucrose	Oral; tablet, sustained action	202	mg
Sucrose	Oral-28; tablet	216.5	mg
Sucrose	Oral; tablet, delayed action, enteric coated	279.495	mg
Sucrose	Oral; tablet, coated	400	mg
Sucrose	Oral; pastille	426	mg
Sucrose	Oral; tablet	900	mg
Sucrose	Oral; tablet (immed./comp. release), uncoated, chewable	1200	mg
Sucrose stearate	Oral; tablet, extended release	44.56	mg
Sucrose syrup	Oral; tablet	182.4	mg
Sugar confectioners	Sublingual; tablet	17	mg
Sugar confectioners	Oral-21; tablet	40	mg
Sugar confectioners	Oral-28; tablet	40	mg
Sugar confectioners	Oral; tablet, delayed action, enteric coated	44.5	mg
Sugar confectioners	Oral; tablet, coated	54	mg
Sugar confectioners	Oral; tablet, sustained action	175	mg
Sugar confectioners	Oral; tablet, film coated	200	mg
Sugar confectioners	Oral; tablet	215.68	mg
Sugar confectioners	Oral; tablet (immed./comp. release), uncoated, chewable	1438	mg
Sugar fruit fine	Oral; tablet	64.924	mg
Synchron oral carrier	Oral; tablet, sustained action	475	mg
Synchron oral carrier base KF	Oral; tablet, sustained action	30	mg
Synchron oral carrier vehicle type EM	Oral; tablet, sustained action	220	mg
Talc	Buccal; tablet	1.5	mg
Talc	Oral; tablet, controlled release	2.5	mg
Talc	Oral; tablet, orally disintegrating, delayed release	3	mg
Talc	Oral-21; tablet	3	mg
Talc	Oral-21; tablet, coated	4.198	mg
Talc	Oral-28; tablet, coated	4.198	mg
Talc	Oral-28; tablet	6.34	mg
Talc	Oral; tablet, enteric coated particles	6.5	mg
Talc	Buccal/sublingual; tablet	15	mg
Talc	Oral; tablet (immed./comp. release), uncoated, chewable	18	mg
Talc	Oral; tablet (immed./comp. release), film coated	22.8	mg
Talc	Oral; tablet, extended release	25	mg
Talc	Oral; tablet, delayed action	27.4	mg

Ingredient	Dosage form	Quantity	Unit
Talc	Oral; tablet, sustained action, coated	29.3	mg
Talc	Oral; tablet, sustained action, film coated	30	mg
Talc	Rectal; tablet	32.4	mg
Talc	Sublingual; tablet	32.4	mg
Talc	Oral; tablet, orally disintegrating	36	mg
Talc	Oral; tablet, film coated	54.72	mg
Talc	Oral; tablet, repeat action	73.933	mg
Talc	Oral; tablet, coated	75	mg
Talc	Oral; tablet, sustained action	91	mg
Talc	Oral; tablet	91.2	mg
Talc	Oral; tablet, delayed action, enteric coated	110	mg
Talcum powder	Oral; tablet, film coated	4.61	mg
Tartaric acid	Oral; tablet, coated	10	mg
Tartaric acid	Oral; tablet	15	mg
Tartaric acid	Oral; tablet, sustained action	29.2	mg
Tartaric acid	Oral; tablet, film coated	30	mg
Tartaric acid	Oral; tablet, orally disintegrating	45	mg
Tartaric acid, DL-	Sublingual; tablet	1.5	mg
Tartaric acid, DL-	Oral; tablet	13.74	mg
Tartaric acid, DL-	Oral; tablet, sustained action	30	mg
Tetrachloroethylene	Oral; tablet, delayed action, enteric coated	702	mg
Titanium dioxide	Oral-21; tablet	0.12	mg
Titanium dioxide	Oral-21; tablet, coated	0.274	mg
Titanium dioxide	Oral-28; tablet, coated	0.274	mg
Titanium dioxide	Oral; tablet, multilayer, extended release	1.1	mg
Titanium dioxide	Oral-28; tablet	1.1748	mg
Titanium dioxide	Oral; tablet (immed./comp. release), film coated	2.11	mg
Titanium dioxide	Oral; tablet, controlled release	2.463	mg
Titanium dioxide	Oral; tablet, orally disintegrating, delayed release	3	mg
Titanium dioxide	Oral; tablet, sustained action, film coated	3	mg
Titanium dioxide	Oral; tablet, sustained action, coated	4.17	mg
Titanium dioxide	Oral; tablet, delayed action	7.8	mg
Titanium dioxide	Oral; tablet, extended release	7.93	mg
Titanium dioxide	Oral; tablet, coated	10.57	mg
Titanium dioxide	Oral; tablet, film coated	12.5	mg
Titanium dioxide	Oral; tablet, enteric coated particles	15	mg
Titanium dioxide	Oral; tablet	27	mg
Titanium dioxide	Oral; tablet, delayed action, enteric coated	358	mg
Titanium dioxide	Oral; tablet, sustained action	358	mg
Tocophersolan	Oral-28; tablet	0.03	mg
Tragacanth	Oral; tablet	4	mg
Tragacanth	Buccal/sublingual; tablet	5	mg
Tragacanth	Oral; tablet, coated	7.5	mg

Ingredient	Dosage form	Quantity	Unit
Triacetin	Oral; tablet (immed./comp. release), film coated	0.72	mg
Triacetin	Oral; tablet, coated	1	mg
Triacetin	Oral; tablet, extended release	1.39	mg
Triacetin	Oral; tablet, sustained action	1.96	mg
Triacetin	Oral; tablet	3.7	mg
Triacetin	Oral; tablet, delayed action, enteric coated	6	mg
Triacetin	Oral; tablet, film coated	15.12	mg
Triacetin	Oral; tablet, controlled release	540	mg
Tribehenin	Oral; tablet	4.8	mg
Triceteareth-4 phosphate	Oral; tablet	180	mg
Triethyl citrate	Oral; tablet, sustained action, film coated	0.5	mg
Triethyl citrate	Oral; tablet, repeat action	0.9	mg
Triethyl citrate	Oral; tablet, sustained action	1.6	mg
Triethyl citrate	Oral; tablet, extended release	1.97	mg
Triethyl citrate	Oral; tablet, sustained action, coated	2.31	mg
Triethyl citrate	Oral; tablet (immed./comp. release), uncoated, chewable	2.8	mg
Triethyl citrate	Oral; tablet, film coated	3.6	mg
Triethyl citrate	Oral; tablet	5.1	mg
Triethyl citrate	Oral; tablet, orally disintegrating, delayed release	18.7	mg
Triethyl citrate	Oral; tablet, delayed action, enteric coated	20.177	mg
Trimyristin	Oral; tablet	16	mg
Trisodium citrate dihydrate	Oral; tablet	110	mg
TY-MED filler, blue	Oral; tablet	80	mg
Urea	Oral; tablet, coated	0.018	mg
Urea	Vaginal; tablet	50	mg
Vanillin	Oral; tablet, enteric coated particles	0.7	mg
Vanillin	Oral; tablet, film coated	0.78	mg
Vanillin	Oral; tablet, delayed action	0.8	mg
Vanillin	Oral; tablet, sustained action, film coated	0.8	mg
Vanillin	Oral; tablet, delayed action, enteric coated	1.16	mg
Vanillin	Oral; tablet	1.5	mg
Vanillin	Oral; tablet (immed./comp. release), uncoated, chewable	2.5	mg
Vanillin	Oral; tablet, sustained action	3.4	mg
Vanillin	Oral; tablet, coated	65.5	mg
Vegetable oil	Buccal; gum, chewing	14.4	mg
Vegetable oil	Oral; tablet	25	mg
Vegetable oil glyceride, hydrogenated	Oral; tablet, sustained action	35	mg
Vegetable oil, hydrogenated	Oral; tablet, coated	2	mg
Vegetable oil, hydrogenated	Oral; tablet (immed./comp. release), uncoated, chewable	8	mg
Vegetable oil, hydrogenated	Oral; tablet, extended release	20	mg
Vegetable oil, hydrogenated	Oral; tablet, film coated	33	mg
Vegetable oil, hydrogenated	Oral; tablet	40	mg
Vegetable oil, hydrogenated	Oral; tablet, sustained action	228.5	mg

Ingredient	Dosage form	Quantity	Unit
Velvetine black powder	Oral; tablet	0.025	mg
Vitamin E	Oral; tablet	0.033	mg
Vitamin E	Oral-21; tablet	0.1	mg
Vitamin E	Oral-28; tablet	0.1	mg
Vitamin E	Oral; tablet, sustained action	1.34	mg
Wax	Oral; tablet	0.02	mg
Wax, vegetable	Oral; tablet, enteric coated particles	2.5	mg
Wax, white	Oral; tablet, repeat action	0.037	mg
Wax, white	Oral; tablet, film coated	0.2	mg
Wax, white	Oral; tablet	0.4	mg
Wax, white	Oral; tablet, coated	3	mg
Wax, white	Oral; tablet, sustained action	14	mg
Wax, yellow	Oral; tablet, coated	0.296	mg
Wax, yellow	Oral; tablet	3.22	mg
Wheat flour	Oral; tablet	1.16	mg
Xanthan gum	Oral; tablet, orally disintegrating	0.15	mg
Xanthan gum	Oral; tablet	14	mg
Xanthan gum	Oral; tablet, sustained action	50	mg
Xanthan gum	Oral; troche	63.2	mg
Xanthan gum	Oral; tablet, sustained action, coated	74.25	mg
Xanthan gum	Oral; tablet, extended release	101.2	mg
Xylitol	Oral; tablet	15.04	mg
Xylitol	Oral; tablet, orally disintegrating	42.3	mg
Xylitol	Buccal; gum, chewing	203.6	mg
Zarzarol	Oral; tablet, coated	8.5	mg
Zein	Oral; tablet, repeat action	4.71	mg
Zein	Oral; tablet, coated	7.1278	mg
Zein	Oral; tablet, sustained action	135	mg
Zeolex	Oral; tablet, sustained action	2	mg
Zinc stearate	Oral; tablet, film coated	4.615	mg
Zinc stearate	Oral; tablet	10.2	mg
Zinc stearate	Oral; tablet, sustained action	36	mg

Part II

Manufacturing Formulations

Pharmaceutical Manufacturing Formulations

Acetaminophen and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetaminophen (fine powder)	500.00
65.00	2	Anhydrous caffeine	65.00
15.00	3	Maize starch	15.00
10.00	4	Povidone (PVP K-30)	10.00
5.00	5	Croscarmellose sodium (Ac-Di-Sol)	5.00
33.00	6	Maize starch	33.00
8.00	7	Povidone (PVP K-90)	8.00
1.00	8	Polysorbate 80 (Tween 80)	1.00
10.00	9	Microcrystalline cellulose (Avicel™ PH102)	10.00
7.00	10	Sodium starch glycolate (Primojel®)	7.00
5.00	11	Croscarmellose sodium (Ac-Di-Sol)	5.00
2.00	12	Stearic acid (fine powder)	2.00
4.00	13	Talc (fine powder)	4.00
–	14	Purified water	155.00

Manufacturing Directions

1. Sift items 1 to 5 through a stainless steel 630-µm sieve. Load into mixer. Mix for 5 minutes at low speed.
2. Dissolve items 7 and 8 in 115 g of purified water (80–90°C) in a vessel.
3. Prepare slurry of item 6 in 40 g of purified water (25–30°C).
4. Add the slurry to the vessel to make a translucent paste. Cool to 45°C to 50°C.
5. Add the binder (item 4) to the paste.
6. Mix at low speed over a period of 3 minutes. Scrape sides and blades. Mix and chop at low speed for 1 to 2 minutes.
7. Check the end point of granulation. If required, add additional purified water to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Unload the wet granules into stainless steel trays for drying.
8. Dry the wet granules at 55°C for 8 hours. After 2 hours of drying, scrape the semidried granules to break the lumps to promote uniform drying. Check the LOD (limit: 1.5–2.0%). If required, dry further at 55°C for 1 hour.
9. Grind the dried granules through a 1.25-mm sieve, using a granulator at medium speed. Collect in stainless steel drums.
10. Load the granules into blender. Sift items 9 to 11 through a 500-µm sieve, using a suitable sifter, and add it to the blender. Mix for 2 minutes.
11. Sift items 12 and 13 through a 500-µm sieve.
12. Add 5 to 10 g of granules from bulk. Mix in.
13. Check temperature and humidity before compressing (recommended: relative humidity 55–60% at a temperature not exceeding 27°C).
14. Compress the granules using a rotary tabletting machine. Average weight of tablet is 665.00 mg.

Acetaminophen and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetaminophen (crystalline)	500
50.00	2	Caffeine (Knoll)	50
90.00	3	Avicel® PH101	90
10.00	4	Kollidon® 30	10
20.00	5	Kollidon® CL	20
10.00	6	Polyethylene glycol (PEG-6000) (powder)	10

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press with high-compression force.
2. Compress into 683-mg tablets, using 12-mm biplanar punches.
3. If the flowability of the powder mixture for tabletting is not high enough, some Aerosil 200 should be added.

Acetaminophen and Codeine Tablets (Tylenol)[a]

Each Tylenol with codeine tablet contains
No. 2 codeine phosphate, 15 mg; acetaminophen, 300 mg
No. 3 codeine phosphate, 30 mg; acetaminophen, 300 mg
No. 4 codeine phosphate, 60 mg; acetaminophen, 300 mg

[a]Tylenol inactive ingredients: Powdered cellulose, magnesium stearate, sodium metabisulfite, pregelatinized starch, starch (corn).

Acetaminophen and Diphenhydramine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
325.00	1	Acetaminophen (fine powder)	325.00
26.00	2	Diphenhydramine HCl	26.00
50.00	3	Maize starch	50.00
07.00	4	Povidone (PVP K-30)	7.00
50.00	5	Microcrystalline cellulose (Avicel™ PH101)	50.00
42.00	6	Cornstarch	42.00
10.00	7	Povidone (PVP K-30)	10.00
09.50	8	Cellulose (powdered)	9.50
65.50	9	Cellulose (microcrystalline) (Avicel™ PH102)	65.50
20.00	10	Sodium starch glycolate (Primojel®)	20.00
08.00	11	Stearic acid (fine powder)	8.00
05.00	12	Talc (fine powder)	5.00
02.00	13	Magnesium stearate	2.00
–	14	Purified water	180.00

Manufacturing Directions

1. Sift items 1 to 5 through a 630-μm stainless steel sieve.
2. Load into mixer. Mix for 5 minutes at low speed.
3. Dissolve item 7 in 135 g of purified water (80–90°C) in a vessel.
4. Prepare a slurry of item 6 in 45 g of purified water (25–30°C).
5. Add the slurry to the vessel to make a translucent paste.
6. Cool to 45°C to 50°C.
7. Add the binder (item 4).
8. Mix at low speed over a period of 3 minutes. Scrape sides and blades. Mix and chop at low speed for 1 to 2 minutes. Check the end point of granulation. If required, add additional purified water to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.)
9. Unload the wet granules into stainless steel trays for drying.
10. Dry the wet granules in an oven at 55°C for 10 hours. After 2 hours of drying, scrape the semidried granules to break the lumps to promote uniform drying. Check the LOD (limit: 1–2%). If required, dry further at 55°C for 1 hour.
11. Grind the dried granules through a 1.25-mm sieve at medium speed.
12. Collect in stainless steel drums. Load the granules into blender.
13. Sift items 8 to 10 through a 500-μm sieve, using a suitable sifter, and add mixture to blender. Mix for 2 minutes.
14. Sift items 11 to 13 through a 500-μm sieve. Add 5 to 10 g of granules from bulk.
15. Mix in polyethylene bag for 1 minute. Add to blender. Blend for 1 minute.
16. Check the temperature and humidity before compressing (limit: temperature not exceeding 27°C; relative humidity 55–65%).
17. Compress the granules with a rotary tabletting machine. Compress to an average tablet weight of 620 mg.
18. Disintegration time is not more than (NMT) 15 minutes; friability NMT is 1.0%.
19. Coating: Use one of the HPMC aqueous formulations described in the Appendix, such as Yellow Opadry.

Acetaminophen and Orphenadrine Citrate Tablets (450 mg/35 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
450.00	1	Acetaminophen powder	450.00
35.00	2	Orphenadrine citrate, 5% excess	35.00
66.00	3	Starch (maize)	66.00
20.00	4	Microcrystalline cellulose (Avicel PH 102)	5.00
7.50	5	Aerosil 200	7.50
0.25	6	Dye yellow	0.25
16.00	7	PVP K30	16.00
5.00	8	Aerosil 200	5.00
7.50	9	Glycerine	7.50
10.00	10	Gelatin powder	10.00
25.00	11	Premojel	25.00
12.00	12	Avicel PH 102	12.00
2.00	13	Aerosil 200	2.00
2.00	14	Magnesium stearate	2.00
–	15	Water, purified, ca	464 mL

Manufacturing Directions

1. Charge items 7 and 6 into a mixer, add 50% of item 15, and mix for 10 to 15 minutes at medium speed.
2. Add item 5 into step 1 slowly, while stirring at medium speed, and disperse well.
3. Add item 9 and mix for 3 minutes.
4. In a separate vessel, add item 10 and the remaining 50% of item 15; mix for 5 minutes at medium speed.
5. Add step 3 into step 4 and mix for 2 to 3 minutes.
6. In a separate mixer, charge items 1 to 5 and mix and chop for 3 minutes at slow speed.
7. Add the solution from step 5 to step 6 and mix for 2 to 3 minutes.
8. Dry the wet mass in a fluid-bed dryer at 60°C for 60 minutes until a loss on drying rate of 1.5% to 2.5% is reached.
9. Pass the dried granules through a 6-mm sieve followed by a 1.5-mm sieve in a granulator.
10. Add to the granules items 11 to 13, previously sieved through a 500-μm sieve. Mix for 3 minutes.
11. Add item 14, previously sieved through a 250-μm sieve, and blend for 1 minute.
12. Compress using 12.7-mm round flat punches to a fill weight of 660 mg.

Acetaminophen and Phenprobamat Tablets (200 mg/200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Acetaminophen powder $<$ 0.5 mm	200.00
200.00	2	Phenprobamat	200.00
35.00	3	Microcrystalline cellulose (Avicel PH 101)	35.00
20.00	4	Kollidon VA 64	20.00
10.00	5	Kollidon CL	10.00
5.00	6	Magnesium stearate	5.00
6.00	7	Aerosil 200	6.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high-compression force.
2. Compress into 475-mg tablets, using 12-mm biplanar punches.

Acetaminophen and Pseudoephedrine Hydrochloride Tablets

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Quantity/1000 Caplets (g)
325.00	1	Acetaminophen (fine powder)	325.00
31.50	2	Pseudoephedrine HCl	31.50
50.00	3	Cornstarch	50.00
7.00	4	Povidone (PVP K-30)	7.00
50.00	5	Microcrystalline cellulose (Avicel™ PH101)	50.00
42.00	6	Cornstarch	42.00
10.00	7	Povidone (PVP K-30)	10.00
9.50	8	Cellulose (powdered)	9.50
60.00	9	Cellulose (microcrystalline) (Avicel™ PH102)	60.00
20.00	10	Sodium starch glycolate (Primojel®)	20.00
8.00	11	Stearic acid (fine powder)	8.00
5.00	12	Talc (fine powder)	5.00
2.00	13	Magnesium stearate	2.00
–	14	Purified water	180.00

Manufacturing Directions

1. Sift items 1 to 5 through a stainless steel 630-μm sieve.
2. Load into mixer. Mix for 5 minutes at low speed.
3. Dissolve item 7 in 135 g of purified water (80–90°C) in a vessel.
4. Prepare a slurry of item 6 in 45 g of purified water (25–30°C).
5. Add the slurry to the vessel to make a translucent paste. Cool to 45°C to 50°C. Add the binder (item 4).
6. Mix at low speed over a period of 3 minutes. Scrape sides and blades. Mix and chop at low speed for 1 to 2 minutes. Check the end point of granulation. If required, add additional purified water to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Unload the wet granules into stainless steel trays for drying.
7. Dry the wet granules in oven at 55°C for 10 hours.
8. After 2 hours of drying, scrape the semidried granules to break up the lumps for uniform drying.
9. Check the LOD (limit: 1–2.0%). If required, dry further at 55°C for 1 hour.
10. Transfer the dried granules to stainless steel drums.
11. Grind the dried granules through a 1.25-mm sieve, using granulator at medium speed. Collect in stainless steel drums. Load the granules into blender.
12. Sift items 8 to 10 through a 500-μm sieve, using a suitable sifter, and add to blender. Mix for 2 minutes.
13. Sift items 11 to 13 through a 500-μm sieve.
14. Add 5 to 10 g of granules.
15. Mix in a polyethylene bag for 1 minute. Add to blender. Blend for 1 minute. Unload in stainless steel drums.
16. Compress into 620-mg tablets, using 6-mm capsule-shaped punches.
17. Coat: The formula for the coating solution is determined to obtain a weight gain of 10 mg per caplet, considering evaporation and loss during the coating operation.

Acetaminophen Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Acetaminophen, milled (Hoechst)	300.00
600.00	2	Sucrose, milled	600.00
550.00	3	Kollidon® CL-M	550.00
30.00	4	Orange flavor (FDO)	30.00
30.00	5	Strawberry flavor (FDO)	30.00
60.00	6	Kollidon® 30	60.00
QS	7	Ethanol (96%)	~425.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with solution of items 6 and 7, pass through a sieve, and press with medium-compression force.
2. Average weight of tablet is 1620 mg, obtained using a 20-mm biplanar punch.
3. Taste is sweet, fruity, and only very slightly bitter.

Acetaminophen, Chlorpheniramine Maleate, and Pseudoephedrine Caplets

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Quantity/1000 Caplets (g)
325.00	1	Acetaminophen (fine powder)	325.00
31.50	2	Pseudoephedrine HCl	31.50
2.10	3	Chlorpheniramine maleate	2.10
50.00	4	Cornstarch	50.00
7.00	5	Povidone (PVP K-30)	7.00
50.00	6	Cellulose (microcrystalline) (Avicel™ PH101)	50.00
42.00	7	Cornstarch	42.00
10.00	8	Povidone (PVP K-30)	10.00
9.50	9	Powdered cellulose	9.50
77.90	10	Cellulose (microcrystalline) (Avicel™ PH102)	77.90
20.00	11	Sodium starch glycolate (Primojel®)	20.00
8.00	12	Stearic acid (fine powder)	8.00
5.00	13	Talc (fine powder)	5.00
2.00	14	Magnesium stearate	2.00
–	15	Purified water	180.00

Manufacturing Directions

1. Sift items 1 to 6 through a 630-μm stainless steel sieve.
2. Load into mixer. Mix for 5 minutes at low speed.
3. Dissolve item 8 in 135 g of item 15 (80–90°C) in a vessel.
4. Prepare a slurry of item 7 in 45 g of item 15 (25–30°C). Add the slurry to the vessel to make a translucent paste. Cool to 45°C to 50°C.
5. Add the binder (item 5) to step above.
6. Mix at low speed over a period of 3 minutes. Scrape sides and blades.
7. Mix and chop at low speed for 1 for 2 minutes. Check the end point of granulation. If required, add additional item 15 to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Unload the wet granules in stainless steel trays for drying.
8. Dry the wet granules at 55°C for 10 hours. After 2 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying. Check the LOD (limit: 1.0–2.0%). If required, dry further at 55°C for 1 hour.
9. Grind the dried granules through a 1.25-mm sieve at medium speed. Collect in stainless steel drums.
10. Load the granules into blender.
11. Sift items 9 to 11 through a 500-μm sieve, using suitable sifter, and add mixture to blender. Mix for 2 minutes.
12. Sift items 12 to 14 through a 500-μm sieve.
13. Add 5 to 10 g of granules from bulk. Mix in a polyethylene bag for 1 minute.
14. Add to blender. Blend for 1 minute.
15. Check temperature and humidity before start of compression; temperature should not exceed 27°C and recommended relative humidity is 55% to 65%.
16. Compress the granules using rotary tabletting machine. Tablet weight is 640 mg.
17. Coating: Select an appropriate coating such as Opadry HPMC. The formula for the coating solution is determined to obtain a weight gain of 10 mg per caplet, considering evaporation and loss during coating operation.

Acetaminophen, Dextromethorphan, and Pseudoephedrine Caplets

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Quantity/1000 Caplets (g)
325.00	1	Acetaminophen (fine powder)	325.00
31.50	2	Pseudoephedrine HCl	31.50
15.50	3	Dextromethorphan HBr	15.50
50.00	4	Cornstarch	50.00
7.00	5	Povidone (PVP K-30)	7.00
50.00	6	Cellulose (microcrystalline) (Avicel™ PH101)	50.00
42.00	7	Cornstarch	42.00
10.00	8	Povidone (PVP K-30)	10.00
9.50	9	Cellulose (powdered)	9.50
64.50	10	Cellulose (microcrystalline) (Avicel™ PH102)	64.50
20.00	11	Sodium starch glycolate (Primojel®)	20.00
8.00	12	Stearic acid (fine powder)	8.00
5.00	13	Talc (fine powder)	5.00
2.00	14	Magnesium stearate	2.00
–	15	Purified water	180.00

Manufacturing Directions

Follow the manufacturing directions provided for acetaminophen, chlorpheniramine, and pseudoephedrine caplets.

Acetaminophen, Dextropropoxyphen Hydrochloride Tablets (325 mg/32 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
325.00	1	Acetaminophen	325.000
32.00	2	Dextropropoxyphen hydrochloride	32.500
8.00	3	Povidone (K29–32)	8.000
7.50	4	Starch (maize)	7.500
QS	5	Water, purified	80.00 mL
10.00	6	Cellulose microcrystalline (Avicel PH 101)	10.000
5.00	7	Talc purified	5.000
2.00	8	Magnesium stearate	2.000
QS	9	Coating solution white opaque methocel-ethocel	160.000 mL

Manufacturing Directions

1. Granulation
   a. Pass acetaminophen, dextropropoxyphen, and starch through a 595-µm aperture screen, transfer to a suitable mixer, and mix for 10 minutes.
   b. Warm the water and dissolve the povidone.
   c. Slowly add the povidone solution to the mixer and mix until a suitable-consistency mass is obtained. Add extra water if needed.
   d. Pass the mass through a 4-mm aperture screen on an oscillating granulator and dry in a tray dryer at 105°C until the LOD is below 2% (Brabender, 105°C, 1 hour) or the equivalent.
   e. Pass the granules through a 1.59-mm aperture screen on a suitable comminuting mill, at medium speed, with knives forward into tared polyethylene-lined drums.
2. Lubrication
   a. Transfer the dried granulation to a suitable blender.
   b. Screen the cellulose microcrystalline, talc, and povidone through a 595-µm aperture screen, add to the blender, and blend for 5 minutes.
   c. Screen the magnesium stearate through a 400-µm aperture screen and add it to the blender. Blend for 2 minutes.
   d. Discharge the granule into polyethylene-lined drums, seal, and weigh for yield.

3. Compression
   a. Compress using 14.5 × 7.5 mm capsule-shaped punches. Weight of 10 tablets is about 4.05 g, not more than 3% variation; thickness is 5.2 to 5.8 mm (range not more than ±5%); hardness is 8 kPa; and disintegration time not more than 15 minutes in water.
   b. Collect in *clean*, tared polyethylene-lined drums, and weigh for yield.
4. Coating
   a. *Pan spray:* Binks Bullow L450 spray gun or equivalent, fitted with a No. 63B material nozzle, a No. 66SF or 66SD atomizing nozzle, or a No. 39 needle.
      i. Divide tablets and solution.
      ii. Load into pan and preheat for 3 hours to 48°C.
      iii. Apply the solution at 10 to 21 psi, with a liquid pressure of 5 to 10 psi, to give a flow rate of 350 to 500 mL/min at a pan speed of 20 to 25 rpm. Rotate pan and commence spraying with continuous application of hot air at 46°C to 49°C (damper fully open). Ensure that the tablet bed does not become too hot. Tablets should be put only just above room temperature. You must switch off hot air when a coating solution is not being sprayed. Continue applying the solution until the average tablet weight has increased by 8 mg. When this weight gain is achieved, roll the tablets in cool air until dry. When completely dry, remove the tablets from the pan, and transfer to polyethylene-lined drums. Leave the drums open for at least 6 hours in a dust-free area.
   b. *Accela Cota:* Airless high-pressure spray system with two guns. Nozzle type: 0.018-in. (0.45-mm) orifice diameter with a 65° spray angle, pan speed of 5 rpm, inlet temperature of 70°C, inlet airflow set at quarter to half available flow, and exhaust sufficient to maintain coating drum under negative pressure (set water gauge at 7 in.).
      i. Divide tablets and solution.
      ii. Load tablets, rotate pan occasionally, and warm tablets until the exhaust temperature is 38°C to 42°C. Do not rotate longer than is necessary to achieve even warming.
      iii. Adjust the pump pressure to give an application rate of approximately 500 to 600 mL/min. Commence spraying with the coating solution. Adjust the pressure to maintain the exhaust temperature of 38°C to 42°C.
      iv. When the average weight gain of 8 mg is obtained, the tablets are dried: reduce pan speed to 7 rpm and maintain the inlet temperature and exhaust settings for 5 minutes. If the exhaust temperature reaches 45°C, switch off heat and control rotation for another 10 minutes; occasionally rotate the pan to ensure even cooling. Remove tablets when the exhaust temperature is 28°C to 32°C.
      v. Ensure that tablets are thoroughly dry, and unload into polyethylene-lined drums; leave the drum unsealed for 1 hour in a dust-free humidity-controlled area.

Acetaminophen Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetaminophenl (powder < 300 μm)	500.00
500.00	2	Sodium bicarbonate	500.00
430.00	3	Tartaric acid (powder)	430.00
200.00	4	Dextrose	200.00
QS	5	Flavoring	QS
20.00	6	Kollidon® 30	20.00
—	7	Isopropanol	100.00 mL
60.00	8	PEG-6000 (powder)	60.00

Manufacturing Directions

1. Granulate the mixture of items 1 to 5 with solution of items 6 and 7.
2. Pass through an 0.8-mm sieve, add item 8, and then mix.
3. Press to tablets (average weight, 1700 mg; 16-mm-diameter biplanar tablet).

Acetaminophen Fast-Dissolving Tablet

Manufacturing Directions

1. To the vortex of a rapidly stirred vessel containing 2.85 kg of deionized water is added 300 g of croscarmellose sodium, forming slurry. This slurry is mixed for 10 minutes.
2. Concurrently, 5.0 kg of powdered acetaminophen is placed in the bowl of a mixer.
3. At the conclusion of the mixing time for the slurry of croscarmellose sodium, the slurry is added slowly to the acetaminophen in the mixer bowl, forming a granulation, which is then placed in trays and dried at 70°C in an oven for 3 hours.
4. The dry granulation is then passed through a US Standard 14-mesh screen (1410 μm).
5. Dry granulation (4796 g) is then placed in a twin-shell blender, and to this are added 1584 g of Avicel AC-815 (85% microcrystalline cellulose coprocessed with 15% of a calcium sodium alginate complex) and 1584 g of microcrystalline cellulose (Avicel PH-302).
6. This is thoroughly blended for 10 to 15 minutes after which 36.24 g of magnesium stearate is added and mixed for an additional 5 minutes.
7. Prior to being added to the blender, the magnesium stearate had been passed through a US Standard 30-mesh screen.
8. The resulting blend is compressed into caplet-shaped tablets with an average weight of 0.884 g and an average thickness of 7.869 mm (0.3098 in.).
9. The hardness of these tablets averaged 11.98 kPa. Friability of these tablets is measured at 0.433% after 10 minutes and 0.847% after 19 minutes.
10. The average disintegration time is 26 seconds in 10 mL of deionized water, forming a suspension with minimal shaking.

Acetaminophen, Ibuprofen, and Orphenadrine Tablets (250 mg/200 mg/200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetaminophen (powder < 300 μm)	250.00
200.00	2	Ibuprofen	200.00
200.00	3	Orphenadine hydrochloride	200.00
200.00	4	Ludipress	200.00
5.00	5	Magnesium stearate	5.00
5.00	6	Aerosil 200	5.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with high-compression force.
2. Compress into 761-mg tablets, using 12-mm planar punches.

Acetaminophen, Ibuprofen, and Orphenadine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetaminophen (powder < 300 μm)	250.00
200.00	2	Ibuprofen	200.00
100.00	3	Orphenadine hydrochloride	100.00
200.00	4	Ludipress®	200.00
5.00	5	Magnesium stearate	5.00
5.00	6	Aerosil® 200	5.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve and mix.
2. Press with high-compression force.
3. Tablet weight is 761 mg for a 12-mm biplanar tablet.

Acetaminophen Microsphere Tablet

Manufacturing Directions

1. Formulation: Acetaminophen (APAP) powder (melting point 169–170.5°C) 85%, carnauba wax 7.5%, Pluronic F68 7.5%.
2. Pluronic is milled through a FitzMill, using a 40-mesh screen.
3. All of the ingredients are blended at 60 Hz of slow speed, with chopper, for 10 minutes.
4. The blend is then subjected to liquiflash processing at 60 Hz and 37% nominal power, using the 5-in. V-groove heater head.
5. The collected microspheres are sieved.
6. The fraction passing through a 40-mesh sieve and retained on 120-mesh sieve is coated.
7. The microspheres selected are coated in a fluid-bed coater for taste-masking at a 30% coating level with a coating solution containing a 1:1 ethylcellulose/hydroxypropylcellulose blend in acetone:isopropyl alcohol solvent.
8. A preblend of 78.25% sucrose, 11.0% sorbitol, 10.0% xylitol, and 0.75% TWEEN (Polysorbate) 80 is prepared.
9. The floss preblend is processed using the 5 in. crown head at a temperature of 250°C and rotational speed of 60 Hz (3600 rpm).
10. The floss collected is mixed with 2% lactose (w/w) for 2 minutes at 100 rpm and 200 proof ethanol sprayed in a quantity equal to 0.5% (w/w) of the quantity of the floss.
11. The floss is then dried at 45°C for 90 minutes with intermittent mixing.
12. The dried floss is screened through a 20-mesh screen.
13. APAP taste-masked microspheres (step 5) 47.97, floss (step 6) 48.88, grape flavor 0.70, citric acid 1.50, acesulfame potassium 0.20, silicon dioxide 0.25, and sodium stearyl fumarate 0.50 are processed.
14. The coated APAP microspheres are blended with the sieved floss for 5 minutes in a mixer, followed by the addition of flavors, sweeteners, and citric acid for another 3 minutes.
15. Thereafter silicon dioxide is added and the mix blended for another 2 minutes. The final addition, sodium stearyl fumarate, is followed by blending for an additional 2 minutes.
16. The blend is then tabletted using flat-faced bevel edge punches (tablet weights are 255 mg for 9-mm punch tooling, equivalent to 80-mg APAP dose, and 510 mg for 12-mm punch tooling, equivalent to 160-mg APAP dose).
17. The hardness values ranged from 0.5 to 2.0 kPa.

Acetaminophen, Norephedrine, and Phenyltoloxamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Acetaminophen (crystalline) (Merck)	300.00
25.00	2	Norephedrine hydrochloride (Knoll)	25.00
22.00	3	Phenyltoloxamine	22.00
200.00	4	Cornstarch	200.00
25.00	5	Kollidon® 30	25.00
–	6	Ethanol (96%)	QS
25.00	7	Kollidon® CL	25.00
5.00	8	Magnesium stearate	5.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with solution of items 5 and 6.
2. Dry, pass through an 0.8-mm sieve, and add items 7 and 8.
3. Press with high-compression force.
4. Tablet weight is 601 mg for 12-mm biplanar tablet.

Acetaminophen, Norephedrine, and Phenyltoloxamine Tablets (300 mg/25 mg/22 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Acetaminophen crystalline	300.00
25.00	2	Norephedrine hydrochloride	25.00
22.00	3	Phenyltoloxamine	22.00
200.00	4	Starch (maize)	200.00
25.00	5	Kollidon 30	25.00
–	6	Alcohol	QS
25.00	7	Kollidon CL	25.00
5.00	8	Magnesium stearate	5.00

Manufacturing Directions

1. Granulate the mixture of items 1 through 4 with a solution of items 5 and 6.
2. Dry, pass through a 0.8-mm sieve, add items 7 and 8, and press with high-compression force.
3. Compress into 601-mg tablets, using 12-mm planar punches.

Acetaminophen, Phenylpropanoloamine, Dextromethorphan, and Chlorpheniramine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Acetaminophen	200.00
12.50	2	Phenylpropanolamine hydrochloride (10% excess)	13.75
10.00	3	Dextromethorphan hydrobromide (10% excess)	11.00
1.00	4	Chlorpheniramine maleate (10% excess)	1.10
64.65	5	Cellulose (microcrystalline) (Avicel™ PH101)	121.72
28.00	6	Sodium starch glycolate (pH 5.5–7.5)	28.00
17.00	7	Povidone (PVP K-29–32)	17.5
–	8	Distilled purified water	~80.0 mL
2.00	9	Magnesium stearate	2.00
125.00	10	Acetaminophen	125.00
50.00	11	Ascorbic acid; use item 12	–
56.25	12	Sodium ascorbate (special grade) (20% excess)	67.50
24.00	13	Sodium starch glycolate (pH 5.5–7.5)	24.00
15.00	14	Povidone (PVP K-29–32)	~15.00
–	15	Alcohol SD 3A (200 proof)	75.0 mL

Manufacturing Directions

1. Dissolve chlorpheniramine and Povidone (item 7) in the purified water.
2. Pass phenylpropanolamine, dextromethorphan, and an equal portion of Avicel (item 5) through a 790-μm screen to break any agglomerates.
3. Blend the screened items in a suitable mixer for 5 minutes.
4. Load acetaminophen (item 1), sodium starch glycolate (item 6), remaining Avicel (item 5), and blended items from the previous step into a suitable planetary mixer.
5. Blend for 10 minutes.
6. Granulate the blend from the solution above.
7. Add the granulating solution in three equal portions, massing for 5 minutes after each addition.
8. Pass the wet mass through a 4.2-mm screen onto paper-lined trays.
9. Dry at 50°C until the granule LOD is 1% to 1.5%.
10. Pass the dried granules through an oscillating granulator fitted with a 790-μm screen.
11. Load the dried granules into a suitable blender.
12. Pass the magnesium stearate through a 600-μm screen and add to the blender.
13. Blend for 5 minutes.
14. Compress to the following specifications: tablet weight of 291.0 mg and tablet thickness of 4.20 to 4.40 mm.

Acetaminophen, Propoxyphenazone, and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetaminophen powder	250.00
150.00	2	Propoxyphenazone (isopropyl antipyrine)	150.00
50.00	3	Anhydrous caffeine	50.00
120.00	4	Avicel™ PH102	120.00
5.00	5	Pharmacoat® 603	5.00
3.25	6	Magnesium stearate	3.25
9.75	7	Talcum	9.75
1.30	8	Silicic acid	1.30
7.00	9	Methocel E-15	7.00
32.50	10	Esmaspreng fine	32.50
21.20	11	Maize starch	21.20
–	12	Water purified	QS

Manufacturing Directions

1. Place into a suitable vessel 5.00 g of Pharmacoat and 74.00 g of purified water; stir until homogeneous aqueous mucilage is obtained.
2. Mix in another vessel 250 g of acetaminophen powder and 17.50 g of Esmaspreng fine; add the above granulating solution and knead for approximately 10 minutes until an evenly moist mass of soft lumps is obtained.
3. Granulate by means of centrifugal granulator with 10-mm screen; dry the moist granulate overnight on trays in drying oven at 45°C (relative humidity of 20–30%).
4. Crush the dried cake through an oscillator with a 1.5-mm perforated plate.
5. In a suitable container, add 65 g of deionized water and 7.0 g of methocel.
6. Stir until homogeneous aqueous mucilage is obtained.
7. Mix into another vessel 150 g of isopropyl antipyrine, 50 g of caffeine, 15 g of Esmespreng fine, and 5.0 g of maize starch.
8. Pass through a centrifugal granulator with 1.0-mm screen; place the mixture into another vessel and knead for approximately 10 minutes until an evenly moist mass of small lumps is obtained.
9. Granulate through centrifugal granulator with 10-mm perforated screen.
10. Dry moist granulate overnight on trays in drying oven at 45°C (relative humidity of 10–20%).
11. Crush the dried granules through oscillator with a 1.5-mm perforated plate; store in airtight container.
12. Mix into a tumbling mixer 4.875 g of talc, 1.625 g of magnesium stearate, 0.65 kg of silicic acid, and 60.00 g of Avicel PH102.
13. Pass through a 0.5-mm round sieve, load acetaminophen granulate and isopropyl antipyrine/caffeine granulate, and add premixture of talc into blender.
14. Mix the mixture well for 30 minutes (relative humidity of 30–35%).
15. Store mix in airtight container.
16. Compress 650-mg tablet to 12.8–13.2 mm; hardness, 6 to 20 kPa; disintegration time, 5 minutes.

Acetaminophen, Salicylamide, Caffeine, and Codeine Tablets (150 mg/200 mg/50 mg/10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Salicylamide	200.00
150.00	2	Acetaminophen powder	150.00
50.00	3	Caffeine anhydrous	50.00
10.00	4	Codeine phosphate	10.00
130.00	5	Starch (maize)	130.00
5.00	6	Gelatin powder	5.00
8.00	7	PVP K30	8.00
1.00	8	Aerosil 200	1.00
30.00	9	Starch (maize)	30.00
–	10	Water, purified	300 mL
10.00	11	Talc powder	10.00
19.00	12	Starch (maize), dried	19.00
1.00	13	Aerosil 200	1.00

Manufacturing Directions

Note: The binding solution is prone to microbiological growth. Use only freshly prepared and properly stored solution.

1. Charge item 6 and about 25 mL of item 10 into a vessel to dissolve item 6. Mix for 10 minutes.
2. In a separate vessel, add and dissolve items 9 and 7 in about 12 mL of water.
3. Charge item 5 into a vessel; add about 40 mL of cold item 10 and 20 mL of hot (70–75°C) water, after first dissolving in cold water.
4. In a separate vessel, charge items 1 to 5 after passing them through a 630-μm sieve. Mix for 5 minutes at medium speed.
5. Add binding solution from step 3 and mix at medium speed. Continue until a satisfactory mass is obtained.
6. Dry the wet mass in a fluid-bed dryer at 50°C for 45 minutes to 1.5% to 2.5% LOD.
7. Pass the dried granules through a 1.5-mm sieve.
8. Load granules in a cone blender and mix for 5 minutes.
9. Add items 11 to 13 (passed through a 500-μm sieve) to blender, and blend for 5 minutes.
10. Compress into 634-mg tablets, using 12.7-mm flag bevel-edge punches.

Acetaminophen Sustained-Release Tablets

Manufacturing Directions

1. 300 g of acetaminophen and 60 g of hydroxypropylmethyl cellulose were dissolved in a mixture of 720 g of methanol and 720 g of dichloromethane.
2. 300 g of Celphere 102 (mean particle diameter of approximately 127 μm, particle diameter of approximately 50–150 μm) was introduced to a fluidized bed granulator and coated with the solution by the side spraying method (spraying liquid volume 14 g/min, spraying air pressure 3 kg/cm^2, product temperature 32°C, and inlet temperature 45°C) to obtain acetaminophen particles.
3. Separately, 48 g of ethyl cellulose and 12 g of hydroxypropylmethyl cellulose were dissolved in a mixture of 57 g of purified water and 1083 g of methanol.
4. Acetaminophen particles (300 g) were introduced to a fluidized bed granulator and coated with this solution by side spraying (spraying liquid volume of 8 g/min, spraying air pressure of 3 kg/cm^2, product temperature of 38°C, and inlet temperature of 67°C) to obtain sustained-release fine particles.
5. 66 g of these sustained-release fine particles and 314.25 g mannitol that had been pulverized by a pin mill pulverizing device were granulated (spraying liquid volume 15 g/min, spraying air pressure of 1.1 kg/cm^2, product temperature of 30°C, inlet temperature of 38°C, and spraying cycle of 30-seconds spraying and 30-seconds drying) with an aqueous 30% w/w solution containing 67.5 g of maltose in a fluidized bed granulator to obtain the final composition.
6. After further mixing 2.25 g of magnesium stearate with the composition that was obtained, 450-mg tablets containing 25-mg acetaminophen per tablet were made under a tableting pressure of 25 kg/punch and an initial hardness of 2.0 kPa, using a rotary tableting machine.
7. Next, these tablets were kept for 24 hours while heating and humidifying at 25°C/75% RH, using a thermostatic chamber at constant humidity. Then they were dried for 3 hours at 30°C and 40% RH.
8. The tablets that were obtained showed a hardness of 3.5 kPa and disintegration time in the buccal cavity of 12 seconds.

Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetaminophen (fine powder)	500.00
44.15	2	Maize starch	44.15
0.84	3	Potassium sorbate	0.84
18.00	4	Povidone (PVP K-30)	18.00
4.00	5	Aerosil® 200	4.00
12.00	6	Gelatin (powder)	12.00
4.00	7	Glycerol	4.00
30.00	8	Cellulose (powder)	30.00
12.00	9	Primojel®	12.00
8.00	10	Stearic acid (fine powder)	8.00
2.00	11	Magnesium stearate	2.00
5.00	12	Talc (fine powder)	5.00
QS	13	Purified water	QS

Manufacturing Directions

1. Binder solution: Prepare in several batches. Add items 3 to 5 with about 50% quantity of water, dissolve item 1 in water, add item 4, and dissolve at medium speed. Avoid foaming.
2. Add item 5 and mix for 3 minutes.
3. Dissolve item 6 in 70°C to 80°C purified water, and mix until clear. Avoid foaming.
4. Add item 7 and mix gently; add to mixture from previous step.
5. Mix items 1 and 2 for 5 minutes.
6. Add binding solution and mix at slow speed until granules form; add extra water if necessary.
7. Dry in fluid-bed dryer at 55°C for 30 minutes; after 15 minutes, scrape granules to break up lumps to promote uniform drying. Dry to 1% to 1.5% LOD.
8. Grind through a 3.0-mm sieve and then through a 1.0-mm sieve; load into a double-cone blender.
9. Pass cellulose powder, Primojel, and stearic acid through a 500-μm sieve; bag-mix magnesium stearate and fine talc powder, and pass through a 250-μm sieve; then add portion of granules from the bulk to the bag and mix for 1 minute.
10. Add both of these parts to the granules.
11. Compress into 17.6 × 7.2-mm caplet punches of 10- to 14-kPa hardness and 5.8- to 6.0-mm thickness.

Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetaminophen (crystalline)	500.00
137.00	2	Avicel™ PH102	137.00
35.00	3	Kollidon® VA 64	35.00
21.00	4	Kollidon® CL	21.00
3.00	5	Magnesium stearate	3.00
4.00	6	Aerosil® 200	4.00

Manufacturing Directions

1. Pass the lubricant through a 200-mm sieve and mix all other components.
2. Pass through 0.8-mm sieve, add the lubricant, and press with a high-compression force of 25 to 30 kN.
3. Fill 699 mg.

Acetaminophen Tablets

Bill of Materials			
Scale (g/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500	1	Acetaminophen (crystalline)	500
150	2	Avicel™ PH102	150
20	3	Kollidon® VA 64	20
15	4	Kollidon® CL	15
15	5	PEG-6000 (powder)	15
2	6	Aerosil® 200	2

Manufacturing Directions

1. Pass the lubricant through a 200-μm sieve and mix all other components.
2. Pass the mix through an 0.8-mm sieve, add the lubricant, and press with a high-compression force of 25 to 30 kN.
3. Weight should be 703 mg.

Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetaminophen (powder)	500.00
30.00	2	Dicalcium phosphate	30.00
12.00	3	Kollidon® CL	12.00
20.00	4	Kollidon® VA 64	20.00
10.00	5	Kollidon® 90F	10.00
–	6	Ethanol (96%)	70 mL (max.)
12.00	7	Kollidon® CL	12.00
10.00	8	Polyethylene glycol (powder)	10.00

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with the solution of items 5 and 6.
2. Dry, sieve, and mix with items 7 and 8.
3. Press with high-compression force of 25 to 30 kN.
4. Tablet weight is 587 mg for an 11-mm biconvex tablet.

Acetaminophen Tablets, Chewable

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
89.90	1	Acetaminophen, use acetaminophen particles coated with cellulose acetate and PVP	89.90
246.00	2	Mannitol granular	246.00
30.00	3	Microcrystalline cellulose	30.00
9.00	4	Aspartame	9.00
1.27	5	Dyes	1.27
2.10	6	Citric acid	2.10
2.30	7	Flavor	2.30
4.40	8	Magnesium stearate	4.40

Manufacturing Directions

1. Acetaminophen is coated with a layer of a taste-masking composition with a thickness of about 3 to 10 μm. The coating should be substantially free of cracks, holes, and other imperfections when examined under a scanning electron microscope at 100 to 500× magnification.
2. Charge items 1 to 7 in a suitable blender and mix for 20 minutes.
3. Add item 8 to step 2 and blend for 2 minutes.
4. Compress the appropriate quantity.

Acetaminophen Tablets for Children

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
210.00	1	Acetaminophen (Merck)	210.00
168.00	2	Avicel™ PH101	168.00
13.00	3	Kollidon® VA 64	13.00
6.00	4	Kollidon® CL	6.00
2.00	5	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix, and press with medium-compression force.
2. Tablet weight is 401 mg for a 12-mm biplanar tablet.

Acetaminophen-Tramadol Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Acetaminophen	200.00
20.00	2	Tramadol hydrochloride	20.00
50.40	3	Microcrystalline cellulose	50.40
19.20	4	Povidone K-90	19.20
4.80	5	Croscarmellose sodium	4.80
3.20	6	Colloidal silicon dioxide	3.20
3.20	7	Magnesium stearate	3.20

Manufacturing Directions

1. Mix the above amounts of items 1 through 6 listed in above formulation in a mixer, such as a high-shear mixer granulator or planetary mixer, to obtain homogeneity.
2. The mix is then granulated in water or other suitable granulation fluids and dried in a dryer.
3. The dried granular mass is then milled and then items 9 and 10 are added for blending.
4. The lubricated granular mass is then compressed into mini-tablets, using a tablet press for individual tablet weight of 160 mg and for regular tablet at 320 mg.
5. The mini-tablets are encapsulated in a capsule containing two immediate-release mini-tablets and two sustained-release mini-tablets.

Acetaminophen-Tramadol Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Acetaminophen	300.00
30.00	2	Tramadol hydrochloride	30.00
8.80	3	Microcrystalline cellulose	8.80
17.60	4	Povidone K-90	17.60
35.20	5	Sodium alginate (Keltone LV)	35.20
39.60	6	Hydroxypropylmethyl cellulose 4KM	39.60
4.40	7	Colloidal silicon dioxide	4.40
4.40	8	Magnesium stearate	4.40

Manufacturing Directions

1. For a portion of sustained release, mix the suitable amounts of items 1 through 3 and 7 and 8 listed in above formulation in a mixer, such as a high-shear mixer granulator or planetary mixer, to obtain homogeneity.
2. The mix is then granulated in water or other suitable granulation fluids and dried in a dryer. The dried granular mass is then milled and then items 9 and 10 are added for blending.
3. The lubricated granular mass is then compressed into mini-tablets, using a tablet press for individual tablet weight of 220 mg and for regular tablet 440 mg.
4. The mini-tablets are encapsulated in a capsule containing two immediate-release mini-tablets and two sustained-release mini-tablets.

Acetylsalicylic Acid, Acetaminophen, and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetylsalicylic acid (crystalline)	250.00
250.00	2	Acetaminophen (crystalline)	250.00
50.00	3	Caffeine	50.00
50.00	4	Kollidon® 90°F	50.00
–	5	Isopropanol	QS
5.00	6	Magnesium stearate	5.00
16.00	7	Kollidon® CL	16.00

Manufacturing Directions

1. Granulate items 1 to 3 with the solution of items 4 and 5; dry and sieve through an 0.8-mm screen.
2. Add items 5 and 6 and press with low-compression force (hardness is 45 N); 12-mm biplanar tablet has an average weight of 670 mg.

Acetylsalicylic Acid, Acetaminophen, and Caffeine Tablets (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Acetylsalicylic acid (crystalline)	400.00
100.00	2	Acetaminophen (crystalline)	100.00
30.00	3	Caffeine	30.00
100.00	4	Ludipress®	100.00
20.00	5	Kollidon® CL	20.00
30.00	6	PEG-6000 (powder)	30.00
5.00	7	Stearic acid	5.00

Manufacturing Directions

1. Mix all components and pass through a 0.8-mm sieve.
2. Press with a compression force of 116 N; 12-mm biplanar tablet has an average weight of 683 mg.

Acetylsalicylic Acid Acetaminophen Caffeine Tablet (250 mg/250 mg/50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetaminophen (Merck)	250.00
50.00	2	Caffeine powder	50.00
250.00	3	Acetylsalicylic Acid	250.00
60.00	4	Kollidon VA 64	60.00
20.00	5	Kollidon CL	20.00
3.00	6	Aerosil 200 200	3.00
4.00	7	Magnesium stearate	4.00

Manufacturing Directions

1. The active ingredients and Kollidon® VA 64 are granulated in a roller compactor.
2. Pass the granules together with magnesium stearate, Aerosil® 200, and Kollidon® CL through an 800-μm sieve.
3. Blend for 10 minutes in a mixer.
4. Compress into tablets with a force of about 12 kN.

Acetylsalicylic Acid and Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetylsalicylic acid (crystalline)	250.00
250.00	2	Acetaminophen (crystalline)	250.00
60.00	3	Avicel™ PH101	60.00
15.00	4	Kollidon® 30 (or Kollidon® VA 64)	15.00
25.00	5	Kollidon® CL	25.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve and mix.
2. Press with medium-compression force.
3. Tablet weight is 605 mg for a 12-mm biplanar tablet.

Acetylsalicylic Acid and Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetylsalicylic acid (40 mesh)	250.00
250.00	2	Acetaminophen (40 mesh)	250.00
15.00	3	Avicel™ PH102	15.00
7.20	4	Croscarmellose sodium (Ac-Di-Sol)	7.20
7.20	5	Stearic acid	7.20
4.00	6	Fumed silica	4.00

Manufacturing Directions

1. Screen all ingredients through a 0.8-mm sieve.
2. Blend all ingredients in a V-blender and mix for 10 minutes.
3. Compress to 670-mg tablet weight, using appropriate tooling.

Acetylsalicylic Acid and Ascorbic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
325.00	1	Acetylsalicylic acid (crystalline) (Merck)	325.00
250.00	2	Ascorbic acid (powder) (BASF)	250.00
120.00	3	Sorbitol (crystalline)	120.00
40.00	4	Avicel™ PH101	40.00
25.00	5	Kollidon® VA 64	25.00
20.00	6	Kollidon® CL	20.00
2.00	7	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve and mix.
2. Press with medium- to high-compression force (hardness is 92 N); 12-mm biplanar tablet has an average weight of 790 mg.

Acetylsalicylic Acid and Ascorbic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
325.00	1	Acetylsalicylic acid (crystalline) (Merck)	325.00
250.00	2	Ascorbic acid (powder) (BASF)	250.00
100.00	3	Avicel™ PH101	100.00
12.00	4	Kollidon® VA 64	12.00
30.00	5	Kollidon® CL	30.00
3.00	6	Magnesium stearate	3.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve and mix.
2. Press with medium- to high-compression force (hardness is 100 N); 12-mm biplanar tablet has an average weight of 726 mg.

Acetylsalicylic Acid + Paracetamol (=Acetaminophen) Tablets (250 mg + 250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Acetylsalicylic acid	250.00
250.00	2	Acetaminophen	250.00
60.00	3	Avicel PH 101	60.00
15.00	4	Kollidon VA 64	15.00
3.00	5	Macrogel 6000 Powder	3.00

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with medium-compression force.

Acetylsalicylic Acid Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Acetylsalicylic acid crystalline	500.00
200.00	2	Avicel PH 101	200.00
15.00	3	Kollidon 30	15.00
25.00	4	Kollidon CL	25.00
3.00	5	Magneisum stearte	3.00

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with low-compression force.

Acetylsalicylic Acid Tablets (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Acetylsalicylic acid (crystalline) (Merck)	400.00
99.00	2	Ludipress®	99.00
1.00	3	Stearic acid	1.00
15.00	4	Kollidon® CL	15.00

Manufacturing Directions

1. Mix all components and pass through an 0.8-mm sieve.
2. Press with low-compression force (hardness is 90 N); 12-mm biplanar tablet has an average weight of 516 mg.

Acetylsalicylic Acid Tablets (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Acetylsalicylic acid, 40 mesh	400.00
55.60	2	Cellulose (microcrystalline) (Avicel™ PH101)	55.60
21.40	3	Starch (pregelatinized)	21.40
2.20	4	Stearic acid	2.20
10.00	5	Croscarmellose sodium (Ac-Disol)	10.00
3.20	6	Fumed silica	3.20

Manufacturing Directions

1. Screen about half of item 1 through a mill, using 12-mesh screen with knives forward.
2. Preblend items 2 to 6 with 25% of item 1, and pass the mixture through the mill.
3. Pass the balance of item 1 through the mill.
4. Mix all the ingredients in a V-blender for 10 minutes and compress using 13/32-in. tooling.
5. For enteric coating, coat with Aquateric (FMC) dispersion.

Acetylsalicylic Acid Tablets (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	2	Avicel™ PH101	200.00
15.00	3	Kollidon® 30	15.00
25.00	4	Kollidon® CL	25.00
3.00	5	Magnesium stearate	3.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve and mix.
2. Press with low-compression force of (hardness is 61 N); 12-mm biplanar tablet has an average weight of 707 mg.

Acetylsalicylic Acid Tablets, Buffered

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Acetylsalicylic acid (40 mesh)	400.00
40.00	2	Magnesium hydroxide	40.00
40.00	3	Aluminum hydroxide	40.00
135.00	4	Cellulose (microcrystalline) (Avicel™ PH101)	135.00
15.30	5	Stearic acid	15.30
15.30	6	Croscarmellose sodium (Ac-D-Sol)	15.30
18.50	7	Hydroxy coatings	18.50

Manufacturing Directions

1. Screen all ingredients except item 7 through a 40-mesh sieve.
2. Blend items 2 and 3 in a V-blender for 10 minutes.
3. Coat items 2 and 3 using Aquacoat (FMC) aqueous polymer dispersion in a fluid-bed column with a 10% by weight formula.
4. Blend 50% of item 1 with items 4 and 5 for 10 minutes in a V-blender.
5. Add remaining item 1 and blend again for 10 minutes.
6. Blend item 7 with the mixture from the previous step for 10 minutes.
7. Add item 6 and blend for 7 minutes.
8. Compress into 625-mg tablets to the desired hardness using appropriate tooling.

Acetylsalicylic Acid + Vitamin C Tablets (400 mg + 250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Acetylsalicylic acid crystalline	400.00
250.00	2	Ascorbic acid	250.00
100.00	3	Ludipress	100.00
20.00	4	Kollidon CL	20.00
3.00	5	Macrogol 6000 powder	3.00

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with medium-compression force.

Acyclovir Fast Melt

Manufacturing Directions

1. Add and mix Acyclovir 50%, sodium bicarbonate 18%, citric acid anhydrous 18%, anhydrous lactose 7%, xylitol 5%, Crodesta F160 2%.
2. Dry the above ingredients to reduce moisture.
3. The ingredients are then blended for 10 minutes and extruded in a hot melt extruder at 70°C to 100°C to soften and melt the thermal binders (sucrose stearate and xylitol) to form granules containing the effervescent ingredients.
4. Granules are then screened and blended with the following ingredients: ACY-EFG (30–60 mesh) 50%, microcrystalline cellulose 18%, Fujicalin SG 18%, L-HPC LH-11 10%, aspartame 3%, redberry flavor 0.4%, magnesium stearate 0.5%, Cab-O-Sil M5P 0.1%.
5. Mix the ingredients in step 4 for 5 minutes prior to compression.
6. Acyclovir tablets are then compressed to a hardness of approximately 1 to 3 kPa and tablets disintegrate in water in approximately 20 to 45 seconds.

Acyclovir Tablets (Zovirax)

Each 800-mg tablet of Zovirax contains 800 mg of acyclovir and the inactive ingredients FD&C Blue No. 2, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. Each 400-mg tablet of Zovirax contains 400 mg of acyclovir and the inactive ingredients magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Acyclovir Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
800.00	1	Acyclovir	800.00
240.00	2	Lactose	240.00
100.00	3	Microcrystalline cellulose (Avicel PH 101)	100.00
24.00	4	Povidone	24.00
32.00	5	Sodium starch glycolate	32.00
8.00	6	Magnesium stearate	8.00
–	7	Alcohol	48.00

Manufacturing Directions

1. Pass items 1 to 3 through 250-μm mesh in a granulating vessel.
2. In a separate container, mix items 4 and 5 in item 6; now add the solution to step 1. Pass the wet mass through #8 mesh, dry, and size the granules.
3. Compress 1204 mg.

Acyclovir Water-Dispersible Tablets (800 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
800.00	1	Acyclovir	800.00
100.00	2	Microcrystalline cellulose (Avicel PH 101)	100.00
53.00	3	Veegum F	53.00
42.00	4	Sodium starch glucolate 42.00	42.00
9.40	5	Magnesium stearate	9.40
–	6	Alcohol	QS

Manufacturing Directions

1. Pass items 1 to 4 through 250-μm mesh into a granulating vessel.
2. Add a sufficient quantity of item 6 to make a wet mass. Pass it through a granulator, dry, and then pass through a #11 sieve.
3. Pass item 5 through a 250-μm sieve and add to step 2.
4. Compress into 1004-mg tablets, using a suitable punch.

Albendazole Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Albendazole	200.00
84.00	2	Starch (maize)	84.00
101.25	3	Lactose monohydrate	101.25
5.00	4	Sodium starch glycolate (Primojel)	5.00
13.00	5	Povidone (PVP K-30)	13.00
5.00	6	Saccharin sodium	5.00
1.00	7	Polysorbate 80 (Tween 80)	1.00
110.00	8	Microcrystalline cellulose (Avicel PH 102)	110.00
50.00	9	Sodium starch glycolate (Primojel)	50.00
5.00	10	Vanilla dry flavor	5.00
5.00	11	Blood orange dry flavor	5.00
4.00	12	Stearic acid	4.00
2.00	13	Magnesium stearate	2.00
2.75	14	Colloidal silicon dioxide (Aerosil 200)	2.75
2.00	15	Sodium lauryl sulfate	2.00
–	16	Alcohol (ethanol 95%)	105.00
–	17	Purified water	73.33

Manufacturing Directions

Note: Avoid overmixing the lubricants, or otherwise, hardness will be reduced.

1. Dissolve item 7 in item 16 by spatula. Dissolve items 5 and 6 in item 17 by stirring with a stirrer. Add item 7 (Tween-80) solution in items 5 and 6 (PVP-saccharin) solutions, while mixing with a stirrer.
2. Sift items 1 to 4 through a 500-μm stainless steel sieve. Collect in a polyethylene bag.
3. Load the sifted powder into the mixer. Mix for 2 minutes at low speed.
4. Add the binding solution from steps 1 and 2, while mixing at low speed over a period of 2 minutes. Scrape the sides and blades of the mixer. Mix and chop at low speed for 2 minutes. Check the end point of granulation. If required, add item 17 to get the end point. (The end point of the granulation is the point when the wet mass consists of little or no lumps of granules.) Unload the wet mass on stainless steel trays to dry.
5. Dry the wet granules in an oven at 55°C for 10 hours. After 2 hours of drying, scrape the semidried granules to break the lumps for uniform drying.
6. Check the LOD. The limit is 1.0% to 1.5%.

7. Grind the dried granules through a 1.25-mm sieve, using the granulator at medium speed.
8. Sift items 8 to 11 through a 500-μm sieve. Add the sieved powder from step 1. Mix manually for 2 minutes.
9. Mix items 12 to 15 in a polyethylene bag. Sift through a 250-μm stainless steel sieve. Collect in a polyethylene bag. Add into step 1. Mix manually for 1 minute.
10. Compress into 10 tablets with weight = 5.900 g ± 2% and hardness = 9 to 11 kPa.
11. Coat using the hydroxypropylmethylcellulose (HPMC) system and add a finishing coat. (See the Appendix.)

Albendazole Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Albendazole	100.00
288.00	2	Ludipress	288.00
4.00	3	Magnesium stearate	4.00
8.00	4	Aerosil 200	8.00

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.

Alendronate Tablets (Fosamax)

Fosamax tablets for oral administration contain either 6.53, 13.05, or 52.21 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, and 40 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate.

Alendronate Tablets, Effervescent (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Alendronate, use alendronate sodium	13.05
650.00	2	Citric acid anhydrous	650.00
367.00	3	Sodium bicarbonate granular	367.00
40.00	4	Sodium carbonate anhydrous	40.00
25.00	5	Flavor	25.00
5.00	6	Color	5.00
7.50	7	Sodium benzoate	7.50
–	8	Water, purified	2.00

Note: For other strengths, adjust with lactose.

Manufacturing Directions

1. Premix sodium benzoate with sodium bicarbonate and alendronate sodium. Mix the color with sodium carbonate. Place citric acid in a bowl of a suitable blender.
2. Slowly add 2 mg of water to the citric acid and mix thoroughly to form a moist blend. Add to the blend, in sequence, while mixing, the sodium bicarbonate mix and the sodium carbonate–color mix. Mix until uniformly distributed.
3. Compress tablets using suitably sized tooling. Cure the tablets, cool, and package in aluminum foil.

Alendronate Sodium Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
13.05	1	Sodium alendronate	13.05
103.95	2	Lactose anhydrous	103.95
80.00	3	Microcrystalline cellulose granular	80.00
2.00	4	Sodium carboxymethylcellulose	2.00
1.00	5	Magnesium stearate	1.00

Manufacturing Directions

Alendronate is first blended with one-third of microcrystalline cellulose and with one-half of anhydrous lactose. The premixture obtained is then blended with both remaining excipients and it is mixed again. Sodium salt of carmellose is added under mixing to be followed with magnesium stearate to finish the mixture blending. When homogenized by forth mixing the mixture is subjected to the compression.

Alendronate Sodium Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
13.05	1	Sodium alendronate	13.05
11.15	2	Maize starch	11.15
104.50	3	Mannitol	104.50
1.30	4	Magnesium stearate	1.30

Manufacturing Directions

A mixture containing alendronate, mannitol, maize starch, and microcrystalline cellulose is blended in a container at the stirrer speed of 14 rpm and under the normal temperature and humidity (25°C, 60% R.H.). Magnesium stearate is added to the premixed mixture. After homogenization, the precompression mixture is compressed on a rotary compression machine to form flat (cylindrical) or oval-shaped tablets of 130 mg in the mass.

Alendronate Sodium Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
13.05	1	Sodium alendronate	13.05
42.00	2	Calcium hydrogen phosphate	42.00
62.50	3	Granulated microcrystalline cellulose	62.50
11.15	4	Maize starch	11.15
1.30	5	Magnesium stearate	1.30

Alendronate Sodium Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Alendronate, use alendronate sodium	52.00
10.00	2	Polyvinyl pyrrolidone	10.00
100.00	3	Lactose anhydrous	100.00
1.50	4	Sodium stearyl fumarate	1.50
–	5	Water, purified	100.00

Manufacturing Directions

1. Pass items 1 to 3 through a 500-μm sieve and blend for 10 minutes.
2. Add item 2 and mix it well with item 5. Add to this to step 1 to granulate, dry, size, and then add item 4.
3. Compress into 163.50-mg tablets, using a suitable punch.

Allopurinol Tablets, 100 mg (Zyloric)

Each scored white tablet contains 100 mg of allopurinol and the inactive ingredients lactose, magnesium stearate, potato starch, and povidone. Each scored peach tablet contains 300 mg of allopurinol and the inactive ingredients cornstarch, FD&C Yellow No. 6 Lake, lactose, magnesium stearate, and povidone.

Allopurinol Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Allopurinol	100.000
1.00	2	Sorbitan monooleate	1.000
73.00	3	Starch (maize)	73.000
100.00	4	Lactose	100.00
10.00	5	Starch (maize)	10.000
8.00	6	Sodium starch glycolate	8.000
QS	7	Purified water (deionized), approximately	65.00 mL
4.50	8	Talc purified	4.5000
1.50	9	Silicon dioxide	1.5000

Manufacturing Directions

Caution: Wear gloves, mask, and protective glasses during all manufacturing operations.

1. Granulation
   a. Prescreen the allopurinol through a 75-μm aperture screen and transfer it to a suitable mass mixer. Dissolve the sorbitan monoleate in 10 mL of water and add the solution to the mixer. Mix until the allopurinol is wetted.
   b. Pass the wetted allopurinol through a 2.00-mm aperture screen on an oscillating granulator and dry in a tray dryer at 50°C until the LOD (Brabender 105°C, 1 hour or equivalent) is less than 2%.
   c. Rescreen the dried allopurinol through a 75-μm aperture screen and transfer it to the mass mixer. Add the starch (item 3) and lactose and mix for 15 minutes.
   d. Add the starch (item 5) to about 15 mL of water and mix until a smooth slurry, free from lumps, is formed.
   e. Heat 40 mL of water to boiling. Reduce the heat, and then, while mixing, add the slurry from step 1d. Continue mixing well, until a smooth translucent paste is formed. Allow to cool to 50°C before moving to the next step in the process. (*Caution:* Control the heat to avoid charring of the paste.)
   f. Add half of the starch paste from step 1e to the blended powders in the mixer and mix for 1 minute. Stop mixing, and scrape the blades and sides of the mixer. Add the second half of the starch paste and mix for another 1 minute. Stop mixing, scrape the blades and sides of the mixer, and examine the mass.
   g. If necessary, add more water at 50°C, in small quantities, mixing for 1 minute after each addition, until a good wet, holding mass is formed. (*Caution:* Do not overwet or overmix the mass.)
   h. Pass the mass through a 2.00-mm aperture screen on an oscillating granulator and dry in a tray dryer at 50°C until the LOD (Bra-bender 105°C, 1 hour or equivalent) is in the range of 1% to 2%.
   i. Arrange for sample.
   j. Pass the granules through a 595-μm aperture screen on an oscillating granulator into tared, polyethylene-lined drums, seal, and weigh.
2. Lubrication
   a. Transfer the dried granulation to a suitable blender.

   b. Screen the sodium starch glycolate, talc, magnesium stearate, and colloidal silicon dioxide through a 595-μm aperture screen. Add to the blender and blend for 15 minutes.
   c. Discharge the granule into polyethylene-lined drums, seal, and weigh for yield.
3. Compression
   a. Compress using 9.52-mm (0.375-in.) diameter concave punches with the bisect on the upper punch.
   b. Compress to the following specifications:
      i. Weight of 10 tablets—3.025 g
      ii. Weight variation—Average weight differs from theoretical weight by not more than 3%
      iii. Thickness—3.5 to 4.3 mm (range: not more than 5%)
      iv. Hardness—NTL 8 kPa
      v. Disintegration time—Not more than 15 minutes in water

Allopurinol Tablets (300 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Allopurinol	300.00
180.00	2	Lactose	180.00
20.00	3	Povidone (K 29)	20.00
50.00	4	Starch (maize)	50.00
QS	5	Water, purified (deionized)	65.00 mL
20.00	6	Croscarmellose sodium	20.00
30.00	7	Starch (maize), dried	30.00

Manufacturing Directions

Caution: Wear gloves, mask, and protective glasses during all manufacturing operations.

1. Granulation
   a. Transfer allopurinol, lactose, povidone, and starch (item 4) to a suitable mass mixer. Mix for 15 minutes and then pass through a 250-μm sieve aperture screen.
   b. Return the screened mix from step 1 to the mixer and add sufficient water until a good wet, holding mass is formed. Pass the mass through a 2.00-mm aperture screen on an oscillating granulator and dry in a tray dryer at 50°C until the LOD (Barbender 105°C, 1 hour or equivalent) is in the range of 1% to 2%.
   c. Pass the granules through a 595-μm aperture screen on an oscillating granulator into tared, polyethylene-lined drums, then seal, and weigh.
2. Lubrication
   a. Transfer the dried granulation to a suitable blender.
   b. Screen the croscarmellose sodium and dried starch through a 595-μm aperture screen and add to the blender. Blend for 15 minutes.
   c. Discharge the granule into polyethylene-lined drums, then seal, and weigh for yield.
3. Compression: Compress using 11.11-mm (0.4375-in.) diameter concave punches with the bisect on the upper punch. (Weight of 10 tablets: 6.00 g; weight variation: average weight differs from theoretical weight by not more than 3%.)

Alprazolam Tablets (0.25 mg/0.50 mg/1.0 mg), Xanax

Each Xanax tablet, for oral administration, contains 0.25, 0.5, 1, or 2 mg of alprazolam and the following inactive ingredients: cellulose, cornstarch, docusate sodium, lactose, magnesium stearate, silicon dioxide, and sodium benzoate. In addition, the 0.5-mg tablet contains FD&C Yellow No. 6, and the 1-mg tablet contains FD&C Blue No. 2.

Alprazolam Tablets (0.25 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.25	1	Alprazolam, with excess	0.252
82.50	2	Dicalcium phosphate	82.50
2.25	3	Starch (maize)	2.25
2.25	4	Gelatin	2.25
33.50	5	Starch (maize)	33.50
0.082	6	Propyl paraben	0.082
0.082	7	Methyl paraben	0.082
1.00	8	Magnesium stearate	1.00
1.00	9	Sodium starch glycolate	1.00
0.30	10	Dye yellow	0.30
–	11	Water, purified, ca	100 mL

Manufacturing Directions

1. Charge items 2 and 5 in a suitable vessel after sifting through an 80-mesh sieve. Mix for 2 minutes.
2. Sift item 1 through a 60-mesh sieve and add to step 1. (*Note:* Because of the small quantity of item 1, use a geometric dilution method to mix the entire amount.)
3. Mix for 5 minutes.
4. In a separate vessel, sift (through 80 mesh) and charge items 3, 4, 6, 7, and 10 and then mix for 2 minutes. Add a sufficient quantity of item 11 to form a suitable lump-free paste.
5. Add step 4 into step 3, and knead and chop to prepare a suitable mass without lumps.
6. Spread the wet mass from step 5 on trays and dry at 50°C for 12 hours to an LOD of not more than 2%; dry for an additional hour, if necessary.
7. Pass dried granules through 20 mesh.
8. Sift items 8 and 9 through a 250-μm sieve screen and add to step 7. Blend for 2 minutes.
9. Compress into 125-mg tablets, using 6-mm punches. For 0.5-mg and 1.0-mg strengths, adjust with item 2 and compress the same weight and size.

Aluminum Acetylsalicylate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Aluminum acetylsalicylate, excess	255.00
213.00	2	Mannitol	213.00
28.00	3	Cornstarch	28.00
10.00	4	Kollidon® 90F	10.00
5.00	5	Lutrol E 6000	5.00
–	6	Isopropanol, QS	50.00 mL
23.00	7	Kollidon® CL	23.00
5.00	8	Magnesium stearate	5.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with solution of items to 6.
2. Dry, pass through an 0.8-mm sieve, and mix with items 7 and 8.
3. Compress with medium-compression force; 12-mm biplanar tablet has an average weight of 540 mg.

Aluminum Hydroxide and Magnesium Hydroxide Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Aluminum hydroxide (Rorer)	200.00
200.00	2	Magnesium hydroxide (Rorer)	200.00
100.00	3	Lactose monohydrate	100.00
30.00	4	Kollidon® VA 64	30.00
QS	5	Water	260.00 mL
315.00	6	Sucrose (crystalline)	315.00
100.00	7	Sorbitol (crystalline) (Merck)	100.00
60.00	8	PEG-6000 (powder)	60.00
12.00	9	Aerosil® 200	12.00
6.00	10	Talc	6.00
6.00	11	Magnesium stearate	6.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with solution of items 4 and 5.
2. Dry and pass through an 0.8-mm sieve, add items 6 to 11, and press with high-compression force (20 kN).
3. The 16-mm biplanar tablet has an average weight of 1013 mg.

Aluminum Hydroxide and Magnesium Hydroxide Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
320.00	1	Aluminum hydroxide (dried gel)	320.00
320.00	2	Magnesium hydroxide powder	320.00
32.00	3	Sucrose	32.00
288.40	4	Mannitol	288.40
QS	5	Povidone (Plasdone®) (10% solution in equal parts water and alcohol)	QS
12.90	6	Glycerin	12.90
19.20	7	Magnesium stearate	19.20
6.40	8	Fumed silica	6.40
0.30	9	Oil of peppermint	0.30

Manufacturing Directions

1. Mix items 1 to 4 in a suitable blender, add items 5 and 6, and use this combination to moisten the mix of items 1 to 4.
2. Granulate by passing through a 20-mesh screen.
3. Add and thoroughly mix items 7 to 9, and compress using 0.5-in., flat-face, beveled-edge punches.

Aluminum Hydroxide and Magnesium Hydroxide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
405.00	1	Aluminum hydroxide gel (dried)	405.00
100.00	2	Magnesium hydroxide powder	100.00
108.00	3	Mannitol	108.00
38.80	4	Sorbitol powder	38.80
2.50	5	Saccharin sodium	2.50
16.70	6	Povidone (PVP K-30)	16.70
7.00	7	Magnesium stearate	7.00
2.00	8	Mint flavor (dry)	2.00
299.00	9	Purified water	299.00

Manufacturing Directions

1. Dissolve items 4 and 5 in 59.0 g of purified water by using stirrer.
2. Add item 6 while mixing until clear solution is obtained.
3. Add items 1 to 3 into mixer and mix for 5 minutes, with mixer and chopper at high speed.
4. Dilute concentrate binding solution with 240.0 g of purified water.
5. Add binding solution at a rate of 9 to 11 g/min to the dry powders in the mixer while mixing at low speed. Mix for 2 to 3 minutes. Scrape the sides, blade, and lid of the mixer. Mix and chop at low speed for an additional 2 to 3 minutes or until the granules stop flying around the chopper. Add extrapurified water, if required, and continue mixing until a satisfactory mass is obtained. Record extra quantity of purified water added.
6. Unload the wet mass into a clean aeromatic bowl for drying. Avoid big lump formation, as this leads to nonuniform drying.
7. Dry the wet mass in an Aeromatic fluid-bed dryer at 60°C for 120 minutes. After 30 minutes of drying, scrape the semidried granules to break the lumps for uniform drying. Check the LOD (limit: NMT 5.5%).
8. Pass the dried granules through 1.5-mm sieve, using granulator at medium speed. Collect in stainless steel drums. Set aside 7 to 9 g of granules for later step.
9. Load the rest of the granules into blender. Pass items 8 and 7 through a sifter, using a 250-μm sieve. Collect in a polyethylene bag.
10. Add about 7 to 9 g of granules and mix gently.
11. Load into blender and blend for 3 minutes.
12. Check temperature and humidity of the room before beginning compression (humidity limit: NMT 60%; temperature, 25 ± 1°C).
13. Compress the granules using a rotary tabletting machine. Compress into 680-mg tablets, using 12.7-mm, flat, beveled-edge punches.

Aluminum Hydroxide, Magnesium Carbonate (or Oxide), and Simethicone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
576.00	1	Sucrose	576.00
157.00	2	Aluminum hydroxide	157.00
160.00	3	Magnesium carbonate (or oxide)	160.00
97.00	4	Magnesium oxide	97.00
45.00	5	Kollidon® 90F	45.00
22.00	6	Aerosil® 200	22.00
300.00	7	Simethicone suspension (30%)	300.00
9.00	8	Menthol	9.00
1.00	9	Saccharin sodium	1.00
49.00	10	Talc	49.00
13.00	11	Magnesium stearate	13.00

Manufacturing Directions

1. Granulate mixture of items 1 to 6 with the simethicone suspension, dry, sieve through an 0.8-mm screen, add items 8 to 11, and press with high-compression force.
2. Tablet has an average weight of 1295 mg.

Aluminum Hydroxide and Magnesium Silicate Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
120.00	1	Aluminum hydroxide dried gel (Giulini)	120.00
250.00	2	Magnesium trisilicate	250.00
232.00	3	Ludipress®	232.00
6.00	4	Aerosil® 200	6.00
6.00	5	Magnesium stearate	6.00
12.00	6	Cyclamate sodium	12.00
1.50	7	Menthol	1.50

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press with a compression force of 20 kN.
2. Because of the poor flowability of the powder, the tabletting machine should be equipped with a special technical device to provide a continuous and homogeneous filling of the dies.
3. The 16-mm biplanar tablet has an average weight of 640 mg.

Ambroxol HCl Sustained-Release Pellets Releasing Tablets

Formulation for 500 tablets: ambroxol HCl/Kollicoat® SR 30D pellets,* 250.0 g; microcrystalline cellulose Vivapur® 200, 250.0 g; magnesium stearate, 2.5 g.

Manufacturing Directions

Mix the ingredients together, pass through a 0.8-mm sieve, and compress into tablets with a force of about 15 kN. This gives 500 tablets.

Aminophylline Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Aminophylline	100.00
196.00	2	Starch (maize)	196.00
2.00	3	Talc	2.00
3.00	4	Magnesium stearate	3.00
QS	5	Water, purified	QS

Manufacturing Directions

1. Charge item 2 in a suitable vessel and add a sufficient quantity of item 5 to prepare a 30% smooth slurry.
2. Add item 1 into step 1 and mix well to form a suitable mass.
3. Pass the wet mass through a #6 sieve to granulate.
4. Dry the granules at 60°C for 10 hours to an LOD of not more than 3%.
5. Pass the dried granules through 1.19-mm sieve and transfer to a blending vessel.
6. Sift items 3 and 4 through a 250-μm sieve and add to step 5. Blend for 2 minutes.
7. Compress into 300-mg tablets, using 9-mm punches.

4-Amino-1-Hydroxybutylidene-1,1-Bisphosphonic Acid Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	4-Amino-1-hydroxybutylidene-1,1-bisphosphonic acid; use monosodium trihydrate	6.55
110.45	2	Lactose anhydrous	110.45
80.00	3	Microcrystalline cellulose	80.00
1.00	4	Magnesium stearate	1.00
2.00	5	Croscarmellose sodium type A	2.00

Manufacturing Directions

1. The active ingredient (equivalent to 5 mg of anhydrous free acid per tablet) is premixed with one-third quantity of the microcrystalline cellulose and one-half the quantity of the anhydrous lactose in a ribbon blender for 5 minutes at 20 rpm.
2. To the premix is added the remaining two-thirds of the microcrystalline cellulose and the remaining one-half of the anhydrous lactose. Blend for 10 minutes at 20 rpm.
3. Add croscarmellose sodium to the blended powders in step 2 and mix for 5 minutes at 20 rpm.
4. Add item 4 to the mixture after passing it through a 90-mesh screen and blend for an additional 5 minutes at 20 rpm.
5. Compress into 192-mg tablets, using a suitable punch.

Aminosalicylic Acid Tablets

Formulation: 5-Aminosalicyclic acid (5-ASA), 73.3%; sodium chloride, 11.7%; povidone, 4.4%; alcohol SDA-3A, q.s.; lactose, 8.8%; calcium stearate/sodium lauryl sulfate, 1.76%; sodium starch glycolate, 0.29%.

Manufacturing Directions

1. Sodium chloride is milled through a Whistler mill, using a small slotted screen.
2. 5-ASA is combined with the sodium chloride and mixed for 5 minutes in a ribbon blender. The powder blend is milled through a FitzMill at high speed (1B band) and returned to the ribbon blender.
3. Povidone/alcohol solution is added to the powder blend while the mixer is running to form a wet mass.
4. The wet mass is passed through a FitzMill (1/2 in., perforated band) with hammers forward at high speed. The wet granulation is trayed and dried for 16 hours at 55°C. The dried mixture is passed through a FitzMill (2A band) with knives forward at medium speed.
5. The resultant blend is placed in a ribbon blender. Lactose, calcium stearate/sodium lauryl sulfate, and sodium starch glycolate is passed through a 40-mesh screen.
6. The screened powders are added to the ribbon blender and mixed for 5 minutes.
7. On a conventional tablet press, the finished granulation is compressed into 3/8-in. tablets, using standard concave tooling. The tablets meet the target weight requirements, are about 0.175-in. thick, have a hardness of 8 to 15 kPa, and a friability of NMT 0.4%.
8. 100 kg of compressed tablets is placed into an Accela-Cota pan and warmed to about 40°C exhaust temperature.
9. 5 kg of Opadry Enteric (Colorcon, Inc.) is dispersed in an alcohol (SDA-3A) and water mixture (composition of alcohol/water is 25.5 and 2.8 kg, respectively).
10. This solution is spray coated on tablets using an air-atomization system as follows: 2 spray guns at 35 psi each set to deliver about 60 g/min, maintaining an exhaust temperature of 35°C to 45°C. The coated tablets are dried in the Accela-Cota pan for 1 hour at 35°C to 45°C.
11. The tablets are polished in the pan, using 1 g powdered carnauba wax.

Amiodarone Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.000	1	Amiodarone hydrochloride	200.000
86.000	2	Lactose monohydrate	86.000
27.500	3	Starch (maize)	27.500
8.500	4	Povidone (PVP K-30)	8.500
25.000	5	Starch (maize)	25.000
2.000	6	Magnesium stearate	2.000
1.000	7	Colloidal silicon dioxide (Aerosil 200)	1.000
–	8	Purified water	116.67

Manufacturing Directions

Note: Avoid overmixing lubricants because it reduces hardness.

1. Sieving and dry mixing: Sift items 1, 3, and 2 through a 500-μm stainless steel sieve. Load into the mixer. Mix for 5 minutes at low speed.
2. Preparation of binder
   a. Dissolve item 4 in 16.67 g of item 8 by using a stirrer at a slow speed in a stainless steel container.
   b. Pass item 5 through a 250-μm sieve.
   c. Make a homogeneous slurry of item 5 in 25.0 g of item 8 (30°C) in a stainless steel container. Ensure that it is free of lumps.
   d. Heat 75.0 g of item 8 to 90°C in a stainless steel container. Add the slurry from step 2. Stir until complete gelatinization occurs. Cool to 50°C.
   e. Add the solution from step 2 into step 3 and stir for 5 minutes.
   f. Check the quantity of the binder: theoretical weight, 150 g. Adjust the weight with purified water by mixing if required.
3. Kneading
   a. Knead the powder in a mixer (Diosna) with the binder, while mixing at low speed over a period of 2 minutes. Scrape the sides and the blades. Mix and chop at low speed for 2 minutes.
   b. Check the end point of granulation. If required, add more purified water to get the end point. (The end point of the granulation is the point when the wet mass consists of little or no lumps of the granules.)
   c. Unload the wet granules in a stainless steel tray for drying.
4. Drying
   a. Dry the wet granules at 550°C for 5 hours.
   b. Check the LOD: the limit is 1.0% to 1.5%. If required, dry further at 550°C for 1 hour. Check the LOD.
   c. Transfer the dried granules to a polyethylene bag.
5. Grinding: Grind the dried granules through a 1.25-mm sieve, using a granulator at medium speed. Collect in a polyethylene bag.
6. Lubrication
   a. Sift items 6 and 7 through a 250-μm sieve in a stainless steel sieve. Collect in a polyethylene bag. Take approximately 66.67 g of granules from step 5 into the polyethylene bag. Mix manually. Add into step 5. Mix for 1 minute.
   b. Store in a polyethylene bag.
7. Compression and specifications: Compress the granules by using a rotary tabletting machine, 10-mm round plain convex punch. (Weight of 10 tablets: 3.5 g ± 3%.)

Amitriptyline Tablets (50 mg), Elavil

Elavil® (amitriptyline HCl) is supplied as 10-, 25-, 50-, 75-, 100-, and 150-mg tablets and as a sterile solution for intramuscular use. Inactive ingredients in the tablets are as follows: calcium phosphate, cellulose, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, starch, stearic acid, talc, and titanium dioxide. The 10-mg amitriptyline HCl tablets also contain FD&C Blue No. 1. The 25-mg amitriptyline HCl tablets also contain D&C Yellow No. 10, FD&C Blue No. 1, and FD&C Yellow No. 6. The 50-mg amitriptyline HCl tablets also contain D&C Yellow No. 10, FD&C Yellow No. 6, and iron oxide. The 75-mg amitriptyline HCl tablets also contain FD&C Yellow No. 6. The 100-mg amitriptyline HCl tablets also contain FD&C Blue No. 2 and FD&C Red No. 40. The 150-mg amitriptyline HCl tablets also contain FD&C Blue No. 2 and FD&C Yellow No. 6.

Amitriptyline Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Amitriptyline	50.00
20.00	2	Starch (maize)	20.00
20.00	3	Lactose monohydrate	20.00
15.00	4	Dicalcium phosphate	15.00
2.00	5	Magnesium stearate	2.00
3.00	6	Talc	3.00
20.00	7	Starch (maize)	20.00
–	8	Water, purified, ca	100 mL

Manufacturing Directions

1. Sift items 1 to 4 through a 250-μm sieve and charge in a suitable mixer.
2. In a separate vessel, charge item 2 and add item 8 at 80°C. Mix until a good paste is formed. Cool to 50°C.
3. Add step 2 into step 1, and knead and chop until granules are formed without lumps.
4. Spread the wet mass onto trays and dry in an oven at 50°C for 15 hours to an LOD of not more than 1.5%.
5. Pass the dried granules through No. 18 mesh and transfer to a suitable blender.
6. Pass item 5 though a 250-μm sieve and item 7 through a 500-μm sieve; add to step 5 and blend for 2 minutes.
7. Compress into 130-mg tablets, using a suitable punch.
8. Coat the tablet with an organic base coating. (See Appendix.)

Amlodipine Besylate Tablets

Amlodipine besylate tablets are formulated as white tablets equivalent to 2.5, 5, and 10 mg of amlodipine for oral administration. In addition to the active ingredient, amlodipine besylate, each tablet contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.

Amlodipine Besylate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.50	1	(–)Amlodipine	0.50
183.00	2	Lactose anhydrous	183.00
15.00	3	Starch pregelatinized	15.00
1.50	4	Magnesium stearate	1.50

Manufacturing Directions

1. Sieve the active ingredient, (–)amlodipine, through a suitable sieve, and blend with lactose and pregelatinized maize starch.
2. Add suitable volumes of purified water to granulate.
3. After drying, screen the granules and blend with the magnesium stearate.
4. Compress using 7-mm-diameter punches to a total weight of 200 mg. Adjust the formula for other strengths with lactose (2.5 and 5.0 mg).

Amlodipine Free Base Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.5	1	Amlodipine base	2.5
31.50	2	Calcium hydrogen phosphate anhydrate	31.50
62.05	3	Microcrystalline cellulose	62.05
2.00	4	Sodium starch glycollate	2.00
1.00	5	Magnesium stearate	1.00

Manufacturing Directions

1. Amlodipine base is sieved through a 500-μm screen and other excipients are sieved through a 850-μm screen.
2. All excipients except magnesium stearate are mixed in a free fall mixer for 15 minutes at about 25 rpm.
3. Magnesium stearate is added and the powder blend is mixed for another 5 minutes at about 25 rpm. Compress into 2.5-mg and 10-mg tablets with total weight of 100 or 400 mg, respectively.

Amlodipine Maleate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
3.21	1	Amlodipine maleate	3.21
31.50	2	Calcium hydrogen phosophate anhydrous	31.50
62.05	3	Microcrystalline cellulose	62.05
2.00	4	Soodium startch glycolate	2.00
1.00	5	Magnesium stearate	1.00

Manufacturing Directions

1. Amlodipine maleate is milled to a particle size of 10 to 20 μm.
2. Amlodipine maleate is sieved through a 500-μm screen and other excipients are sieved through a 850-μm screen.
3. All excipients except magnesium stearate are mixed in a free fall mixer for 15 minutes at about 25 rpm. Value of pH is checked at 20% aqueous slurry (should be around 5.9).
4. Magnesium stearate is added and the powder blend is mixed for another 5 minutes at about 25 rpm.
5. Tablets are compressed at approximately 100 mg to give 2.5 mg strength and proportionally higher for amounts up to 10 mg per tablet.

Amoxacillin and Clavulanate Potassium Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Amoxicillin, use amoxicillin trihydrate compacted, with excess	587.50
125.00	2	Clavulanate, use clavulanate potassium with Avicel (1:1)	305.00
25.00	3	Sodium starch glycolate	25.00
30.00	4	Aerosil 200	30.00
10.00	5	Sodium carmellose	10.00
10.00	6	Talc	10.00
5.00	7	Magnesium stearate	5.00

Manufacturing Directions

1. Dry item 1 at 45°C for 2 hours.
2. Dry items 6, 7, 5, and 3 at 80°C for 4 hours.
3. Sift items 1 to 7 through #40 mesh screen, charge in a drum mixer, and mix for 30 minutes.
4. Slug the mixture in step 3 using 16-mm punches and a hardness of 6 to 7 kPa.
5. Break the slugs by passing through 2.5-mm mesh sieves on a mill.
6. Transfer the comminuted slugs to a blender and add items 6 and 7 for 15 minutes.
7. Compress using 19 × 9 mm punches.
8. Coat the tablets with HPMC organic coating. (See Appendix.)

Amoxacillin Fast-Disintegrating Tablets

1. 970 g of cefaclor (as monohydrate) and 30 g of microcrystalline cellulose and sodium carboxymethyl cellulose (Avicel RC591) are mixed for 5 minutes in a planetary mixer.
2. Gradually about 320 mL of water is added to this blend and mixing is continued for another 5 minutes.
3. The wet granulate is dried in a fluidized bed dryer at an air inlet temperature of 50°C and subsequently sieved through a 1.00- and 0.630-mm screen, respectively.
4. 864 g of the granulate obtained in step 3 is mixed with 98 g of a mixture of microcrystalline cellulose and crosslinked polyvinylpyrrolidone (1:1), flavors, and sweetening agents in a TURBULA-mixer for 10 minutes.
5. After a lubricant is added, mixing is continued for another 3 minutes and the mixture is compressed into tablets with a mean weight of 625 mg. Friability, <0.01%; hardness, 6.9 kPa; disintegration time, 22 seconds.

Amoxicillin and Potassium Clavulanate Tablets (250 mg/62.5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Amoxicillin, use amoxicillin trihydrate	250.00
62.50	2	Clavulanic acid, use potassium clavulanate	62.50
23.00	3	Polyplasdone XL, dried	23.00
23.00	4	Syloid AL1	23.00
4.50	5	Magnesium stearate	4.50
450.00	6	Microcrystalline cellulose	450.00

Manufacturing Directions

1. Polyplasdone XL, dried, is present as a disintegrant. Syloid AL1 is a desiccant used to prevent hydrolytic degradation of the actives. Magnesium stearate is present as a lubricant. Microcrystalline cellulose is a tablet binder and disintegrant.
2. Mill amoxicillin trihydrate, using a swing hammer mill at fast speed through a 0.063-in. screen, with knives forward.
3. Mix the milled amoxycillin trihydrate with potassium clavulanate, polyplasdone, Syloid AL1, part of magnesium stearate, and part of microcrystalline cellulose.
4. Slug the blend from step 3, or use a roller compacted.
5. Mill the compacts or flake from step 4 through a swing hammer mill at medium speed, with knives forward, and fitted with a 0.063-in. screen.
6. Blend granules with remaining magnesium stearate and remaining microcrystalline cellulose.
7. Compress to a core weight of 450 mg and a hardness of 15 to 20 kPa.
8. Provide a film subcoating with an aqueous suspension of hydroxypropyl methyl cellulose, further coated with a Eudragit enteric coating, and finally, with a further overcoating of hydroxypropyl methyl cellulose. (See Appendix.)

Amoxicillin Tablets (250 mg/500 mg/1 g), Acid Trihydrate

Tablets—Each tablet contains 500 or 875 mg of amoxicillin as the trihydrate. Each film-coated, capsule-shaped, pink tablet is embossed with AMOXIL, centered over 500 or 875, respectively. The 875-mg tablet is scored on the reverse side. The inactive ingredients are colloidal silicon dioxide, crospovidone, FD&C Red No. 30 Aluminum Lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

Chewable tablets—each cherry-/banana-/peppermint-flavored tablet contains 125, 200, 250, or 400 of amoxicillin as the trihydrate. The 125- and 250-mg pink oval tablets are imprinted with the product name AMOXIL on one side and 125 or 250 on the other side. The inactive ingredients are citric acid, cornstarch, FD&C Red No. 40, flavorings, glycine, mannitol, magnesium stearate, saccharin sodium, silica gel, and sucrose. Each 125-mg chewable tablet contains 0.0019 mEq (0.044 mg) of sodium; the 250-mg chewable tablet contains 0.0037 mEq (0.085 mg) of sodium. Each 200-mg chewable tablet contains 0.0005 mEq (0.0107 mg) of sodium; the 400-mg chewable tablet contains 0.0009 mEq (0.0215 mg) of sodium. The 200- and 400-mg pale pink, round tablets are imprinted with the product name AMOXIL and 200 or 400 along the edge of one side. The inactive ingredients are aspartame, crospovidone, FD&C Red No. 40 Aluminum Lake, flavoring, magnesium stearate, and mannitol.

Amoxacillin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Amoxicillin (871 mcg/mg activity)[a]	287.00
28.50	2	Cellulose microcrystalline NC (Avicel PH 101)	28.50
20.00	3	Povidone K 29–32	20.00
QS	4	Alcohol 190 proof, approximately	70.00 mL
3.50	5	Magnesium stearate	3.50

[a]Adjust according to potency. Adjust the tablet size as given below to yield 1-g, 500-mg, and 250-mg tablets.

Manufacturing Directions

Caution: Handle with extreme care. Protect face and hands because some individuals may be sensitive and reactions may occur.

1. Granulation
   a. Pass amoxicillin through a 595-μm aperture screen using a FitzMill, with knives forward, at medium speed.
   b. Charge the following ingredients in a suitable mixer: cellulose microcrystalline, sodium starch glycolate, and milled amoxicillin. Mix for 30 minutes.
   c. Add 100 g of alcohol and mix for an additional 15 minutes.
   d. Dissolve povidone in approximately 150 g of alcohol. Add povidone solution to the mixture from step 3, with continuous mixing. Mix for 15 minutes, until a suitable granulating mass is obtained. If necessary, add more alcohol.
   e. Pass the wet mass through a 4.76-mm aperture screen.
   f. Spread the wet granulation onto trays. Oven dry at 38°C or until the LOD is 2% to 3.5% (vacuum 60°C, 3 hours).
   g. Pass the dry granulation through a 1.2-mm aperture screen in an oscillating granulator.
2. Lubrication
   a. Charge half of the amount of dried granulation into a suitable mixer. Pass magnesium stearate through a 500-μm aperture screen and add to the mixer. Mix for 10 minutes.
   b. Add the balance of granulation and mix for an additional 5 minutes.
   c. Charge into polyethylene-lined drums.
3. Compression
   a. Compress into 1-g tablets, using 20 × 9 mm bisected ovaloid punches (thickness 9.6–10.6 mm; hardness not less than 15 kPa).
   b. Compress into 500-mg tablets, using 18 × 8.5-mm ovaloid punches (thickness is 6.5–6.7 mm; hardness is 12–18 kPa).
   c. Compress into 250-mg tablets, using 10.3-mm-diameter punches (thickness is 5.1–5.3 mm; hardness is 12 kPa).

Amoxicillin Trihydrate and Clavulanate Potassium Tablets (500 mg/125 mg) Augmentin

Each Augmentin tablet contains 0.63 mEq of potassium. Each 125-mg chewable tablet and each 5 mL of reconstituted Augmentin 125 mg/5 mL oral suspension contain 0.16 mEq of potassium. Each 250-mg chewable tablet and each 5 mL of reconstituted Augmentin 250 mg/5 mL oral suspension contain 0.32 mEq of potassium. Each 200-mg chewable tablet and each 5 mL of reconstituted Augmentin 200 mg/5 mL oral suspension contain 0.14 mEq of potassium. Each 400-mg chewable tablet and each 5 mL of reconstituted Augmentin 400 mg/5 mL oral suspension contain 0.29 mEq of potassium.

Inactive ingredients:

Chewable tablets—colloidal silicon dioxide, flavorings, magnesium stearate, mannitol, and one or more of the following: aspartame, D&C Yellow No. 10, FD&C Red No. 40, glycine, sodium saccharin, and succinic acid.

Tablets—colloidal silicon dioxide, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

Amphetamine Salts Tablets

This is a single-entity amphetamine product combining the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextroisomer of amphetamine saccharate, and 6,L-amphetamine aspartate.

Each Tablet Contains	5 mg	10 mg	20 mg	30 mg
Dextroamphetamine saccharate	1.25 mg	2.5 mg	5 mg	7.5 mg
Amphetamine aspartate	1.25 mg	2.5 mg	5 mg	7.5 mg
Dextroamphetamine sulfate	1.25 mg	2.5 mg	5 mg	7.5 mg
Amphetamine sulfate	1.25 mg	2.5 mg	5 mg	7.5 mg
Total amphetamine base equivalence	3.13 mg	6.3 mg	12.6 mg	18.8 mg

Inactive ingredients: Sucrose, lactose, cornstarch, acacia, and magnesium stearate.

Ampicillin Tablets (250 mg)

Formulation: Ampicillin trihydrate, 250 g; Ludipress, 250 g; magnesium stearate, 10 g.

Manufacturing Directions

Mix all components, pass through a sieve, and press with low-compression force at 500 mg.

Apomorphine and Nicotine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4.00	1	Apomorphine hydrochloride	4.00
1.00	2	Nicotine base	1.00
4.00	3	Acesulfame-K	4.00
37.50	4	Microcrystalline cellulose	37.50
2.50	5	Peppermint flavor	2.50
2.00	6	Chocolate natural flavor	2.00
3.00	7	Citric acid	3.00
13.00	8	Hydroxypropyl methylcellulose	13.00
80.00	9	Mannitol	80.00
3.00	10	Magnesium stearate	3.00

Manufacturing Directions

1. Pass all ingredients through a #35 mesh screen (sieve opening of about 0.51 mm) to ensure granulation.
2. A solution containing apomorphine HCL, citric acid, half the acesulfame-K, half the peppermint flavor, and half the chocolate flavor is prepared by dissolving the ingredients into a mixture of equal volumes of purified water and ethanol, USP.
3. The solution is mixed until clear, and then absorbed into the listed amount of microcrystalline cellulose (Avicel 302).
4. The resulting wet mass, labelled "part A," is mixed in a porcelain dish at room temperature (20°C) for 30 minutes, and then partially dried to obtain a solid mass.
5. The mass is next granulated by screening through a #50 mesh (ASTM) (sieve opening of about 0.297 mm) stainless steel screen. The wet granules are dried at about 60°C to 70°C for about 1 to 1.5 hours. The resulting dried granules are then passed through a #35 mesh screen (sieve opening of about 0.51 mm).
6. Separately, nicotine is added to and blended with all the remaining ingredients except for the magnesium stearate. More specifically, nicotine is added to the second half of the acesulfame-K, half the peppermint flavor, half the chocolate flavor, the hydroxypropylmethylcellulose (methocel E4M, premium), and the mannitol.
7. The resulting blend is labelled "part B." Parts A and B are then combined and mixed for about 5 minutes in a V-shaped blender. Next, magnesium stearate is added to the blender and blended continuously for about 2 minutes.
8. The final mix is removed from the blender and compressed into 150-mg tablets.

Apomorphine and Prochlorperazine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4.00	1	Apomorphine hydrochloride	4.00
5.00	2	Prochlorperazine hydrochloride	5.00
4.00	3	Acesulfame-K	4.00
37.50	4	Microcrystalline cellulose	37.50
2.50	5	Peppermint flavor	2.50
2.00	6	Chocolate natural flavor	2.00
3.00	7	Citric acid	3.00
10.00	8	Hydroxypropyl methylcellulose	10.00
80.00	9	Mannitol	80.00
3.00	10	Magnesium stearate	3.00

Manufacturing Directions

1. Pass all ingredients through a #35 mesh screen (sieve opening of about 0.51 mm) to ensure granulation.
2. A solution containing prochlorperazine HCL, citric acid, half the acesulfame-K, half the peppermint flavor, and half the chocolate flavor is prepared by dissolving the ingredients into a mixture of equal volumes of purified water and ethanol, USP.
3. The solution is mixed until clear, and then absorbed into the listed amount of microcrystalline cellulose (Avicel 302).
4. The resulting wet mass, labelled "part A," is mixed in a porcelain dish at room temperature (20°C) for 30 minutes, and then partially dried to obtain a solid mass.
5. The mass is next granulated by screening through a #50 mesh (sieve opening of about 0.297 mm) stainless steel screen. The wet granules are dried at about 60°C to 70°C for about 1 to 1.5 hours. The resulting dried granules are then passed through a #35 mesh screen (sieve opening of about 0.51 mm).
6. Separately, nicotine is added to and blended with all the remaining ingredients except for magnesium stearate. More specifically, nicotine is added to the second half of the acesulfame-K, half the peppermint flavor, half the chocolate flavor, the hydroxypropylmethylcellulose (methocel E4M, premium), and the mannitol.
7. The resulting blend is labelled "part B." Parts A and B are then combined and mixed for about 5 minutes in a V-shaped blender. Next, magnesium stearate is added to the blender and blending continued for about 2 minutes.
8. The final mix is removed from the blender and compressed into 150-mg tablets.

Asparagus Extract + Parsley Extract Tablets (200 mg + 200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Asparagus extract powder	200.00
200.00	2	Parsley extract powder	200.00
200.00	3	Sorbitol crystalline	200.00
20.00	4	Kollidon VA 64	20.00
10.00	5	Kollidon CL	10.00
4.00	6	Magnesium stearate	4.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve and mix.
2. Press to tablets with low-compression force at 636 mg.

Aspartame Effervescent Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
00.00	1	Aspartame	20.00
10.40	2	Sorbitol crystalline	10.40
14.30	3	Tartaric acid powder	14.30
18.70	4	Sodium carbonate	18.70
1.70	5	Kollidon 25	1.70
1.10	6	PEG 6000 powder	1.10

Manufacturing Directions

1. Mix all components and pass through a 0.5-mm sieve.
2. Press to tablets at 66 mg.

Aspartame Tablets (25 mg), DC

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
27.00	1	Aspartame	27.00
76.00	2	Ludipress	76.00
12.00	3	Kollidon® CL	12.00
1.00	4	Magnesium stearate	1.00
3.00	5	Lutrol F68	3.00

Manufacturing Directions

1. Mix all components and pass through a 0.8-mm sieve.
2. Press to tablets with low-compression force at 120 mg.

Aspartame Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Aspartame	20.00
4.00	2	Cellulose (microcrystalline) (Avicel™ PH101), NF	4.00
4.00	3	Sodium starch glycolate (pH 5.5–7.5), NF International	4.00
0.50	4	Silicon dioxide (colloidal)	0.50
0.50	5	Povidone (PVP K-29–32), USP	0.50
14.00	6	Anhydrous alcohol (isopropyl, refined) USP	~14.00
34.00	7	Lactose (granulated)	34.00
4.00	8	Leucine, USP	4.00
3.00	9	Sodium benzoate (powder), NF	3.00

Manufacturing Directions

1. Charge aspartame, cellulose microcrystalline, sodium starch glycolate, silicon dioxide, and Povidone in a suitable mixer.
2. Blend for 20 minutes or until uniform.
3. While mixing, slowly add isopropyl alcohol to blended powders until a suitable granulating mass is obtained. Avoid overwetting.
4. Pass wet mass through a 2.38-mm screen on an oscillating granulator and spread onto paper-lined trays.
5. Oven dry at 45°C to 50°C until LOD is NMT 1.2%.
6. Pass dried granulation through an 840-μm screen on an oscillating granulator.
7. Charge dried granulation into a suitable mixer.
8. Add granulated lactose, leucine, and sodium benzoate, and blend for ~10 minutes.
9. Discharge into polyethylene-lined drums.
10. Compress tablets in a low-humidity area not to exceed 40% relative humidity at 23°C.
11. Compress, using 7/32-in. concave punches, to the following specifications: weight of 10 tablets is 0.7 g; thickness of a tablet is 2.9 to 3.3 mm.

Aspartame Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25	1	Aspartame	25
25	2	Dibasic calcium phosphate	25
3	3	Kollidon® VA 64	3
10	4	Water	10
3	5	Kollidon® CL	3
3	6	PEG-6000 (powder)	3

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with items 4 and 5.
2. Pass through an 0.8-mm sieve and mix with item 6.
3. Press to tablets (60 mg in weight) with a 5-mm biplanar shape.

Aspartame Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Aspartame	27.00
76.00	2	Ludipress®	76.00
12.00	3	Kollidon® CL	12.00
1.00	4	Magnesium stearate	1.00
3.00	5	Lutrol F 68	3.00

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press to tablets with low-compression force.
2. Each 8-mm biplanar tablet has an average weight of 120 mg.

Aspartame Tablets, Effervescent

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Aspartame	20.00
10.40	2	Sorbitol (crystalline)	10.40
14.30	3	Tartaric acid (powder)	14.30
18.70	4	Sodium bicarbonate	18.70
1.70	5	Kollidon® 25	1.70
1.10	6	PEG-6000 (powder)	1.10

Manufacturing Directions

1. Mix all items, pass through a 0.5-mm sieve, and press to tablets.
2. Each 6-mm biplanar tablet has an average weight of 66 mg.

Aspirin, Acetaminophen, and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
225.00	1	Aspirin (40 mesh)	225.00
250.00	2	Acetaminophen (20 mesh)	250.00
30.00	3	Caffeine (granular)	30.00
100.00	4	Cellulose (microcrystalline) (Avicel™ PH-102)	100.00
45.00	5	Anhydrous lactose	45.00
10.00	6	Croscarmellose sodium (Ac-Di-Sol)	10.00
5.00	7	Fumed silica	5.00
10.00	8	Stearic acid	10.00

Manufacturing Directions

1. Mix items 1 to 6 in a suitable blender.
2. Pass the mixture through a mill, using a 12-mesh screen with knives forward.
3. Add items 7 and 8, and blend the milled mixture for 20 minutes in a V-blender.
4. Compress to tablet weight of 675 mg.

Aspirin, Acetaminophen, Caffeine, and Salicylamide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Aspirin (40 mesh)	200.00
100.00	2	Salicylamide	100.00
100.00	3	Acetaminophen (40 mesh)	100.00
60.00	4	Caffeine (Granular)	60.00
150.00	5	Cellulose (microcrystalline) (Avicel™ PH101)	150.00
13.00	6	Stearic acid, USP	13.00
3.00	7	Fumed silica	3.00

Manufacturing Directions

1. Screen all ingredients through a 20-mesh sieve.
2. Blend all the ingredients in a V-blender for 20 minutes.
3. Compress into 615-mg tablets, using 5/8-in. tooling.

Aspirin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
325.00	1	Aspirin	325.00
25.52	2	Starch 1500	25.52
21.33	3	Microcrystalline cellulose (50 um)	21.33
6.33	4	Powdered cellulose	6.33

Manufacturing Directions

1. Blend in a twin-shell blender.
2. Compress into 378.00-mg tablets.

Atenolol Tablet

Formulation: Atenolol, 100.00 mg; citric acid (anhydrous), 4.00 mg; microcrystalline cellulose, 169.00 mg; sodium starch glycollate, 3.00 mg; magnesium stearate, 4.00 mg. Total 280.00 mg.

Manufacturing Directions

1. Citric acid is dissolved in purified water to provide a 20% citric acid solution.
2. Atenolol is granulated with this solution in a planetary mixer and the resultant granules were dried in a tray dryer to less than 3% by weight loss on drying.
3. The atenolol/citric acid premixture is hammer milled and blended with the other excipients. This material is compressed into 280-mg tablets.

Atenolol Tablets (50 mg/100 mg), Tenormin

Tenormin is available as 25-, 50-, and 100-mg tablets for oral administration. The inactive ingredients are magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Atenolol Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Atenolol	50.00
87.50	2	Magneisum carbonate heavy	87.50
29.70	3	Starch (corn)	59.70
3.30	4	Sodium lauryl sulfate	3.30
30.00	5	Starch (corn)	30.00
2.00	6	Gelatin	2.00
5.00	7	Magnesium stearate	5.00
QS	8	Purified water	QS

Note: The above formula is used for both 50- and 100-mg strengths; see below for fill weights to obtain the correct strengths.

Manufacturing Directions

1. Massing
   a. Mix starch (item 5) with approximately 27.3 mL of purified water (item 8) in a glass or stainless steel vessel, avoiding the formation of lumps.
   b. Boil the remaining 52.8 mL of purified water (item 8), and add the mix from step 1 with continuous stirring until a gel is formed. Further heat may be necessary. (*Note:* A mix temperature greater than 95°C must be exceeded before a gel is formed.)
   c. Pass gelatin through a 1.59-mm aperture, and add water at 50°C, dissolve, and add to step 2.
   d. Add sodium lauryl sulfate to step 3 without excessively mixing (to avoid foaming).
   e. Mill the atenolol through a 1.59-mm aperture screen at medium speed with knives forward, then charge into a suitable mixer.
   f. Pass magnesium carbonate heavy, starch (corn) (#3) through a 1.00-mm aperture stainless screen, and add to the mixer. Mix at 60 rpm for 10 minutes.
   g. Pass the mixed powders from step 4 through a 1-mm aperture stainless steel screen, and return to the mixer.
   h. Add, in one charge, the starch and gelatin and sodium lauryl sulfate gel from step 4 at 70°C to 80°C, and mix for 5 minutes at 60 rpm.
   i. Stop the mixer and inspect the mass. Add the extra 6.88 mL of purified water (#9) at 50°C to complete the granulation while mixing. Mix for a further 5 minutes at 60 rpm.
2. Drying/granulation: Proceed to step 1 or 2.
   a. Oven drying
      i. Pass the wet mass through a granulator fitted with a 4.76-mm aperture stainless steel screen. Collect the granules on paper-lined trays.
      ii. Dry the granules in a hot air oven at 60°C (not more than 65°C). After 1 hour of drying, pass the granules through a granulator fitted with a 2.38-mm aperture stainless steel screen. Collect the granules on paper-lined trays and return to the hot air oven at 60°C.
   b. Fluid-bed drying
      i. Pass the wet mass through a granulator fitted with a 4.76-mm aperture stainless steel screen into the fluid-bed dryer bowl.
      ii. Dry the granules in the fluid-bed dryer at 60°C for 30 minutes, turning over after 15 minutes. Then pass the granules through a granulator fitted with a 2.38-mm aperture stainless steel screen, and then return to the fluid-bed dryer bowl with the air inlet and outlet fully open. Proceed to step 3.
   c. Continue drying the granules until the LOD is between 1.5 and 2%.
   d. Pass the dried granules through a granulator fitted with a 1-mm aperture stainless steel screen. Collect the granules in a polyethylene-lined drum, and close securely.
3. Lubrication
   a. Place the dried granules from step 2 ("drying/granulation") in a suitable blender.
   b. Add magnesium stearate and the remainder of the starch via a 0.6-mm aperture stainless steel screen, and mix for 25 minutes.
   c. Transfer to a polyethylene-lined drum and close securely until ready for compression.
4. Compression: Compress on a suitable tablet machine using round punches—weight of 10 tablets is 2.075 g for 50-mg strength and 4.15 g for 100-mg strength; hardness more than 5 kPa; disintegration time not more than 15 minutes.
5. Coating: Use either organic coating or aqueous methocel as needed. Follow with a clear gloss.

Atenolol Tablets (90 mg)

Formulation: Atenolol (Stober), 93.0 g; Ludipress, 287.0 g; Kollidon CL, 52.0 g; magnesium stearate, 2.2 g; aerosil 200, 0.9 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press to tablets with low-compression force at 436 mg.

Atorvastatin Tablets (10 mg/20 mg), Atrovastatin Calcium Lipitor

Lipitor tablets for oral administration contain 10, 20, or 40 mg of atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1–7040 (hydroxypropylmethylcellulose, polyethylene glycol, talc, titanium dioxide); polysorbate 80; and simethicone emulsion.

Atorvastatin Calcium Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00 11.00	1	Atorvastatin, use atorvastatin calcium trihydrate	10.00 11.00
36.00	2	Calcium carbonate	36.00
65.00	3	Lactose monohydrate	65.00
30.00	4	Microcrystalline cellulose (Avicel PH 102)	30.00
3.00	5	Polyvinylpyrrolidone (Povidone K-30)	3.00
0.40	6	Polysorbate 80 (Tween 80)	0.40
4.00	7	Croscarmellose sodium (Ac-Di-Sol)	4.00
0.60	8	Magnesium stearate	0.60
–	9	Purified water	QS

Manufacturing Directions

1. Sift atorvastatin calcium trihydrate, calcium carbonate, lactose monohydrate, and Avicel PH 102 through a 0.500-mm stainless steel sieve.
2. Dissolve PVP K-30 and Polysorbate-80 in purified water (50°C) by slow stirring until it becomes clear. Cool the solution to 30°C. This is the granulating solution.
3. Knead the powder mix with granulating solution to get the desired granules.
4. Dry the granules to a targeted LOD of 2%.
5. Pass the dried granules through #16 mesh.
6. Sift Ac-Di-Sol and magnesium stearate through 0.500 mm.
7. Load the ground granules from step 5 and the powder mix from step 6 into a suitable blender. Blend for 1 minute.
8. Compress into 150-mg tablets, using 12-mm punches. For 20-mg strength, compress 300 mg in 15-mm punches.
9. Prepare a hypromellose and polyethylene glycol 4000 solution in the mixture of purified water and ethanol 95%. Keep overnight for complete gelation. (See Appendix.)
10. Add talc and titanium dioxide into step 10, and homogenize for a uniform coating dispersion.
11. Coat the tablets using the coating dispersion Accel Cota to a targeted weight.

Attapulgite Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
475.00	1	Attapulgite (regular)	475.00
275.00	2	Attapulgite (colloidal)	275.00
12.00	3	PVP K 30	12.00
7.00	4	Ac-Di-Sol	7.00
15.00	5	Kollidon® CL	15.00
30.00	6	Sucrose	30.00
50.00	7	Klucel® EF	50.00
40.00	8	Sucrose	40.00
35.00	9	Ac-Di-Sol	35.00
25.00	10	Kollidon® CL	25.00
14.00	11	Talc (fine powder)	14.00
5.00	12	Pectin	5.00
7.00	13	Glyceryl behenate	7.00
5.00	14	Aerosil 200	5.00
5.00	15	Magnesium stearate	5.00
–	16	Purified water	32.00
–	17	Ethanol (95%)	23.00

Manufacturing Directions

Caution: Use face-mask, hand gloves, and clean uniform. Avoid dust and inhalation of powder.

1. Dissolve sucrose (item 6) in purified water by using an appropriate stirrer at slow speed in a stainless steel container.
2. Dissolve Klucel EF in the ethanol by using an appropriate stirrer at slow speed in stainless steel container.
3. Mix the contents of steps 1 and 2 in a stainless steel drum by using an appropriate stirrer at slow speed.
4. Take item 8 (sucrose) and pass through a FitzMill using sieve number 24250 (impact forward, high speed). Collect the sieved contents in a stainless steel drum.
5. Add items 1 to 5 and sift the material through a 500-μm sieve using a Russell sifter.
6. Mix for 3 minutes.
7. Add the binding solution prepared earlier at a speed of 6 to 8 kg/min to the dry powder in an appropriate mixer at slow speed. After addition, scrape sides and blades, and then mix and chop further for 1 minute at slow speed. Check for satisfactory wet mass. Add additional purified water, if required, to obtain satisfactory wet mass.
8. Spread the granules onto stainless steel trays to a thickness of 1/4th of the tray thickness and load the trays on the trolley.
9. Load the trolleys into the oven and dry the granules at 55°C for 16 hours.
10. After 4 hours of drying, stir the granules on the trays and change the position of the trays for uniform drying.
11. Check the LOD of dried granules (limit: 2.5–3.5%).
12. The LOD should be strictly maintained; otherwise, tablet hardness and friability are affected. If required, dry further to obtain the desired LOD.
13. Grind the dried granules first using a 2.5-mm sieve and then with a 1.25-mm sieve.
14. Load the ground material into a double-cone blender.
15. Sift items 9, 10, 12, and 14 through a 500-μm sieve and add mixture to the double-cone blender.
16. Mix for 5 minutes.
17. Sift items 11, 13, and 15 through a 250-μm sieve and collect in a polyethylene bag.
18. Add about 2 to 3 kg bulk granules from earlier step, mix, and add to the double-cone blender.
19. Mix for 1 minute.
20. Compress the granules using an 18 × 8 mm, oblong, capsule-shaped, parallel, concave, plain punch for a 1-g tablet weight of hardness 12 to 18 kPa.
21. Coat the tablets using one of the HPMC coating solutions (see Appendix).

Azithromycin Chewable Tablets

Formulation: Azithromycin dihydrate (1619.870 g, 60% of total composition), F.D. and C. Red #40 (1.125 g), magnesium oxide (309.757 g, 11.5% of total composition), calcium gluconate (46.4160 mg, 1.7% of total composition), and sodium starch glycolate (139.248 g) are combined in an eight-quart V-blender and blended for 30 minutes.

Manufacturing Directions

1. The blend is passed through a Fitzpatrick JT Comminutor fitted with a #0 plate (0.027 in. opening) at medium speed with the hammers forward.
2. The mixture is then returned to the blender and blended for an additional 30 minutes. The blend is transferred to an eight-quart Hobart Planetary Mixer (Model C-100) and mixed at slow (#1) setting.
3. During mixing, the mixture is wet massed by adding 50 g of hydroxypropyl cellulose solution (prepared by adding 45 g of hydroxypropyl cellulose to 405 g of warm (60°C) water with stirring). Water (108 g) is added and the mixture is mixed for 10 minutes. An additional 85 g of water is added to the granulation to achieve the endpoint.
4. The mixer is continued at the slow setting for an additional 5 minutes to granulate the mass. The wet mixture is transferred to a polyethylene-lined tray and heated at 50°C in a forced air over overnight (16 hours).
5. The dried mass is passed through a Fitzpatrick JT Comminutor fitted with a #2 A plate (0.093-in. opening) at slow speed with the knives forward.
6. The granulation is transferred to an eight-quart V-blender, flavors are added, and the flavored granulation is blended for 30 minutes.
7. Magnesium stearate (45 g) is added and the mixture is blended for 5 minutes. The mixture is compressed into tablets to achieve a final tablet weight of 750 mg.

Azithromycin Dihydrate Tablets (600 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000Tablets (g)
630.00	1	Azithromycin dihydrate equivalent to azithromycin 600 mg	630.00
107.25	2	Dibasic calcium phosphate anhydrous, DC grade	107.25
50.00	3	Pregelatinized starch	50.00
35.00	4	Sodium croscarmellose	35.00
12.75	5	Sodium lauryl sulfate	12.75
15.00	6	Magnesium stearate	15.00
16.00	7	Hypromellose	16.00
5.00	8	Triacetin	5.00
7.00	9	Lactose	7.00
2.00	10	Titanium dioxide	2.00
–	11	Water, purified	200.00

Manufacturing Directions

1. Pass item 1 and 75% of item 5 (=9.5 g) through 0.5-mm sieve and charge in a tumbler. Mix for 5 minutes.
2. Pass item 2, item 3, and 70% of item 4 (=24.5 g) through 0.5-mm sieve and add to step 1.
3. Mix the contents of step 1 for 10 minutes, using tumbler.
4. Pass 50% of item 6 (=7.5 g) through 0.250-mm sieve and add to step 3.
5. Mix the contents of step 4 for 2 minutes.
6. Slug the granules of step 5 with a suitable punch (18.0 mm, round).
7. Grind the slug into granules with 1.25-mm sieve followed by 3-mm sieve.
8. Charge the granules of step 7 in a tumbler.
9. Pass the rest quantity of item 5 and item 4 through 0.5-mm sieve and add to step 8.
10. Mix the contents of step 9 for 5 minutes.
11. Pass the rest quantity of step 6 through 0.250-mm sieve and add to step 10.
12. Mix the contents of step 11 for 2 minutes.
13. Compress into 850-mg tablets, using a suitable punch (19.5 mm × 9.5 mm, oblong).
14. Charge item 11 in a stainless steel vessel. Add item 7 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hypromellose.
15. Add items 8 through 10 to step 14 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
16. Load core tablets from step 13 in coating pan and apply coating dispersion from step 15 to get 2.75% to 3.25% weight gain.

Azithromycin Tablets (250 mg), Zithromax

Zithromax is supplied for oral administration as film-coated, modified capsule-shaped tablets containing azithromycin dihydrate equivalent to 250 mg of azithromycin and the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate, hydroxypropyl methylcellulose, lactose, titanium dioxide, triacetin, and D&C Red No. 30 Aluminum Lake.

Azithromycin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Azithromycin, 5% excess	262.50
22.50	2	Microcrystalline cellulose	22.50
5.00	3	Sodium carmellose	5.00
10.00	4	Starch (maize)	10.00
3.50	5	Talc	3.50
3.50	6	Magnesium stearate	3.50
3.50	7	Aerosil 200	3.50
1.00	8	Sodium lauryl sulfate	1.00
32.50	9	Starch (maize)	32.50

Manufacturing Directions

1. Sift items 1 to 3 through a 250-μm sieve and charge in a mixer.
2. Mix for 15 minutes.
3. Charge item 4 in a suitable vessel, add hot item 10 (80°C), and mix. Allow to cool to room temperature.
4. Add the contents of step 3 to those of step 2, and mix to make wet mass without lumps.
5. Spread wet mass on trays and dry at 50°C for 12 hours.
6. Pass dried granules through #20 mesh and transfer to a tumble mixer.
7. Add items 5 to 9 (sifted through a 250-μm sieve) and mix for 2 minutes.
8. Compress into 340-mg tablets, using 16 × 6 mm punches.
9. Coat tablets with HPMC methylene chloride coating. (See Appendix.)

Benazepril Hydrochloride Tablets Lotensin

Lotensin is supplied as tablets containing 5, 10, 20, and 40 mg of benazepril for oral administration. The inactive ingredients are cellulose compounds, colloidal silicon dioxide, crospovidone, hydrogenated castor oil (5-, 10-, and 20-mg tablets), iron oxides, lactose, magnesium stearate (40-mg tablets), polysorbate 80, propylene glycol (5- and 40-mg tablets), starch, talc, and titanium dioxide.

Benazepril Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Benazepril hydrochloride	20.00
32.90	2	Lactose monohydrate	32.90
5.00	3	Starch, pregelatinized	5.00
1.00	4	Silicon dioxide colloidal	1.00
2.00	5	Crospovidone	2.00
10.00	6	Microcrystalline cellulose	10.00
4.00	7	Hydrogenated castor oil	4.00
–	8	Water, purified	QS

Manufacturing Directions

1. Mill items 1 to 3 and blend together.
2. Add water to granulate the blend, screen wet granules, and oven dry.
3. Mill dried granules after mixing with items 5 to 7.
4. Screen item 4 and add to step 3; blend for 1 minute.
5. Compress.
6. Coat using HPMC 2910 3 cps (4.88 mg) and polysorbate 80 (0.119 mg) in aqueous dispersion; dust tablets with talc.

Benzafibrate Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Benzafibrate	200.00
84.00	2	Lactose monohydrate	84.00
25.00	3	Starch (maize)	25.00
5.800	4	Methocel E5	5.80
13.00	5	Gelatin	13.00
14.90	6	Microcrystalline cellulose (Avicel PH 102)	14.90
14.90	7	Premojel	14.90
6.90	8	Talc	6.90
5.80	9	Magnesium stearate	5.80
QS	10	Water, purified, ca	80 mL

Manufacturing Directions

1. Dissolve item 5 into 50% of item 10 at 70°C to 80°C by mixing at medium speed and avoiding foam formation.
2. Cool to 50°C prior to use.
3. In a separate mixer, drymix items 1 to 4 at medium speed for 5 minutes.
4. Add the gelatin solution from step 2 slowly to the powder mix; add more of item 10, if necessary, to achieve a satisfactory mass, avoiding big lumps.
5. Spread the granules on stainless steel trays to a 10-mm thickness, and load in the oven for drying at 55°C for 12 hours to an LOD of not more than 1%.
6. Grind the dried granules through a 1.25-mm sieve in a granulator and transfer to a double-cone blender.
7. Pass items 6 to 8 through a 250-μm sieve in a sifter, load the mixture in a double-cone blender (step 6), and blend for 5 minutes.
8. Pass item 9 through a 250-μm sieve sifter and collect in a bag. Take a small amount of granules from step 7, mix with item 9 manually, and then add the mixture to the double-cone blender in step 7.
9. Compress into 370-mg tablets, using 11-mm round, concave punches.
10. Coat the tablets with hypermellose. (See Appendix.)

Berberine Tablets (5 mg)

Formulation: Berberine sulfate, 5.7 g; lactose monohydrate, 54.1 g; Ludipress, 54.1 g; magnesium stearate, 1.2 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.

Berberine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Berberine sulfate	5.70
54.10	2	Lactose monohydrate	54.10
54.10	3	Ludipress®	54.10
1.20	4	Magnesium stearate	1.20

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press with low-compression force.
2. The 6-mm biplanar tablet has an average weight of 115 mg.

Betamethasone Tablets (0.50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.50	1	Betamethasone base, 10% excess	0.55
20.00	2	Maize starch	20.00
85.90	3	Lactose monohydrate	85.95
3.00	4	Maize starch	3.00
0.50	5	Magnesium stearate	0.50
QS	6	Purified water	25.00

Manufacturing Directions

1. Pass item 2 through a 250-μm sieve, and make a homogenous slurry in cold purified water (5 kg) to assure it is free of lumps.
2. Add the slurry to a container with water (20 kg) at 80°C, stir until completely gelatinized, and cool to 50°C.
3. Mix item 1 gradually with item 3 and pass through a 250-μm sieve; pass item 4 through a similar sieve and mix the powders for 15 minutes.
4. Add starch paste and mix for 10 minutes; pass the wet mass through a FitzMill sieve 24205 at medium speed.
5. Dry granules at 55°C for 10 hours; do not exceed a moisture content of 2%. Pass dried granules through a 1-mm sieve into a double-cone blender.
6. Pass item 5 through a 250-μm sieve, mix with granules, and mix for 1 minute.
7. Compressed average tablet weight is 1.10 g; hardness not less than 2.0 kPa.

Beta Carotene Effervescent Tablets (7 mg)

Formulation: Lucarotin® dry powder 10% CWD (BASF), 70 g; Ludipress, 113 g; citric acid, anhydrous, 200 g; sodium bicarbonate, 120 g; sodium carbonate, 12 g; sodium cyclamate, 20 g; aspartame, 15 g; orange flavor, 20 g; polyethylene glycol 6000, powder, 30 g.

Manufacturing Directions

Pass all components through an 0.8-mm sieve, mix, and press with medium- or high-compression force at maximum 30% of relative atmospheric humidity.

Beta-Carotene Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
7.00 mg	1	Beta-carotene; use Lucarotin® CWD (dry powder, 10%) (BASF)	70.00
113.00 mg	2	Ludipress®	113.00
200.00 mg	3	Anhydrous citric acid	200.00
120.00 mg	4	Sodium bicarbonate	120.00
12.00 mg	5	Sodium carbonate	12.00
20.00 mg	6	Sodium cyclamate	20.00
15.00 mg	7	Aspartame	15.00
20.00 mg	8	Orange flavor	20.00
30.00 mg	9	PEG-6000 (powder)	30.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve and mix.
2. Press with medium- or high-compression force at maximum 30% relative humidity.
3. Use 12-mm biplanar punches for 602-mg tablets.

Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Beta-carotene (dry powder, 10% with excess)	160.00
240.00	2	Ludipress®	240.00
175.00	3	Dicalcium phosphate, granulated with 5% Kollidon® 30	175.00
6.00	4	Kollidon® CL	6.00
2.00	5	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press with medium-compression force.
2. Compress into 400-mg tablets, using 12-mm biplanar punches.

Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Beta-carotene (dry powder, 10%)	150.00
175.00	3	Dicalcium phosphate, granulated with 5% Kollidon® 30	175.00
100.00	4	Avicel™ PH101	100.00
5.00	5	Kollidon® CL	5.00
2.50	6	Aerosil® 200	2.50
20.00	7	Talc	20.00
2.50	8	Calcium arachinate	2.50

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press with a medium-compression force.
2. Compress into 502-mg tablets, using 12-mm biplanar punches.

Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Beta-carotene (dry powder, 10%)	220.00
250.00	2	Avicel™ PH101	250.00
20.00	3	Kollidon® CL	20.00
2.00	4	Aerosil® 200	2.00

Manufacturing Directions

1. Mix all components, and press with a low-compression force.
2. Compress into 518-mg tablets, using 12-mm biplanar punches.

Beta-Carotene, Vitamin C, and Vitamin E Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Beta-carotene (dry powder, 10%)	100.00
250.00	2	Ascorbic acid (crystalline) (BASF)	250.00
280.00	3	Sodium ascorbate (crystalline)	280.00
500.00	4	Vitamin E acetate (dry powder, SD 50)	500.00
600.00	5	Sorbitol (crystalline)	600.00
500.00	6	Ludipress®	500.00
350.00	7	Fructose	350.00
50.00	8	PEG-6000 (powder)	50.00

Manufacturing Directions

1. Mix all components, pass through a sieve, and press with high-compression force.
2. The 20-mm biplanar tablet has an average weight of 2.6 g.

Beta Carotene + Vitamin C + Vitamin E Chewable Tablets (10 mg + 500 mg + 250 mg)

Formulation: Beta carotene dry powder 10%, 100 g; Ascorbic acid, crystalline (BASF), 250 g; Sodium ascorbate, crystalline, 280 g; Vitamin E acetate dry powder SD 50, 500 g; (BASF) sorbitol, crystalline [10], 600 g; Ludipress, 500 g; fructose, 350 g; polyethylene glycol 6000, powder, 50 g.

Manufacturing Directions

Mix all components, pass through a sieve and press with high-compression force at 2600 mg.

Beta Carotene + Vitamin C + Vitamin E Effervescent Tablets (12 mg + 150 mg + 25 mg)

Formulation: Lucarotene dry powder 10% CWD G/Y (BASF), 120 g; Ascorbic acid, crystalline (BASF), 150 g; Dry vitamin E acetate 50% DC (BASF), 50 g; Ludipress LCE [1], 705 g; Kollidon VA64 [1], 50 g; citric acid, anhydrous, 450 g; sodium bicarbonate, 320 g; polyethylene glycol 6000, powder [10], 75 g; orange flavor (Dragoco), 50 g; aspartame (Searle), 30 g.

Manufacturing Directions

1. Mix all components, and pass through a sieve.
2. Press with high-compression force at a maximum of 30% of relative atmospheric humidity at 2.045 mg.

Beta Carotene + Vitamin C + Vitamin E Tablets (12 mg + 250 mg + 125 mg)

Formulation: Beta Carotene dry powder 10%, 125 g; Ascorbic acid, crystalline (BASF), 125 g; Sodium ascorbate, crystalline (BASF), 141 g; Vitamin E acetate dry powder SD 50, 250 g; (BASF) Ludipress or Sorbitol, crystalline [10], 119 g; Polyethylene glycol 6000, powder [10], 5 g; Orange flavor (FDO), 15 g; Sodium cyclamate, 10 g.

Manufacturing Directions

Mix all components, pass through a sieve, and press with medium-compression force at 790 mg.

Beta Carotene + Vitamin C + Vitamin E Tablets (7 mg + 60 mg + 25 mg)

Formulation: Betavit® dry powder 10% (BASF), 75 g; ascorbic acid, powder (BASF), 60 g; vitamin E acetate dry powder 50%, 50 g; sorbitol, crystalline [10], 240 g; Kollidon CL, 30 g; magnesium stearate, 5 g.

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and then press with low-compression force at 497 mg.

Beta-Carotene, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
12.00	1	Beta-carotene (dry powder, 10% with excess)	125.00
125.00	2	Ascorbic acid (crystalline) (BASF)	125.00
141.00	3	Sodium ascorbate (crystalline) (BASF)	141.00
250.00	4	Vitamin E acetate (dry powder, SD 50)	250.00
119.00	5	Ludipress® or sorbitol (crystalline)	119.00
5.00	6	PEG-6000 (powder)	5.00
15.00	7	Orange flavor (FDO)	15.00
10.00	8	Sodium cyclamate	10.00

Manufacturing Directions

1. Mix all components, and pass through a sieve.
2. Press with medium-compression force.
3. Compress into 790-mg tablets, using 12-mm biplanar tablets.

Beta-Carotene, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
6.00	1	Beta-carotene; use Betavit® (dry powder, 10% with excess) (BASF)	65.00
100.00	2	Ascorbic acid (powder) (BASF)	100.00
60.00	3	Vitamin E acetate (dry powder, 50%)	60.00
369.00	4	Ludipress®	369.00
6.00	5	Magnesium stearate	6.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix.
2. Press with medium- or high-compression force.
3. Compress into 790-mg tablets, using 12-mm biplanar tablets.

Beta-Carotene, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
6.00	1	Beta-carotene; use Betavit® (dry powder, 10% with excess) (BASF)	65.00
100.00	2	Ascorbic acid (powder) (BASF)	100.00
60.00	3	Vitamin E acetate (dry powder, 50%)	60.00
233.00	4	Sorbitol (crystalline) (Merck)	233.00
30.00	5	Kollidon® VA 64	30.00
8.00	6	Kollidon® CL	8.00
4.00	7	Magnesium stearate	4.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve and mix.
2. Press with medium- or high-compression force.
3. Compress into 502-mg tablets, using 12-mm biplanar tablets.

Beta-Carotene, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
7.00	1	Beta-carotene; use Betavit® (dry powder, 10% with excess) (BASF)	75.00
60.00	2	Ascorbic acid (powder) (BASF)	60.00
50.00	3	Vitamin E acetate (dry powder, 50%)	50.00
240.00	4	Sorbitol (crystalline)	240.00
30.00	5	Kollidon® CL	30.00
5.00	6	Magnesium stearate	5.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve and mix.
2. Press with low-compression force.
3. A colorant pigment should be added to obtain a homogeneous appearance of tablets.
4. Use 12-mm biplanar punches for 497-mg tablets.

BIRB 796 Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	BIRB 796	100.00
200.00	2	3-cyclodextrin	200.00
225.00	3	Microcrystalline cellulose	225.00
165.00	4	Lactose	165.00
7.50	5	Colloidal silicon dioxide	7.50
30.00	6	Starch, pregelatinized	30.00
15.00	7	Sodium starch glycolate	15.00
7.50	8	Magnesium stearate	7.50

Note: Item 2 can be replaced with item 4 (a total of 365 mg of lactose).

Manufacturing Directions

1. Charge items 1 to 7 in a suitable mixer after passing through a 250-μm sieve; mix for 10 minutes.
2. Add item 8 and blend for 3 minutes.
3. Compress into 750-mg tablets, using a 15-mm biplanar punch.

Bisacodyl Delayed-Release Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
05.00	1	Bisacodyl	5.00
20.00	2	Cellulose (microcrystalline) (Avicel™ PH102)	20.00
45.27	3	Lactose (spray dried)[a]	45.27
04.00	4	Maize starch (dried)[b]	4.00
00.73	5	Magnesium stearate	0.73

[a] Particle size distribution: minimum, 98% 250 μm, 30% to 60% 100 μm; maximum 15% 45 μm.
[b] LOD NMT 4.5%, when dried at 120°C for 4 hours.

Manufacturing Directions

Handle bisacodyl carefully; it can cause itching if it comes into contact with skin. Over-mixing of lubricants reduces the hardness. Check the temperature and relative humidity of the room before beginning processing. Limit relative humidity to 50% to 60% and temperature to 27°C to 30°C.

1. Mix items 1 and 2 in a stainless steel drum for 2 to 3 minutes.
2. Pass the mixed powder through a 500-μm sieve using sifter.
3. Collect in stainless steel drum.
4. Pass item 3 through a 500-μm sieve using sifter.

5. Collect in stainless steel drum.
6. Load the sieved material into the drum mixer, and mix for 5 minutes.
7. Mix items 4 and 5 in a polyethylene bag for 1 minute.
8. Pass the mix through a 250-μm sieve.
9. Collect in a polyethylene bag.
10. Add 3 to 5 g powder to it, and mix for 1 minute.
11. Add this mixture, and mix for 1 minute in a drum blender.
12. Check the moisture content (limit: 1.0–1.5%).
13. Compress the granules using a rotary tabletting machine; 6-mm biconvex tablets have an average weight of 750 mg and hardness of 4 to 5 kPa.
14. Apply enteric coating.

Bismuth Subsalicylate and Calcium Carbonate Tablets

Formulation: Bismuth subsalicylate, 262.5 mg; microcrystalline cellulose, NF, 213.3 mg; calcium carbonate, 67.5 mg; mannitol, 67.5 mg; sodium starch glycolate, 40.5 mg; polyvinyl pyrrolidone, 13.5 mg; magnesium stearate, 5.4 mg; polysorbate, 80 3.4 mg; silica, 0.7 mg; dye, 0.7 mg. Total 675.0

Manufacturing Directions

1. The ingredients are added to a mixer or granulator in the following order: part of microcrystalline cellulose, calcium carbonate, part of sodium starch glycolate, Polysorbate 80, dye, and bismuth subsalicylate.
2. After adding bismuth subsalicylate and mixing at high shear, the mixture is dried at 86°C to less than 2% moisture.
3. Additional powders (microcrystalline cellulose, sodium starch glycolate, mannitol, and polyvinyl pyrrolidone) are added, and granules are formed by spraying water (approximately 10% by weight of the composition) onto the mixture under high shear.
4. After additional drying to less than 3% moisture, silica (glidant) and magnesium stearate (lubricant) are added and mixed for about 1 minute.
5. Caplets are then formed on a rotary tablet press.

Bismuth Subsalicylate Swallow Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
262.50	1	Bismuth subsalicylate	262.50
213.30	2	Microcrystalline cellulose	213.30
67.50	3	Calcium carbonate	67.50
67.50	4	Mannitol	67.50
40.50	5	Sodium starch glycolate	40.50
13.50	6	Polyvinylpyrrolidone	13.50
5.40	7	Magnesium stearate	5.40
3.40	8	Polysorbate 80	3.40
0.70	9	Silica	0.70
0.70	10	Dye	0.70

Manufacturing Directions

1. Mix the above ingredients in a mixer in the following order: part of microcrystalline cellulose, calcium carbonate, part of sodium starch glycolate, Polysorbate 80, dye, and bismuth subsalicylate.
2. After adding bismuth subsalicylate and mixing at high shear, the mixture is dried at 86°C to less than 2% moisture.
3. Additional powders (microcrystalline cellulose, sodium starch glycolate, mannitol, and polyvinyl pyrrolidone) are added, and granules are formed by spraying water (approximately 10% by weight of the composition) onto the mixture under high shear.
4. After additional drying to less than 3% moisture, silica (glidant) and magnesium stearate (lubricant) are added and mixed for about 1 minute.
5. Caplets are then formed on a rotary tablet press.

Bisoprolol Fumarate and Hydrochlorothiazide Tablets

Each bisoprolol fumarate HCTZ 2.5-mg/6.25-mg tablet for oral administration contains bisoprolol fumarate 2.5 mg and hydrochlorothiazide 6.25 mg. Each bisoprolol fumarate HCTZ 5-mg/6.25-mg tablet for oral administration contains bisoprolol fumarate 5 mg and hydrochlorothiazide 6.25 mg. Each bisoprolol fumarate HCTZ 10-mg/6.25-mg tablet for oral administration contains bisoprolol fumarate 10 mg and hydrochlorothiazide 6.25 mg. Inactive ingredients include colloidal silicon dioxide, cornstarch, dibasic calcium phosphate, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide. The 5-mg/6.25-mg tablet also contains red and yellow iron oxide. The 2.5-mg/6.25-mg tablet also contains crospovidone, pregelatinized starch, and yellow iron oxide.

Bran Sucrose Gelatin Calcium Carbonate Tablets

Manufacturing Directions

1. Gelatin–sucrose syrup is prepared by placing the following ingredients in a mixing kettle equipped with a heater and agitator: distilled water, 24000.0 g; gelatin, 3000.0 g; sucrose, granular, 31995.0 g.
2. The mixture is heated up to about 150°F with agitation until solution is effected and the gelatin–sucrose syrup then slowly stirred and held at a temperature of about 150°F until needed.
3. Wheat bran is comminuted in a Schutz-O'Neill Airswept Pulverizer to provide a particle size whereby a minimum of 94% passes through a United States Standard number 20-mesh screen and a maximum of 60% passes through a United States Standard number 80-mesh screen. [The required amount of bran for the batch is calculated by the following formula: 44250 g × 100/(100 –percent moisture in bran.]
4. After pulverizing, the bran is transferred to a heavy-duty double sigma arm mixer and mixed with 1500 g of calcium carbonate, and the previously prepared gelatin–sucrose syrup added rapidly thereto with stirring.
5. When the bran appears to be damp, the mixture is stirred for a 30-minute period and then stopped.
6. Powdered sucrose (16600.0 g) is added and the mixture agitated for an additional 2 to 5 minutes.
7. The wet mix is then discharged through an Ambrette screw extruder and the extrudate spread on drying trays and dried in an oven at 225°F to 3% moisture content.
8. The dried extrudate is granulated employing a FitzMill (2A plate) and then pressed into 1-g tablets by a conventional tableting machine.

Bran Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Bran wheat (milled <1 mm)	250.00
200.00	2	Ludipress®	200.00
5.00	3	Kollidon® 30	5.00
4.00	4	Aerosil® 200	4.00
4.00	5	Magnesium stearate	4.00

Manufacturing Directions

1. Mix all components, pass through a sieve, and press with medium-compression force.
2. If the bran is not milled, the hardness of the tablet is higher but the content uniformity is less.
3. Compress into 477-mg tablets, using 12-mm punches.

Bromhexine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
8.00	1	Bromhexine HCl	8.00
78.00	2	Lactose monohydrate	78.00
30.40	3	Cornstarch	30.40
3.00	4	Gelatin (powder)	3.00
QS	5	Purified water	12.00
0.60	6	Magnesium stearate	0.60

Manufacturing Directions

Note: The binding solution is susceptible to microbiological growth, and so prepare the solution immediately before the granulation process. Protect bromhexine HCl from light.

1. Make slurry in a separate container by dissolving item 4 in hot item 5 (70–80°C).
2. Mix for 10 minutes using stirrer at medium speed.
3. Pass items 2, 1, and 3 through a 630- μm sieve using a sifter.
4. Charge the sieved material into the mixer.
5. Mix, using mixer and chopper, for 5 minutes at high speed. Add binding solution to the dry powders in the mixer while mixing at low speed.
6. After the addition is complete, mix for an additional 4 minutes at low speed or until a satisfactory mass is obtained.
7. Spread the wet granules onto the trays.
8. Load the trolleys into the drying oven.
9. Dry the granules at 60°C for 10 hours.
10. Turn the granules after 4 hours of drying in order to obtain uniform drying.
11. Transfer the dried granules in stainless steel drums.
12. Check moisture content (limit: NMT 2.0%).
13. Pass the dried granules first through a 1.5-mm and then a 1.0 mm sieve using a granulator. Collect in stainless steel drums.
14. Load the granules into the blender.
15. Pass item 6 through a 250- μm sieve using a sifter, and add to the granules in blender; blend for 2 minutes.
16. Compress the granules using a rotary tabletting machine.
17. Use a 7-mm flat, beveled edge punch to compress 1.20 g per tablet at a hardness of NLT 3.0 kPa.

Bromazepam Tablets (3 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
3.00	1	Bromazepam	3.00
0.23	2	Aluminum lake erythrosine (19.4%)[a]	0.23
1.80	3	Talc	1.80
100.00	4	Microcrystalline cellulose (Avicel PH 102)	100.00
94.37	5	Lactose crystalline	94.37
0.60	6	Magnesium stearate	0.60

[a]If a different dye is used, adjust the weight with lactose crystalline (item 5).

Manufacturing Directions

1. Charge item 1 and 3% of item 5 in a mixer and mix for 10 minutes.
2. Pass the mixture through an oscillating granulator with a 0.5-mm screen.
3. Rinse the oscillator with 2% of item 5 and add it to the mixture in step 2.
4. In a separate mixer, add item 2 (if used), item 3, and 5% of item 4, and then mix for 3 minutes.
5. Pass the mixture in step 4 through a mill at medium speed.
6. Transfer the mixture in steps 5 and 3 into an oscillating granulator, add the balance of item 5, add item 3, pass through a 0.5-mm sieve, and then mix for 1 hour.
7. Transfer the mixture to a blender, add item 6, and blend for 30 minutes.
8. Compress at 4- to 5-ton pressure; compress into 200-mg tablets, using 9 mm × 2.5 mm cylindrical biplanar punches.

Bromhexine Tablets (8 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
8.00	1	Bromhexine hydrochloride	8.00
78.00	2	Lactose monohydrate	78.00
30.40	3	Starch (maize)	30.40
3.00	4	Gelatin	3.00
–	5	Water, purified, ca	120 mL
0.60	6	Magnesium stearate	0.60

Manufacturing Directions

1. Charge item 4 in a suitable vessel, add item 5 at 70°C to 80°C to dissolve item 4, and mix for 10 minutes.
2. Charge items 1 to 3 in a suitable container after passing them through a 630-μm sieve. Mix and chop for 5 minutes.
3. Add binding solution from step 1 to the mixer in step 2, and mix for 5 minutes at high speed and then slow speed until a suitable mass is obtained (add more of item 5 if needed).
4. Spread the wet mass on trays and dry at 60°C for 10 hours, turning granules over every 4 hours until not more than 2% moisture remains.
5. Pass the dried granules through a 1.5-mm sieve and then a 1.0-mm sieve.
6. Pass item 6 through a 250-μm sieve, add to step 5, and blend for 2 minutes.
7. Compress into 120-mg tablets, using 7-mm flat punches.

Bromocriptine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
6.00	1	Bromocriptine mesylate, with excess	6.10
205.50	2	Ludipress	205.50
2.20	3	Magnesium stearate	2.20

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with high-compression force.
2. Compress to 214-mg tablets, using 9-mm biconvex punches.

Buflomedil Hydrochloride Tablets (150 mg/300 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Buflomedil hydrochloride	300.00
74.00	2	Lactose	74.00
14.00	3	Povidone K 29–32	14.00
2.00	4	Magnesium stearate	2.00
QS	5	Water, purified	55.00 mL

Note: For 150-mg strength, adjust all components proportionally.

Manufacturing Directions

1. Granulation
   a. Dissolve povidone in purified water, using a glass or stainless steel vessel.
   b. Pass through a 500-μm aperture screen and add buflomedil hydrochloride and lactose. Charge into a suitable planetary or ribbon mixer. Mix at 15 to 30 rpm for 10 minutes.
   c. Granulate the mixed powders with povidone solution, adding 20-mL aliquots every 2 to 3 minutes, with a mixer speed of 30 rpm.
   d. Stop the mixer and inspect the mass. Additional purified water may be added to complete the granulation.
   e. Pass the wet mass through a suitable granulator fitted with a 2000-μm aperture stainless steel screen. Collect granules on paper-lined trays and spread out evenly, 1/2 to 1 in. (1–2.5 cm) deep.
   f. Dry the granules in a hot air oven at 40°C for 3 hours or until the LOD is between 0.7 and 2.8%.
2. Lubrication
   a. Pass the dry granules through a 100-μm aperture stainless steel screen and charge into a cone or ribbon blender.
   b. Mix the magnesium stearate with one scoopful of granules from the previous step and add to the bulk. Blend for 10 minutes at 20 to 30 rpm, and empty the blender into polyethylene-lined drums for compression.
3. Compression: The tablet can be compressed using 9.5-mm or 11.11-mm punches: 385.40 mg per tablet. The weight of a 150-mg tablet is 246 mg.
4. Coating: Use a clear CAP/Carbowax coating to control the release of the active ingredient. (See Appendix.)

Buflomedil Hydrochloride Tablets (600 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
600.00	1	Buflomedil hydrochloride	600.00
160.00	2	Sodium calcium alginate (Kelset)	160.00
30.00	3	Povidone K 29–32	30.00
QS	4	Water, purified, ca	300 mL
4.35	5	Magnesium stearate	4.35

Manufacturing Directions

Caution: Wear a face mask and rubber gloves. When wett, alginate materials result in slippery surfaces—exercise care.

1. Granulation (standard method using planetary or horizontal mixer). (*Note:* Temperature of the water used should not exceed 30°C, so cool it if necessary.)
   a. Pass any agglomerated materials through a 375-μm screen.
   b. Load buflomedil, sodium alginate, sodium calcium alginate, and povidone into suitable mixing equipment. Blend for 10 minutes. Add while mixing 250 mL water over a period of 5 to 10 minutes and then mix for 5 minutes. Add additional water in small portions with mixing, until granulation is complete. Record the amount of water added. Stop mixing and allow the mixture to stand for approximately 5 minutes. (The granulation end point occurs when the mass is of a slightly wet but crumbly consistency. Avoid overwetting. The quantity of water and the mixing time must be sufficient to dissolve the povidone.)
   c. Load granules onto paper-lined oven trays, and dry at 50°C until the LOD is 3% to 5% (IR balance or similar at 100°C for 15 minutes). The drying time is 5 to 8 hours depending on tray loading. Should the LOD be above 5% at the completion of the drying period, increase the temperature of the drying oven to 60°C and continue until the LOD is satisfactory. It is important that you do not increase the temperature until the initial drying period is complete.
   d. After drying, screen granules through an 840-μm screen fitted on the oscillating granulator. Pack into tightly sealed polyethylene-lined drums and store in an air-conditioned area.
2. Lubrication
   a. Blend magnesium stearate with a portion of granules and then screen through a 600-μm screen fitted to the oscillating granulator. Incorporate the remaining granules by serial dilution, mixing between additions. Do not overblend.
3. Compression: Compress into oval-shaped tablets.
4. Coating: Coat using methocel coatings. (See Appendix.)

Bupropion Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Bupropion hydrochloride	150.00
9.00	2	Kollidon 90F	9.00
171.00	3	Purified water	171.00
3.20	4	Stearic acid	3.20

Manufacturing Directions

1. Povidone is first dissolved in water.
2. Bupropion hydrochloride is placed in the top spraying chamber of Glatt GPCG1 fluidized bed apparatus. The solution of povidone is sprayed onto the active ingredient, with the following parameters: Air flow = 100–110 m^3/h, liquid flow = 6–7 g/min, inlet temperature = 65°C, and spraying pressure = 2.8 bar.
3. Once the granulation is completed, granules are passed through a sieve (1 mm mesh) and stearic acid is weighed, added, and blended in a drum mixer (Turbula T2C, Bachoffen, Switzerland). The resulting mixture is pressed into tablets (7-mm diameter and 7-mm curvature) with average hardness being between 60 and 120 N.
4. The tablet cores (step 3) are then coated with the following formulation: Tablet cores (step 3) 162.20 mg, Ethocel PR100 (ethylcellulose) 7.05 mg, Kollidon 90F (povidone USP) 7.05 mg, PEG 1450 2.10 mg, Denatured alcohol 210.00 mg to give total dry weight of 178.40 mg.

   Ethocel, povidone, and PEG 1450 are first dissolved in denatured alcohol. The coating solution is then sprayed onto the tablet cores in a coating pan (Vector LCDS), with the following spraying parameters: Air flow = 100–110 m^3/h, liquid flow = 6–7 g/min, inlet temperature = 65°C, and spraying pressure = 2.8 bar.

Bupropion Hydrochloride Tablets Wellbutrin

Immediate-release tablets—Wellbutrin is supplied for oral administration as 75-mg (yellow-gold) and 100-mg (red) film-coated tablets. Each tablet contains the labeled amount of bupropion HCl and the following inactive ingredients: (a) *75-mg tablet*— D&C Yellow No. 10 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide. (b) *100-mg tablet*—FD&C Red No. 40 Lake, FD&C Yellow No. 6 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.

Sustained-release tablets—(a) *Wellbutrin SR:* Wellbutrin SR tablets are supplied for oral administration as 100-mg (blue) and 150-mg (purple), film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion HCl and the following inactive ingredients: carnauba wax, cysteine hydrochloride, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, and titanium dioxide and is printed with edible black ink. In addition, the 100-mg tablet contains FD&C Blue No. 1 Lake and polysorbate 80; the 150-mg tablet contains FD&C Blue No. 2 Lake, FD&C Red No. 40 Lake, and polysorbate 80. (b) *Zyban:* Zyban (bupropion HCl for smoking cessation) is supplied for oral administration as 150-mg (purple), film-coated, sustained-release tablets. Each tablet contains the labeled amount of bupropion HCl and the following inactive ingredients: carnauba wax, cysteine HCl, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide and is printed with edible black ink. In addition, the 150-mg tablet contains FD&C Blue No. 2 Lake and FD&C Red No. 40 Lake.

Bupropion Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Bupropion hydrochloride	100.00
68.50	2	Microcrystalline cellulose	68.50
6.90	3	Sodium starch glycolate	6.90
3.80	4	L-Cysteine hydrochloride	3.80
17.30	5	Talc	17.30
0.20	6	Silicon dioxide colloidal	0.20
–	7	Water, purified	8.00
–	8	Alcohol SD3A anhydrous	24.00

Manufacturing Directions

1. Sift bupropion hydrochloride, microcrystalline cellulose, and sodium starch glycolate through a 30-mesh Russell–Finex sifter.
2. Blend the sifted items in 1 for 15 minutes in a slant-cone blender.
3. In a separate container, dissolve cysteine hydrochloride in purified water.
4. Add item 8 to step 3 and mix thoroughly.
5. Add to step 1 in a granulating vessel: make a wet mass, dry granules in a fluid-bed dryer until the LOD is between 1% and 2%.
6. Sift dried granule through a 20-mesh Russell–Finex sifter.
7. Sift items 4 and 6 and blend with step 6.
8. Compress into 172.6-mg tablets, using round 7.8-mm punches.

Bupropion Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Bupropion hydrochloride uncoated	100.00
121.30	2	Pharmatose DCL	121.30
15.00	3	Methocel A4M	15.00
121.30	4	Pharmatose DCL21	121.30
27.00	5	Talc	27.00
0.70	6	Magnesium stearate	0.70
85.00	7	Kollidon SR	85.00

Manufacturing Directions

Mix, granulate, and compress into 334.00-mg tablets.

Buspirone Fast-Melt Tablets

Formulations: Mix buspirone, 8%; sodium bicarbonate, 25%; citric acid anhydrous, 25%; avicel PH113, 12%; anhydrous lactose, 17%; xylitol, 11%; crodesta f160, 2%.

Manufacturing Directions

1. Dry all ingredients at 40°C to 60°C to significantly reduce the moisture content of each material.
2. Blend for 10 minutes and extrude in a hot melt extruder at 70°C to 100°C to soften and melt the thermal binders (sucrose stearate and xylitol) and to form granules containing the effervescent ingredients.
3. Mix BUS-EGF (20–80 mesh) 50%, microcrystalline cellulose (Avicel PH113) 31%, mannitol (Mannogen 3215) 10%, AcDiSol 5%, aspartame 3%, redberry flavor 0.4%, magnesium stearate 0.5, and fumed silicon dioxide 0.1%.
4. Screen and blend for 5 minutes prior to compression.
5. Buspirone tablets are then compressed to a hardness of approximately 1–3 kPa and tablets disintegrate in water in approximately 15–35 seconds.

Buspirone Hydrochloride Tablets, BusPar

BuSpar is supplied for oral administration in 5-mg and 10-mg, white, ovoid-rectangular, scored tablets. BuSpar tablets, 5 mg and 10 mg, contain the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

Buspirone Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Buspirone hydrochloride	15.00
7.00	2	Polyvinylpyrrolidone	7.00
1.50	3	Silicon dioxide	1.50
150.00	4	Lactose	150.00
1.50	5	Glyceryl behenate	1.50
	6	Water qs	

Manufacturing Directions

1. Buspirone and lactose are placed in a fluidized bed apparatus.
2. An aqueous PVP solution (in 85 g of water) is sprayed to get granules.
3. The granules thus obtained are subsequently dried and passed through a sieve (1-mm mesh) and glyceryl behenate is weighed, added, and blended in a drum mixer.
4. The resulting mixture is pressed into 175-mg tablets.
5. These tablet cores are then coated with the following formulation: ethylcellulose 10.00, hydroxypropylcellulose 10.00, stearic acid 2.00, and alcohol 188.00 g.
6. Ethocel, povidone, and stearic acid are first dissolved in denatured alcohol (188 g). The coating solution is then sprayed onto the tablet cores in a coating pan.

Buspirone Hydrochloride Tablets, Controlled-Release (30 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
30.00	1	Buspirone hydrochloride	30.00
120.00	2	Polyvinyl chloride	120.00
11.00	3	Polyvinyl acetate C10-V7	11.00
1.60	4	Magnesium stearate	1.60
–	5	Alcohol	QS

Manufacturing Directions

1. Dry mix buspirone hydrochloride with polyvinyl chloride.
2. Granulate the powder mixture with a solution of polyvinyl acetate in ethanol.
3. Mill dried granules and compress into 7-mm round tablets (162.60 mg).

Cabenoxolone Tablets

Formulations: Carbenoxolone sodium, 20 mg; mannitol, 400 mg; alginic acid, 200 mg; sodium alginate, 200 mg; aluminium hydroxide, dried gel 80 mg; sodium bicarbonate, 70 mg; magnesium trisilicate, 20 mg; magnesium stearate, 12 mg; gum acacia, 35 mg; peppermint oil, 2 mg. Total 1039 mg.

Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Caffeine powder	150.00
36.00	2	Cellulose (microcrystalline) (Avicel™ PH-102)	36.00
46.00	3	Anhydrous lactose	46.00
48.50	4	Di-Pac granular	48.50
3.00	5	Croscarmellose sodium (Ac-Di-Sol SD-711)	3.00
1.50	6	Fumed silica	1.50
0.75	7	Stearic acid	0.75
0.75	8	Magnesium stearate	0.75
1.20	9	Flavor	1.20

Manufacturing Directions

1. Screen items 1, 7, and 8 separately through a 40-mesh sieve.
2. Blend items 1 to 6 and 9 in a V-shaped blender, and mix for 3 minutes.
3. Add item 8 to the blender and mix for another 5 minutes.
4. Compress, using 7 kg pressure and 3/8-in., flat, beveled-edge punches to produce tablets with an average weight of 311 mg.

Calcium and Vitamin D Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Anhydrous calcium phosphate (dibasic)	500.00
133 IU	2	Vitamin D (as vitamin D3) (3.33 μg/tablet)	3.33 mg
15.00	3	Starch (pregelatinized, NF)	15.00
55.00	4	Cellulose (microcrystalline, NF)	55.00
6.00	5	Magnesium stearate, NF	6.00
5.00	6	Talc (powder), USP	5.00
12.00	7	Wax (hydrogenated vegetable oil) (Sterotex K)	12.00
15.50	8	Sodium starch glycolate, NF	15.50

Manufacturing Directions

1. Charge one half of the dibasic calcium phosphate through a mesh screen into a blender.
2. Premix by hand the pregelatinized starch with vitamin D3 beadlets in a suitable container, and sift through a mesh screen into the blender.
3. Charge the microcystalline cellulose and the remaining calcium phosphate through a mesh screen into the blender.
4. Mix for 20 minutes.
5. Discharge approximately one third of the granulation into polyethylene-lined drums.
6. Mix the magnesium stearate, talc, hydrogenated vegetable oil wax, and sodium starch glycolate.
7. Mill through a #40-mesh screen into the blender.
8. Return granulation from step above to the blender. Blend together.
9. Compress.

Calcium Carbonate and Glycine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Calcium carbonate (precipitated)	400.00
200.00	2	Glycine (aminoacetic acid)	200.00
QS	3	Starch	QS
6.50	4	Mineral oil (light)	6.50
QS	5	Purified water	QS

Manufacturing Directions

1. Add starch to a planetary mixer, and add 10 times the quantity of purified water.
2. Heat to boil with constant stirring until a thick, translucent white paste is formed. Use this paste in granulation.
3. Charge calcium carbonate and glycine in a sigma-blade or a planetary mixer, and mix for 10 minutes.
4. Granulate this powder with the starch paste until a suitable mass is obtained.
5. Force the wet mass through a #12-mesh screen onto dryer trays.
6. Dry in an air-forced oven at 130°F to 140°F or in a fluid-bed dryer.
7. Pass the dried granules through a #12-mesh screen, then through a #18-mesh screen.
8. Pass the granules over a 30-mesh screen, remove the portion passing through the screen, and regranulate.
9. Charge the particles retained on 30-mesh screen in a tumble mixer, add mineral oil, and mix for 8 minutes.
10. Compress into 640-mg tablets, using 7/16-in. punches.

Calcium Carbonate and Vitamin D Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
600.00	1	Calcium (elemental); use calcium carbonate (90%) for direct compression	1665.00
0.235	2	Vitamin D3 (200.00 IU); use vitamin D3 beadlets	0.282
4.16	3	Magnesium stearate	4.16
83.25	4	Sodium starch glycolate	83.25

Manufacturing Directions

1. Make a premix of vitamin D3 successively in three portions of calcium carbonate (total amount equivalent to ~3% of total calcium carbonate), using the geometric dilution.
2. Mix for 10 minutes each time (total time: 30 minutes).
3. Add the premix to the sodium starch glycolate. Mix for 10 minutes.
4. Set the blend aside, protected from light, until the next step.
5. Pass the magnesium stearate through a 420-μm aperture screen, if required, and blend it with another portion of calcium carbonate (~10% of total calcium carbonate).
6. Mix for 5 minutes. Set aside.
7. Add the blended material to the balance of the calcium carbonate. Mix for 10 minutes.
8. Add the premix to blend from above. Mix for 5 minutes.
9. Compress on specially shaped, 0.8100 × 0.3700-in., ovaloid, bisected punches with a monogram on one side.
10. Theoretical weight of 10 tablets = 17.527 g.
11. Coat using one of the HPMC formulae (see Appendix).

Calcium Carbonate Chewable Tablets

Formulations: Granulated calcium carbonate (93.3% calcium carbonate, 6.3% glucose and 0.4% gelatin), 42.87%; magnesium stearate, 2.50%; colored speckles, 0.75%; flavorants, 0.78%; MPD (31-menthoxy propane 1,2diol), 0.07%; WS-3 (methyl-*p*-menthane-3-carboxamide), 0.05%; aspartame, 0.198%; sodium saccharin, 0.102%; mannitol Q.S.

Manufacturing Directions

1. The above ingredients are dry blended in a mixer until homogeneous, and then direct compressed in a tabletting machine to approximately 8.5 Strong Cobb units hardness to produce chewable antacid tablets each weighing 1.25 g (500 mg calcium carbonate per tablet).
2. These tablets may also be prepared by using granulated calcium carbonate, which is a 50/50 coblend of calcium carbonate/mannitol.

Calcium Carbonate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Calcium carbonate (precipitated)	500.00
65.00	2	Kollidon® 30	65.00
97.00	3	Water	97.00
32.00	4	Kollidon® CL	32.00
53.00	5	Ludipress®	53.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with the water (item 3).
2. Pass through a 0.8-mm sieve, mix the dry granules with items 4 and 5, and press with low-compression force.
3. Fill 656 mg in 12-mm planar punches.

Calcium Chewable Tablets (200 mg Ca)

Formulation: Calcium gluconate (Merck), 845.0 g; calcium citrate (Merck), 500.0 g; Ludipress LCE [1], 297.5 g; citric acid anhydrous, fine granular, 100.0 g; polyethylene glycol 6000, powder, 80.0 g; orange flavor (Dragoco), 30.0 g; aerosil 200, 17.0 g. aspartame, potassium (Searle), 5.0 g.

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with high-compression force at 2417 mg.

Calcium D-Pantothenate Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
600.00	1	Calcium D-pantothenate (BASF)	610.00
150.00	2	Sorbitol (crystalline)	150.00
140.00	3	Avicel™ PH101	140.00
30.00	4	Kollidon® CL	30.00
50.00	5	PEG-6000 (powder)	50.00
QS	6	Flavors	QS

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix, and press with low-compression force.
2. Compress into 987-mg tablets, using 12-mm biplanar punches.
3. Kollidon® CL may be omitted and the tablet weight adjusted.

Calcium D-Pantothenate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Calcium D-pantothenate (BASF)	100.00
150.00	2	Ludipress®	150.00
10.00	3	Kollidon®	10.00
3.00	4	Magnesium stearate	3.00

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve.
2. Press into 252-mg tablets using medium-compression force and biplanar 8-mm punches.

Calcium D-Pantothenate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
280.00	1	Calcium D-pantothenate (BASF)	285.00
50.00	2	Avicel™ PH101	50.00
150.00	3	Dibasic calcium phosphate	150.00
20.00	4	Kollidon® CL	20.00
3.00	5	Stearic acid	3.00
3.00	6	Magnesium stearate	3.00

Manufacturing Directions

1. Mix all components, and pass through an 0.8-mm sieve.
2. Press into 518-mg tablets using medium-compression force and 12-mm biplanar punches.

Calcium Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
634.00	1	Calcium lactate	634.00
610.00	2	Calcium gluconate	610.00
185.21	3	Calcium carbonate	185.21
400.00	4	Sodium bicarbonate	400.00
468.25	5	Tartaric acid	468.25
46.25	6	Povidone (Kollidon® 30)	46.25
11.75	7	Povidone (Kollidon® 30)	11.75
QS	8	Isopropyl or ethyl alcohol (96%)	QS
97.50	9	Crospovidone (Kollidon® CL)	97.50
46.25	10	PEG-6000	46.25
QS	11	Flavor	QS

Manufacturing Directions

1. Granulate items 1 to 6 in a solution of items 7 and 8.
2. Dry, sieve, and mix well with items 9 to 11.
3. Compress at low pressure to form 2.5-g tablets, 20 mm in diameter.

Calcium Gluconate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
350.00	1	Calcium gluconate (powder)	360.00
117.00	2	Lactose monohydrate	117.00
11.00	3	Kollidon® 30	11.00
QS	4	Isopropanol	90.00
25.00	5	Kollidon® CL	25.00
2.00	6	Magnesium stearate	2.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with item 4.
2. Dry, pass through an 0.8-mm sieve, and mix with items 5 and 6.
3. Press into 500-mg tablets using high-compression force and 12-mm biplanar punches.

Calcium Glycerophosphate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Calcium glycerophosphate	500.00
117.50	2	Cornstarch	117.50
15.00	3	Kollidon® 90F	15.00
60.00	4	Water	60.00
15.00	5	Kollidon® CL	15.00
2.50	6	Magnesium stearate	2.50

Manufacturing Directions

1. Granulate items 1 to 3 with item 4; dry, sieve, and mix with items 5 and 6.
2. Press into 650-mg tablets using medium- to high-compression force and 12-mm biplanar punches.

Calcium Glycerophosphate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Calcium glycerophosphate	200.00
297.50	2	Ludipress®	297.50
2.50	3	Magnesium stearate	2.50
QS	4	Aerosil® 200	QS

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, and mix.
2. Press into 470-mg tablets using high-compression force and 12-mm biplanar punches.

Calcium Glycerophosphate Tablets (200 mg)

Formulation: Calcium glycerophosphate, 200.0 g; Ludipress, 297.5 g; Magnesium stearate, 2.5 g; Aerosil 200. q.s.

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with high-compression force at 470 mg.

Calcium Phosphate Tablets for Cats and Dogs

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Dicalcium phosphate	400.00
100.00	2	Wheaten flour	100.00
1.00	3	Citric acid crystalline	1.00
262.00	4	Lactose monohydrate	262.00
QS	5	Flavors	QS
30.00	6	Kollidon® 30F	30.00
150.00	7	Water	150.00 mL
4.00	8	Magnesium stearate	4.00

Manufacturing Directions

1. Granulate items 1 to 6 in item 7, dry, add item 8, and pass through an 0.8-mm sieve.
2. Compress 800-mg tablets, using 12-mm biplanar punches.

Calcium Phosphate Tablets for Cats and Dogs (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Dicalcium phosphate	400.00
100.00	2	Wheaten flour	100.00
1.00	3	Citric acid crystalline	1.00
272.00	4	Lactose monohydrate	272.00
QS	5	Flavors	QS
20.00	6	Kollidon® 90F	20.00
4.00	7	Magnesium stearate	4.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix.
2. Press with medium- to high-compression force (20 kN).
3. Compress into 800-mg tablets, using 12-mm biplanar punches.

Captopril Tablets (25 mg), Capoten

Capoten is available in potencies of 12.5, 25, 50, and 100 mg as scored tablets for oral administration. Inactive ingredients include microcrystalline cellulose, cornstarch, lactose, and stearic acid.

Captopril Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Captopril	25.00
91.00	2	Ludipress	91.00
2.00	3	Kollidon CL	2.00
2.00	4	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium-compression force to meet the following specifications.
2. Compress into 122-mg tablets, using 8-mm biplanar punches.

Carbamazepine Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.000	1	Carbamazepinea	208.00
25.880	2	Microcrystalline cellulose (Avicel PH 101)	25.880
9.000	3	Croscarmellose sodium (Ac-Di-Sol)	9.000
1.520	4	Carboxymethylcellulose sodium (CMC sodium)	1.520
1.500	5	Poloxyl 40 stearate	1.500
0.500	6	Colloidal silicon dioxide (Aerosil 200)	0.500
6.000	7	Sodium starch glycolate (Primojel)	6.000
7.000	8	Croscarmellose sodium (Ac-Di-Sol)	7.000
0.600	9	Magnesium stearate	0.600
–	10	Purified water	104.000

Carbamazepine 8.0 mg/tablet added to compensate the assay (98.0–102.0%) and LOD of the material.

Manufacturing Directions

Note: Avoid overmixing lubricants, otherwise hardness is reduced. *Critical note:* Hardness is critical for this product. Increasing or decreasing hardness from the specified limit will affect the dissolution.

1. Sieving and dry mixing: Sift items 1 to 3 through a 630-μm stainless steel sieve in the sifter. Load into the mixer. Mix for 5 minutes at low speed.
2. Preparation of the binder: Dissolve item 5 in 104 g of item 10 (55–65°C). Cool to 30°C. Dissolve item 4 while stirring with a stirrer. Check the weight (theoretical weight: 107.02 g).
3. Kneading
   a. Knead the powder mix with the binding solution at a rate of 28 to 32 g/min while mixing at low speed. Scrape sides and blades. Mix and chop at low speed for 2 minutes. Check the end point of granulation, consisting of free-flowing granules with little lumps. If required, add more purified water to get to the end point.
   b. Sift the granules in the granulator through a 3.5-mm stainless steel sieve, and follow by sifting through a 1-mm stainless steel sieve.
   c. Unload the wet granules into stainless steel trays for drying.
4. Drying
   a. Dry the wet granules in an oven at 55°C for 8 hours.
   b. Check the LOD (limit: 0.5% to 1%).
   c. If required, dry further at 55°C for 1 hour.
5. Grinding and lubrication
   a. Grind the dried granules through a 1-mm sieve using a granulator at medium speed. Collect in stainless steel drums. Load the granules into a drum blender.
   b. Sift items 6 to 8 through a 500-μm sieve, using a sifter, and add it to the drum blender. Mix for 2 minutes.
   c. Sift item 9 through a 250-μm sieve. Add 4- to 8-g granules from the bulk (step 5a). Mix in a polyethylene bag for 1 minute. Add to blender and blend for 1 minute.
   d. Unload in stainless steel drums. Check and record the weight of the granules (theoretical weight: 260 g).
6. Compression
   a. Check temperature and humidity before starting compression.
   b. Limits are that the temperature should not exceed 27°C, and the recommended relative humidity is 55% to 60%.
   c. Compress the granules using a rotary tabletting machine. At 9 mm, the weight of 10 caplets is 2.6 g ± 2%.

Carbamazepine Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Carbamazepine	200.00
300.00	2	Ludipress	300.00
2.00	3	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress into 496-mg tablets, using 12-mm biplanar punches.

Carbetapentane Tannate and Chlorpheniramine Tannate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Carbetapentane tannate	60.00
5.00	2	Chlorpheniramine tannate	5.00
65.00	3	Starch	65.00
150.00	4	Methylcellulose	150.00
32.00	5	Polygalacturonic acid	32.00
65.00	6	Dibasic calcium phosphate dehydrate	65.00
25.00	7	Povidone	25.00
5.40	8	Talc	5.40
3.93	9	FD&C Red #40 Aluminum Lake 40%	3.93
1.00	10	D&C Blue #1 Aluminum Lake 29%	1.00
4.00	11	Magnesium stearate	4.00
qs	12	Alcohol denatured 190 proof	qs

Carbidopa and Levodopa Tablets Sinemet

The inactive ingredients are cellulose, magnesium stearate, and starch. Tablets Sinemet 10–100 and 25–250 also contain FD&C Blue No. 2. Tablets Sinemet 25–100 also contain D&C Yellow No. 10 and FD&C Yellow. Sinemet CR (car-bidopa–levodopa) is a sustained-release combination of carbidopa and levodopa for the treatment of Parkinson's disease and syndrome. The inactive ingredients in Sinemet CR 50–200 are D&C Yellow No. 10, magnesium stearate, iron oxide, and other ingredients. Inactive ingredients in Sinemet CR 25–100 are magnesium stearate, red ferric oxide, and others. The Sinemet CR tablet is a polymeric-based drug delivery system that controls the release of carbidopa and levodopa as it slowly erodes. Sinemet CR 25–100 is available to facilitate titration and as an alternative to the half-tablet of Sinemet CR 50–200.

Carbidopa and Levodopa Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Carbidopa	25.00
100.00	2	Levodopa	100.00
224.00	3	Microcrystalline cellulose (Avicel PH 101)	224.00
15.00	4	Croscarmellose sodium	15.00
3.00	5	Silicon dioxide colloidal	3.00
3.00	6	Magnesium stearate	3.00
50.00	7	Carbidopa	50.00
200.00	8	Levodopa	200.00
80.00	9	Methocel E4M premium CR	80.00
61.00	10	Microcrystalline cellulose	61.00
2.00	11	Silicon dioxide colloidal	2.00
2.00	12	Magnesium stearate	2.00

Manufacturing Directions

1. This is a bilayer or two-compartment tablet consisting of a core layer of sustained-release carbidopa–levodopa overcoated with a layer of immediate-release carbidopa–levodopa.
2. The core ingredients (items 7–10) are blended separately (as are the outer layer [items 1–4] ingredients), compressed to produce core tablets, and then overcoated with the compressed outer-layer blend using a suitable coating press.

Carbinoxamine Maleate, Phenylpropanolamine, and Acetaminophen Sustained-Release Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Cabinoxamine maleate	5.00
75.00	2	Phenylpropanolamine hydrochloride	75.00
50.00	3	Acetaminophen	50.00
143.35	4	Sucrose and maize starch microgranules	143.35
6.34	5	Polyvidone (PVP)	6.34
0.01	6	Dye	0.01
0.075	7	Dye	0.075
0.025	8	Dye	0.025
23.99	9	Talc	23.99

Manufacturing Directions

Note: This product requires separate preparation of microgranules for each active ingredient. This preparation requires a coating pan equipped with air suction and hot air heating system, mixer, automatic airless pump with a spray gun, vibrating sieve, and capsule-filling machine with triple-feed microgranular system.

1. Place the neutral microgranules in the coating pan; prepare a 20% solution of PVP.
2. Maintain the temperature of microgranules at 20 ± 2°C.
3. Using the pump, apply the solution of PVP, then project the active ingredient onto the microgranules with a plastic scoop until they are dry.
4. Repeat these operations until all the active ingredients have been incorporated.
5. Sieve the microgranules with a 1.11-mm sieve.
6. Dry the microgranules at 30 ± 5°C for 3 hours.
7. Prepare a 40% solution of shellac in alcohol and the required quantity of talc.
8. Apply the shellac solution, maintaining a microgranule temperature of 20 ± 2°C, and add talc simultaneously.
9. Sieve the microgranules through a 1.18-mm sieve.
10. Dry the microgranules at 18°C to 23°C for 8 hours. Store until used.
11. Test for dissolution and rework if necessary.

Carbonyl Iron, Copper Sulfate, and Manganese Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
24.00	1	Carbonyl iron (BASF)	24.00
0.16	2	Copper sulfate	0.16
3.50	3	Manganese sulfate	3.50
100.00	4	Ludipress	100.00
2.00	5	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, and mix.
2. Press into131-mg tablets using medium-compression force and 8-mm biplanar punches.

Carisoprodol Tablets Soma

Soma tablets are available as 350-mg round, white tablets. Carisoprodol is present as a racemic mixture. Other ingredients include alginic acid, magnesium stearate, potassium sorbate, starch, and tribasic hydrogen phosphate.

Carvedilol Tablets Coreg

Coreg (carvedilol) is a white, oval, film-coated tablet containing 3.125, 6.25, 12.5, or 25 mg of carvedilol. The 6.25-, 12.5-, and 25-mg tablets are Tiltab® tablets. Inactive ingredients consist of colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide.

Carvedilol Talets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Carvedilol	25.00
25.00	2	Saccharose	25.00
28.00	3	Lactose monohydrate	28.00
1.78	4	Polyvinyl pyrrolidone 25 K	1.78
20.17	5	Polyvinyl pyrrolidone cross-linked	20.17
10.00	6	Microcrystalline cellulose	10.00
5.32	7	Silicon dioxide colloidal	5.32
2.17	8	Magnesium stearate	2.17
–	9	Purified water	115.00

Manufacturing Directions

1. Charge the following in a mixing vessel: item 3 sieved, item 2 (half), and item 4; add and mix item 9, and then mix by stirring for 30 minutes.
2. Add item 7 and item 1, and stir for another 30 minutes until a homogenous suspension is obtained.
3. Pass the suspension in step 2 through a colloid mill, and keep circulating.
4. Add items 2 and 5 to a fluid-bed dryer, and then pour the suspension in step 3 to obtain dry granules.
5. Sieve the granules through a 1.2-mm mesh sieve.
6. Lubricate granules and compress.

Cefadroxil Dispersible Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Cefadroxil, use cefadroxin anhydrous	268.65
2.00	2	PVP potassium 30	2.00
–	3	Isopropyl alcohol	10.80
77.00	4	Lactose monohydrate	77.00
93.50	5	Starch (maize)	93.50
13.00	6	Aspartame	13.00
1.50	7	Aerosil 200	1.50
0.45	8	Methyl paraben	0.45
0.05	9	Propyl paraben	0.05
4.00	10	Starch (maize)	4.00
5.00	11	Magnesium stearate	5.00
5.00	12	Talc	5.00
QS	13	Water, purified	QS

Manufacturing Directions

1. Charge items 2 and 3, and prepare a binding solution.
2. Sift item 1 through a 250-µm sieve.
3. Add step 1 into step 2, and prepare a wet mass.
4. Spread granules on trays, and dry in a dehumidified room.
5. Pass dried granules through a 595-µm sieve.
6. Prepare a paste of item 5 using purified water.
7. Sift items 4 and 6 into 9 through a 250-µm sieve. Mix for 15 minutes.
8. Add the paste from step 6, and mix until a wet mass is obtained without lumps.
9. Dry the granules obtained in step 8 in a fluid-bed dryer at 50°C for 2 hours.
10. Mix granules from steps 5 and 9, and charge into a tumble mixer.
11. Sift items 10 to 12 through a 250-µm sieve, add to step 10, and blend for 2 minutes.
12. Compress into 630-mg tablets, using 11.3-mm punches.

Cefdinir Tablets (300 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Cefdinir bulk powder	306.80
29.20	2	Microcrystalline cellulose (Avicel PH 101)	29.20
29.20	3	L-HPC (LH-21, Shin-Etsu Chemical)	29.20
3.70	4	Polyvinylpyrrolidone (Kollidon 30)	3.70
0.90	5	Silicic acid light anhydorus (Aerosil 200)	0.90
4.40	6	Magnesium stearate	4.40
15.00	7	Saccharin sodium	15.00
5.60	8	Strawberry flavor	5.60

Manufacturing Directions

1. Charge items 1 to 4 after passing through a 250-µm mesh into a mixing vessel. Mix for 10 minutes.
2. Add items 5 to 8, one at a time, and blend for 1 minute each time.
3. Compress 395 to 400 mg.

Cefixime and Amoxacillin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Cefixime	100.00
250.00	2	Amoxacillin	250.00
90.00	3	Microcrystalline cellulose	90.00
8.00	4	Hydroxypropylcellulose	8.00
2.00	5	Magnesium stearate	2.00

Manufacturing Directions

1. Cefixime, amoxicillin, microcrystalline cellulose, and hydroxypropylcellulose are thoroughly blended and the mixture is granulated.
2. The granules are vacuum-dried at 40°C and subjected to grain size adjustment on a duplex sieve.
3. Magnesium stearate is added to these granules and the resulting mixture is compressed.
4. The above tablets are coated with the coating solution (hydroxypropylmethylcellulose 10 mg in water) at a feed air temperature of 55°C and an exhaust gas temperature of 40°C.

Cefixime Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Cefixime bulk powder	448.90
38.90	2	Microcrystalline cellulose (Avicel PH 101)	38.90
38.90	3	L-HPC (LH-21, Shin-Etsu Chemical)	38.90
4.90	4	Polyvinylpyrrolidone (Kollidon® 30)	4.90
1.20	5	Silicic acid light anhydrous (Aerosil 200)	1.20
5.90	6	Magnesium stearate	5.90
20.00	7	Saccharin sodium	20.00
7.50	8	Strawberry flavor	7.50

Manufacturing Directions

1. Charge items 1 to 4 after passing through a 250-μm mesh into a mixing vessel. Mix for 10 minutes.
2. Add items 5 to 8, one at a time, and blend for 1 minute each time.
3. Compress 566 to 570 mg.

Cefpoxomine Tablets

Manufacturing Directions

1. The tablet formula consisted of cefpodoxime proxetil (53.6%), HPMC 4000 cps (35%), Avicel PH 101 (10.4%), and magnesium stearate (1%).
2. Materials are blended in a polybag, using the geometric dilution principle.
3. The blend is compressed using 19.0 mm × 8.8 mm caplet-shaped concave punches with a target weight of 1.1 g/tablet.

Cefprozil Tablets (250 mg) Cefzil

Cefzil® tablets contain cefprozil equivalent to 250 or 500 mg of anhydrous cefprozil. In addition, each tablet contains the following inactive ingredients: cellulose, hydroxypropylmethylcellulose, magnesium stearate, methylcellulose, simethicone, sodium starch glycolate, polyethylene glycol, polysorbate 80, sorbic acid, and titanium dioxide. The 250-mg tablets also contain FD&C Yellow No. 6.

Cefprozil Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Cefprozil	250.00
30.00	2	Starch (maize)	30.00
3.00	3	Magnesium stearate	3.00

Manufacturing Directions

1. Dry blend items 1 and 2 for 20 minutes.
2. Sieve item 3 through a 250-μm mesh, and blend with step 1. Blend for 2 minutes.
3. Compress.

Cephalexin Tablets Keflex

Each pulvule contains cephalexin monohydrate equivalent to 250 mg (720 mcmol) or 500 mg (1439 mcmol) of cephalexin. The pulvules also contain cellulose, FD&C Yellow No. 10, FD&C Blue No. 1, FD&C Yellow No. 6, gelatin, magnesium stearate, silicone, titanium dioxide, and other inactive ingredients. Each tablet manufactured by Biocraft contains cephalexin monohydrate equivalent to 250 mg (720 mcmol) or 500 mg (1439 mcmol) of cephalexin. Inactive ingredients include hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 90, sodium starch glycolate, and titanium dioxide.

Cetirizine and Pseudoephedrine Delayed-Release Tablets (5 mg/120 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Cetirizine dihydrochloride, excess	6.25
120.00	2	Pseudoephedrine hydrochloride	120.00
25.00	3	Hydroxypropyl methylcellulose (Methocel DE5)	25.00
110.00	4	Hydroxypropyl methylcellulose (Methocel F4N)	110.00
10.00	5	Hydroxypropyl methylcellulose (Methocel K5M)	10.00
174.00	6	Microcrystalline cellulose	174.00
1.00	7	Dye yellow	1.00
2.50	8	Aerosil 200	2.50
2.50	9	Magnesium stearate	2.50
5.00	10	Ethyl cellulose (7PPS)	5.00
0.001 mL	11	Propylene glycol	1.00 mL
0.06 mL	12	Dichloromethane	60.00
0.16 mL	13	Water, purified	16.60 mL

Manufacturing Directions

1. Charge items 2 to 6 and 8 in a suitable mixer. Mix for 5 minutes.
2. Compress the mixture in step 1 at 445 mg per tablet.

Cetirizine Chewable Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Cetirizine hydrochloride	10.00
130.8	2	Mannitol DC grade	130.80
25.00	3	Lactose monohydrate	25.00
15.00	4	Microcrystalline cellulose	15.00
10.00	5	Betadex	10.00
2.00	6	Acesulfame potassium	2.00
0.70	7	Blue dye	0.70
1.50	8	Red dye (carmine)	1.50
2.00	9	Grape flavor	2.00
2.00	10	Colloidal silicon dioxide (Aerosil-200)	2.00
1.00	11	Magnesium stearate	1.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 5, and 6 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 10% (=6.5 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity of step 4 into step 2.
6. Charge 10% (=6.5 g) powder from step 1 in a stainless steel container.
7. Pass item 7 and item 8 through 0.5-mm sieve and add to step 6 and mix well.
8. Transfer half quantity of step 7 into step 2.
9. Pass item 3, item 4 and item 10 through 0.7-mm sieve and add to step 2.
10. Transfer balance quantity of step 4 into step 2.
11. Transfer balance quantity of step 7 into step 2.
12. Transfer balance quantity of step 1 into step 2.
13. Mix step 2 for 20 minutes using tumbler.
14. Pass item 11 through 0.250-mm sieve and add to step 13.
15. Mix step 14 for 2 minutes.
16. Compress into 200-mg tablets, using a suitable punch (8 mm, round).

Cetirizine Hydrochloride Tablets (10 mg) Zyrtec

Zyrtec tablets are formulated as white, film-coated, rounded-off rectangular-shaped tablets for oral administration and are available in 5- and 10-mg strengths. The inactive ingredients are as follows: lactose, magnesium stearate, povidone, titanium dioxide, hydroxypropyl methylcellulose, polyethylene glycol, and cornstarch.

Cetirizine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Cetirizine hydrochloride	10.20
39.00	2	Maize starch	39.00
70.55	3	Lactose monohydrate	70.55
2.60	4	PVP K-30	2.60
7.00	5	Maize starch, dried	7.00
0.65	6	Magnesium stearate	0.65
QS	7	Purified water	30.00

Manufacturing Directions

1. Prepare the binding solution by dissolving item 4 in item 7 at 25°C to 30°C until the solution becomes clear.
2. Sift item 1 through a 500-μm sieve in portions.
3. Add binding solution slowly, and granulate.
4. Add water if necessary. Dry granules at 55°C for 10 hours.
5. Pass granules through a 1.25-mm sieve in a V-shaped blender. Add items 5 and 6, and mix for 1 minute. Compress tablets of 130 mg with hardness of 5 to 8 kPa.
6. Coat using the HPMC. (See Appendix.)

Cetirizine Hydrochloride Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Cetirizine hydrochloride	5.00
90.75	2	Mannitol DC Grade	90.75
25.00	3	Lactose monohydrate	25.00
15.00	4	Microcrystalline cellulose	15.00
7.50	5	Betadex	7.50
1.50	6	Acesulfame potassium	1.50
0.50	7	Blue Dye	0.50
1.00	8	Red dye (carmine)	1.00
1.50	9	Grape flavor	1.50
1.50	10	Colloidal silicon dioxide (Aerosil-200)	1.50
0.75	11	Magnesium stearate	0.75

For other strengths adjust quantity with item 2.

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 5, and 6 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 15% (=6.8 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity of step 4 into step 2.
6. Charge 10% (=4.5 g) powder from step 1 in a stainless steel container.
7. Pass item 7 and item 8 through 0.5-mm sieve and add to step 6 and mix well.
8. Transfer half quantity of step 7 into step 2.
9. Pass items 3, 4, and 10 through 0.7-mm sieve and add to step 2.
10. Transfer balance quantity of step 4 into step 2.
11. Transfer balance quantity of step 7 into step 2.
12. Transfer balance quantity of step 1 into step 2.
13. Mix step 2 for 20 minutes using tumbler.
14. Pass item 11 through 0.250-mm sieve and add to step 13.
15. Mix step 14 for 2 minutes.
16. Compress into 150-mg tablets, using a suitable punch (6.0 mm $\times$ 7.0 mm, oval).

Cetirizine Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Cetirizine hydrochloride	5.00
87.2	2	Lactose spray dried	87.2
5.00	3	Cornstarch	5.00
2.00	4	Povidone K30	2.00
0.80	5	Magnesium stearate	0.80
2.20	6	Hypromellose	2.20
0.50	7	Polyethylene glycol 4000	0.50
0.80	8	Titanium dioxide	0.80
–	9	Water, purified	30.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 3, and 4 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 10% (=4.4 g) lactose from step 1 to step 3 and mix well.
5. Transfer step 4 into step 2.
6. Transfer balance quantity of lactose from step 1 into step 2.
7. Mix step 2 for 15 minutes using tumbler.
8. Pass item 5 through 0.250-mm sieve and add to step 7.
9. Mix step 8 for 2 minutes.
10. Compress into 100-mg tablets, using a suitable punch (5.5 mm, round).
11. Charge item 9 in a stainless steel vessel. Add item 6 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hypromellose.
12. Add item 7 and item 8 to step 11 with stirring. Stir for 5 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
13. Load core tablets from step 10 in coating pan and apply coating dispersion from step 12 to get 2.5% to 3.0% weight gain.

Cetirizine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Cetirizine hydrochloride	15.00
3.00	2	Polyvinylpyrrolidone	3.00
1.50	3	Silicon dioxide	1.50
135.00	4	Lactose	135.00
1.50	5	Glyceryl behenate	1.50
	6	Water qs	

Manufacturing Directions

1. Cetirizine and lactose are placed in a fluidized-bed apparatus.
2. An aqueous PVP solution (in 85 g of water) is sprayed to get granules.
3. The granules thus obtained are subsequently dried and passed through a sieve (1 mm mesh) and glyceryl behenate is weighed, added, and blended in a drum mixer.
4. The resulting mixture is pressed into tablets 156.00 mg.
5. These tablet cores are then coated with the following formulation: ethylcellulose 10.00, hydroxypropylcellulose 10.00, stearic acid 2.00, and alcohol 188.00 g.
6. Ethocel, povidone, and stearic acid are first dissolved in denatured alcohol (188 g).
7. The coating solution is then sprayed onto the tablet cores in a coating pan.

Cetylpyridinium Lozenges (2.5 mg)

Formulation: Cetylpyridinium chloride (Merck), 2.5 g; Ludipress LCE [1], 370.0 g; polyethylene glycol 6000, powder, 20.0 g; menthol, crystalline, 6.0 g; aspartame, potassium (Searle), 1.5 g.

Manufacturing Directions

1. Mix all components, and pass through a 0.8-mm sieve.
2. Press with low-compression force at 402 mg.

Charcoal Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Activated charcoal	250.00
150.00	2	Bolus alba (Merck)	150.00
28.00	3	Kollidon® 25	28.00
38.00	4	Acacia gum	38.00
QS	5	Water + isopropanol (10 + 3)	575.00 mL
15.00	6	Cremophor EL	15.00
QS	7	Isopropanol	300.00 mL

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with item 5, and pass through a 1-mm sieve.
2. Dry until a relative powder humidity of 90% is reached.
3. Add solution of items 6 and 7, and pass again through a 0.8-mm sieve.
4. Dry the granules, and press into 481-mg tablets using low-compression force and 12-mm planar punches.
5. Dry the obtained tablets.

Chlorcyclizine Hydrochloride Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Chlorcyclizine hydrochloride	50.00
109.75	2	Lactose monohydrate	109.75
4.28	3	Povidone (K 29–32)	4.28
11.30	4	Alcohol ethanol 190 proof	11.30
QS	5	Water, purified	QS
95.71	6	Starch (corn)	95.71
6.21	7	Talc	6.21
2.60	8	Magnesium stearate	2.60

Manufacturing Directions

1. Charge chlorcyclizine hydrochloride, lactose, and povidone into a mass mixer. Mix well.
2. Add alcohol (diluted with an equal weight of purified water) and QS to mass.
3. Granulate through a 15.88-mm aperture or similar.
4. Dry at 41°C to less than 1% LOD (1 hour Bra-bender or equivalent at 105°C).
5. Sift and grind through a 1.19-mm aperture or similar screen.
6. Lubricate by adding cornstarch (#6), talc, and acid stearic (or magnesium stearate) sifted through a 600-μm aperture or similar.
7. Compress using 7.94-mm standard round convex punches with logo.
8. Coating is optional; use organic coatings, preferably.

Chlordiazepoxide and Clinidium Bromide Tablets (5 mg/2.5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.50	1	Clinidium bromide, 5% excess	2.625
5.00	2	Chlordiazepoxide, 5% excess	5.25
131.02	3	Lactose powder	131.02
8.50	4	Starch (maize)	8.50
2.30	5	Talc	2.30
0.30	6	Magnesium stearate	0.30
QS	7	Water, purified	QS

Manufacturing Directions

1. Prepare a paste with maize starch and water. Use this for separately granulating items 1 and 2. Use a 1:4 starch and water mixture, and heat to 50°C with continuous stirring.
2. Knead, granulate, dry, and sieve item 1 using step 1 paste. Mix a 1:5 ratio of items 1 to 3, and mix together for 5 minutes. Pass the mixture through an oscillating granulator using a 1-mm sieve. Add paste from step 1 and mix for 5 minutes. Add item 3 (part) and pass the wet mass through a 7-mm sieve. Dry at an humidity of 40% to 50%. Pass the dried granules through a 1.5-mm perforated sieve.
3. Knead, granulate, dry, and sieve item 2 using step 1 paste. Use a 1:3 ratio of item 2 to lactose, and mix for 5 minutes. Then pass the mixture through a 1-mm oscillating granulator. Pass the wet mass through a 7-mm sieve and dry at 60°C overnight in a relative humidity of granules that is 34% to 43%. Pass the dried granules through a 1.5-mm perforated sieve.
4. Mix the granules from steps 2 and 3, and tumble the mix for 1 hour at low rpm.
5. Premix items 5 and 6 for 5 minutes, and then blend this mixture with step 4. Tumble the mix for a half hour at low rpm.
6. Compress into 150-mg tablets, using 8-mm cylindrical biconvex punches at 4 to 5 tons of pressure.
7. Apply a sugar coating (see Appendix) to the final weight of 300 mg.

Chlordiazepoxide Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Chlordiazepoxide	10.00
61.70	2	Lactose	61.70
6.17	3	Starch (maize)	6.17
0.60	3	Talc	0.60
0.30	4	Magnesium stearate	0.30
QS	5	Water, purified	QS

Manufacturing Directions

1. Mix items 1 and 2 in a blender for 10 minutes at medium speed.
2. In a separate vessel, prepare a paste of item 3 with item 5, at 50°C, and maintain this temperature until fully gelatinized without lumps.
3. Transfer the hot paste to the blender in step 1, and mix for 30 minutes. Then pass it through a granulator with a 10-mm perforated screen.
4. Dry the granules overnight at 45°C.
5. Sift the dry granules in an oscillating granulator with a 1-mm sieve.
6. Add item 4, and mix in a tumbler for 10 minutes.
7. Compress into 80-mg tablets, using 6 × 3-mm cylindrical biconvex punches.
8. Sugarcoat the tablets. (See Appendix.)

Chlorhexidine Lozenges

Bill of Materials			
Scale (mg/lozenge)	Item	Material Name	Quantity/1000 lozenges (g)
5.00	1	Chlorhexidine	5.00
150.00	2	Sorbitol (crystalline)	150.00
5.00	3	Kollidon® VA 64	5.00
5.00	4	Menthol (crystalline)	5.00
5.00	5	Eucalyptol (crystalline)	5.00
1.00	6	Aspartame, potassium	1.00
0.10	7	Saccharin sodium	0.10
2.00	8	Aerosil® 200	2.00
1.00	9	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press with medium-compression force.
2. Compress into 175-mg lozenge, using 8-mm biplanar punches.

Chloroquine Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Chloroquine diphosphate	250.00
100.00	2	Dicalcium phosphate (Ditab)	100.00
10.00	3	Kollidon 30	10.00
–	4	Isopropyl alcohol	83.00
10.00	5	Kollidon CL	10.00
2.00	6	Aerosil 200	2.00
3.00	7	Talc	3.00

Manufacturing Directions

1. Granulate the mixture of items 1 and 2 with a solution of items 3 and 4. Then dry, pass through a 0.8-mm sieve, add the mixture of items 5 to 7, and press with low-compression force.
2. Compress into 361-mg tablets, using 8-mm biplanar punches.

Chlorpheniramine and Pseudoephedrine Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
3.35	1	Chlorpheniramine maleate	3.35
100.00	2	Pseudoephedrine hydrochloride	100.00
396.65	3	Cab-o-sil MS	396.65
200.00	4	Water	200.00

Manufacturing Directions

1. Chlorpheniramine maleate and pseudoephedrine hydrochloride are mixed in the water until thoroughly dissolved.
2. Cab-o-sil M5 (silicon dioxide) is poured into a planetary mixer to which the dissolved drug solution is added and mixed at slow speed.
3. This is continued for 5 minutes until the solution and Cab-o-sil are completely mixed.
4. The mixture is dried in a forced hot air oven for 5 hours to an LOD of less than 2.0%.
5. Magnesium stearate is then added as a lubricant, and tartaric acid is added as an acidulent.
6. The excipients are then thoroughly mixed and the entire composition is compressed into 1-g tablets, each one possessing a potency of 4.0-mg chlorpheniramine maleate and 120-mg pseudoephedrine hydrochloride.

Chlorpheniramine, Pseudoephedrine, and Dextromethorphan Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
8.00	1	Chlorpheniramine maleate	8.00
120.00	2	Pseudoephedrine hydrochloride	120.00
60.00	3	Dextromethorphan hydrobromide	60.00
812.00	4	Cab-o-Sil M5	812.00
200.00	5	Water	200.00

Manufacturing Directions

1. Chlorpheniramine maleate dextromethrophan HBr and pseudoephedrine hydrochloride are mixed in the water until throughly dissolved.
2. Cab-o-sil M5 (silicone dioxide) is poured into a planetary mixer to which the dissolved drug solution is added and mixed at slow speed.
3. This is continued for 5 minutes until the solution and Cab-o-sil are completely mixed.
4. The entire composition is dried in a forced hot air oven for 7 hours at 50°C.
5. The composition is dried to an LOD of 1.25%.
6. The dried material is then screened through a No. 30 U.S. standard mesh screen.
7. The excipients are added as mentioned before and the blend is compressed into 1.0 g. tablets, each one possessing a potency of 4 mg; chlorpheniramine maleate and 60 mg; pseudoephedrine hydrochloride and 30 mg dextromethorphan HBr.

Chlorpheniramine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4.00	1	Chlorpheniramine maleate	4.00
75.00	2	Starch 1500	75.00
65.62	3	Microcrystalline cellulose (50 um)	65.62
2.96	4	Stearic acid	2.96
1.11	5	Fumed silica	1.11
0.37	6	Magnesium stearate	0.37

Manufacturing Directions

1. Blend half of the Starch 1500 with the fumed silica and chlorpheniramine for 5 minutes.
2. Pass this mixture through a 40-mesh screen and return to blender.
3. Add the remaining starch 1500 to the material in step 1 and blend for 5 additional minutes.
4. Add the microcrystalline cellulose and stearic acid to the material from step 2 and blend for an additional 10 minutes.
5. Add the magnesium stearate to the material from step 3 and blend for an additional 5 minutes.

Choline Theophyllinate Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Choline theophylline	100.00
244.00	2	Ludipress	244.00
6.00	3	Magnesium stearate	6.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve. Mix and press with very low-compression force.
2. Compress into 350-mg tablets, using 8-mm biplanar punches.

Chymotrypsine Tablets (25 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Chymotrypsin	27.50
71.50	2	Ludipress	71.50
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm screen, and press with low-compression force.
2. Compress into 100-mg tablets, using 8-mm biplanar punches.

Cilazapril Tablets (2.5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.50	1	Cilazapril anhydrous	2.50
37.00	2	Lactose powder	37.00
2.87	3	Talc	2.87
57.43	4	Starch (maize)	57.43
7.65	5	Hydroxypropyl methylcellulose 2910/3C	7.65
1.91	6	Sodium stearyl fumarate	1.91
QS	7	Water, purified	QS

Manufacturing Directions

1. Disperse item 5 in 50 mL of item 7, and allow this to stand overnight.
2. In a tumble mixer, add item 1 and 10 g of item 2, and mix for 5 minutes.
3. Add the balance of item 2 and 20 g of item 4, and mix well.
4. Add the granulating solution from step 1, and knead. Then pass through a 7-mm sieve in a granulator.
5. Spread on paper-lined trays, and dry at 45°C overnight.
6. Pass the dried granules through a 1.5-mm sieve at 20% to 25% RH.
7. In a tumble mixer, add the balance of item 4, and then add items 3 and 6. Mix for 6 minutes.
8. Compress into 200-mg tablets, using a suitable punch.
9. Coat using the Opadry coating. (See Appendix.)

Cimetidine Chewable Tablets

Manufacturing Directions

1. Cimetidine Premix Granules—Cimetidine, 200.0 mg; Eudragit E100, 20.0 mg; antacid (Al/Mg) granules sorbitol: direct compression grade, 590.0 mg; lactose: direct compression grade spray dried, 325.0 mg; lactose crystalline, 325.0 mg; dried aluminium hydroxide gel, 250.0 mg; magnesium hydroxide, 200.0 mg; croscarmellose sodium type A, 30.0 mg; magnesium stearate, 15.0 mg. Total 1735.0 mg.
2. Tableting mix for compression—Cimetidine 220.0 mg; premix granules antacid (Al/Mg), 1735.0 mg; granules microcrystalline cellulose, 200.0 mg (Avicel PH102); aspartame, 10.0 mg; aniseed, 20.0 mg, butterscotch, 20.0 mg; magnesium stearate, 15.0 mg. Total 2220.0 mg.
3. A 40% (w/w) solution of the Eudragit E100 in methylene chloride is added with mixing to the cimetidine and blended until granules are formed.
4. The resulting granules are dried and then sieved through a 16-mesh screen.
5. Aluminium hydroxide, magnesium hydroxide, and other ingredients for the antacid granules are sieved through a 12-mesh (1.4 mm) screen and mixed together.
6. The resulting mix is compressed on a rotary tablet press and the resulting compacts are milled using a 12-mesh screen.
7. Cimetidine granules, antacid granules, and extragranular excipients are put into a cone blender and mixed thoroughly.
8. The resulting mix is discharged from the blender and compressed on a suitable rotary tablet press fitted with the appropriate punches.

Cimetidine Tablets (200 mg)

Formulation: Cimetidine, 200 g; Ludipress, 295 g; magnesium stearate, 5 g.

Manufacturing Directions

1. Pass the mixture through 0.8-mm screen.
2. Press with low-compression force at 510 mg at low humidity 30%.

Cimetidine Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Cimetidine[a]	202.00
48.89	2	Microcrystalline cellulose (Avicel PH 102)	48.89
6.00	3	Povidone (PVP K-30)	6.00
0.40	4	Sodium lauryl sulfate	0.40
0.26	5	Dispersed blue E132	0.26
0.26	6	Ferric oxide (iron oxide yellow)	0.26
13.11	7	Starch (maize)[b]	14.41
9.44	8	Sodium starch glycolate (Primojel)	9.44
1.40	9	Magnesium stearate	1.40
–	10	Purified water	77.78

Note: For higher strength (400- and 800-mg tablets), adjust formula and fill weights accordingly.
[a]Cimetidine 2.0 mg/tablet (1%) is added as an extra to compensate for the moisture.
[b]Maize starch 1.3 mg/tablet (10%) is added as an extra to compensate for the moisture.

Manufacturing Directions

1. Prepare a slurry of item 7 in 15.56 g of item 10 (30–40°C). Then make a translucent paste by adding 44.44 g of item 10 (90–95°C). Cool to 45°C to 50°C.
2. Disperse items 5 and 6 in 4.44 g of item 10 (25–30°C) by homogenizing. Add the color dispersion to the starch paste at step 1, and mix well.
3. Dissolve item 3 in 13.33 g of item 10. Stir until the solution is clear. Add item 4 to the solution. Stir just to dissolve. Do not produce foam by stirring. Add this solution to the colored paste at step 2, and mix for 5 minutes.
4. Pass items 1 and 2 through a 1200-μm sieve using a sifter. Collect in an s.s. drum. Load to a mixer. Mix at a high speed for 10 minutes.
5. Add colored starch paste from step 3 to the dry powder in the mixer. When the addition is over, mix at medium speed to get the satisfactory wet mass.
6. Add item 10 if required. Record extra quantity if used.
7. Pass the wet mass through a FitzMill using sieve 24250, knives forward, at medium speed.
8. Collect and spread the granules onto the trays, one-third the thickness of the tray, and dry the granules at 55°C for 16 hours. After 4 hours of drying, stir the granules in the trays, and change the positions of the trays for uniform drying. *Note:* Stirring is a very important step to avoid migration of color. Migration leads to mottling of the tablet.
9. Check the moisture of dried granules. The limit is not more than 1.5%. Dry further if required to get a moisture content of 1.5%.
10. Pass the granules through a 1.25-mm sieve using a granulator at medium speed. Do not fill the hopper completely. This increases excess fines.
11. Pass item 8 through a 500-μm sieve using a sifter. Collect in a polyethylene bag, and add to the blender. Mix for 5 minutes
12. Pass item 9 through a 250-μm sieve using a sifter. Collect in a polyethylene bag, and add 4.4 to 6.7 g powder from the bulk. Mix it, and then add it to the blender. Mix for 1 minute.
13. Check temperature and humidity before starting compression. The limits are as follows: temperature 25°C to 27°C; RH 45% to 55%.
14. Compress the granules using round concave punches. The weight of 10 tablets is 2.80 g ± 2%.
15. Coat tablets. (See the details in the Appendix.)

Ciprofloxacin Tablets (500 mg) Cipro

Cipro film-coated tablets are available in 100-, 250-, 500-, and 750-mg (ciprofloxacin equivalent) strengths. The inactive ingredients are starch, microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and water.

Ciprofloxacin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00, 582.19	1	Ciprofloxacin Ciprofloxacin HCl·H_2O	582.19
10.00	2	Crospovidone (Kollidon CL)	10.00
60.00	3	Sodium starch glycolate (Primojel)	60.00
9.50	4	Povidone (PVP K-30)	9.50
54.37	5	Microcrystalline cellulose (Avicel PH 101)	54.37
20.00	6	Crospovidone (Kollidon CL)	20.00
20.00	7	Sodium starch glycolate (Primojel)	20.00
6.00	8	Magnesium stearate	6.00
3.46	9	Colloidal silicon dioxide (Aerosil 200)	3.46
–	10	Absolute alcohol (ethanol, dehydrated alcohol)	268.00

Manufacturing Directions

Note: It is important to note the following:

- Avoid overmixing lubricants because this could reduce hardness.
- Process the products in an explosion-proof area. Relative humidity should not be more than 50%, and the temperature should be not more than 27°C.

1. Granulating solution: Dissolve item 4 in item 10 under slow stirring by stirrer.
2. Dry powder mixing: Sift items 1, 3, and 2 through a stainless steel sieve (900-μm) in sifter. Load into a mixer. Mix and chop for 3 minutes at low speed.
3. Kneading
   a. Knead the mixed powder with granulating solution for 2 minutes while mixing at low speed. Then mix and chop at high speed for 2 minutes.
   b. If required, add more absolute alcohol, and mix and chop at low speed to get to the end point of granulation. Record the additional quantity of absolute alcohol. Unload the wet mass in a stainless steel tray for drying.
4. Drying
   a. Dry the wet mass in the oven. Start air circulation without the heater "on" for 2 hours, keeping the door open. Then dry at 55°C for 5 hours.
   b. Check the LOD. The limit is 1.5% to 2.0%.
   c. If required, continue drying at 55°C for another half an hour to get the desired LOD.
5. Grinding: Pass the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect in stainless steel drums.
6. Lubrication
   a. Sift items 5, 7, 6, and 9 through a 500-μm sieve, and add it to the dry granules in the drum.
   b. Pass item 8 through a 250-μm sieve using a sifter. Add 40 to 60 g of granules from bulk. Mix in polyethylene bag for 1 minute. Add to a drum blender and mix for 1 minute.
7. Compression: Compress the granules using a rotary tabletting machine with 18 × 8 mm oblong concave punches. Compress into 770-mg tablets.
8. Coating: Coat using HPMC coating. (See Appendix.)

Ciprofloxacin Tablets (750 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
750.00, 900.00	1	Ciprofloxacin Ciprofloxacin HCl·H_2O	900.00
15.00	2	Crospovidone (Kollidon CL)	15.00
70.00	3	Sodium starch glycolate (Primojel)	70.00
11.00	4	Povidone (PVP K-30)	11.00
70.00	5	Microcrystalline cellulose (Avicel PH 101)	70.00
25.00	6	Crospovidone (Kollidon CL)	25.00
30.00	7	Sodium starch glycolate (Primojel)	30.00
7.50	8	Magnesium stearate	7.50
3.50	9	Colloidal silicon dioxide (Aerosil 200)	3.50
–	10	Absolute alcohol (ethanol, dehydrated alcohol)	400.00

Manufacturing Directions

See the manufacturing directions for the 500-mg tablet.

Cisapride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
52.92	1	Cirapride-(L)-tartarate	52.92
346.08	2	Lactose	346.08
66.000	3	Hydroxypropylmethylcellulose 2208	66.000
2.85	4	Magnesium stearate	2.85
5.70	5	Colloidal anhydrous silica	5.70
28.60	6	Talc	28.60

Cisapride Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Cisapride	5.20
80.90	2	Lactose monohydrate	80.90
10.80	3	Starch (maize)	10.80
3.00	4	Povidone (PVP K-30)	3.00
0.15	5	Polysorbate 20 (Tween 20)	0.15
19.40	6	Microcrystalline cellulose (Avicel PH 102)	19.40
0.60	7	Magnesium stearate	0.60
–	8	Purified water	18.00

Manufacturing Directions

Note: Avoid overmixing lubricants, otherwise hardness can be reduced.

1. Preparation of binding solution
   a. Dissolve item 4 in 16.0 g of item 8 (30°C), while mixing at slow speed by stirrer.
   b. Add item 5 to 2.0 g of item 8 (60–70°C). Stir manually with a spatula to make a clear solution.
   c. Add the previous step into step 1. Mix manually.
2. Sieving and mixing: Sift items 1 to 3 through a 500-μm sifter. Load into a mixer and mix for 5 minutes at low speed.

3. Kneading
   a. Add the binding solution to the dry powders, while mixing at speed I for 2 minutes. After the binding solution is added, mix further for 1 minute, using the mixer and chopper at low speed. Scrape sides and blade. Check for satisfactory granules with little or no lumps.
   b. If required, add extrapurified water, and record.
   c. Unload the granules into a stainless steel tray for drying.
4. Drying
   a. Dry the granules in an oven at 55°C for 10 hours. After 4 hours of drying, scrape the semidried granules to break the lumps for uniform drying.
   b. Check the LOD. The limit is 0.7% to 1.0%.
   c. Transfer the dried granules into stainless steel drums.
5. Grinding
   a. Pass the dried granules through a 1-mm sieve at medium speed. Collect in stainless steel drums.
   b. Load granules into the drum blender.
6. Lubrication
   a. Sift item 6 through a 500-μm sieve using a sifter. Add to step 2, in a drum blender. Mix for 5 minutes.
   b. Sift item 7 through a 500-μm stainless steel sieve in sifter. Add 4- to 6-g granules in a polyethylene bag to sieve item. Mix manually for 1 minute. Add to drum blender, and blend for 1 minute.
   c. Unload in stainless steel drums.
7. Compression: Compress the granules using a rotary tabletting machine with 7-mm round punches and a compression weight of 120 mg.

Cisapride Tartarate Mini Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
6	1	Cisapride tartarate	6
3.54	2	Explotab	3.55
25.36	3	Avicel PH 101	25.36
3.54	4	Aerosil 200	3.54
3.54	5	Magnesium stearate	3.54

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
6	1	Cisapride tartarate	6
6.92	2	Methocel K100M	6.92
3.45	3	Klucel LF	3.45
17.68	4	Avicel pH 101	17.68
3.45	5	Aerosil 200	3.45
3.45	6	Magnesium stearate	3.45

Manufacturing Directions

1. The ingredients (1–5), with the exception of magnesium stearate, are blended for 45 minutes.
2. Magnesium stearate is then added and blending continued for 5 minutes.
3. The blend is then tabletted in a 3.8-mm round deep concave punches with fill weight of 35.48 mg in the first formula and 34.54 in the second formula.
4. Coat the tablets using the following formulation: Eudragit L 12.5, 49.87%; talc 2.47%; diethyl phthalate 1.27%; isopropyl alcohol 43.33%; purified water 3.07%. Coat to provide 12.5% weight gain.

Citalopram Hydrobromide Tablets Celexa

Celexa is a film-coated, oval-scored tablet containing citalopram HBr in strengths equivalent to a 20- or 40-mg citalopram base. The inactive ingredients are copolyvidone, cornstarch, croscarmellose sodium, glycerin, lactose, monohydrate, magnesium stearate, hydroxypropyl methyl cellulose, microcrystalline cellulose, polyethylene glycol, titanium dioxide, and iron oxides are used as coloring agents in the pink 20-mg tablets.

Clarithromycin Tablets (250 mg/500 mg) Biaxin

Each yellow oval film-coated Biaxin tablet contains 250 or 500 mg of clarithromycin and the following inactive ingredients: cellulosic polymers, cros-carmellose sodium, D&C Yellow No. 10, FD&C Blue No. 1, magnesium stearate, povidone, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, stearic acid, talc, titanium dioxide, and vanillin. The 250-mg tablet also contains pregelatinized starch.

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Clarithromycin[a]	256.00
80.90	2	Microcrystalline cellulose (Avicel PH 102)	80.90
8.00	3	Croscarmellose sodium (Ac-Di-Sol)	8.00
9.00	4	Povidone (PVP K-30)	9.00
1.10	5	Polysorbate 80 (Tween 80)	1.10
51.50	6	Microcrystalline cellulose (Avicel PH 102)	51.50
10.00	7	Croscarmellose sodium (Ac-Di-Sol)	10.00
22.00	8	Pregelatinized starch (starch 1500)	22.00
2.25	9	Magnesium stearate	2.25
4.50	10	Talc (fine powder)	4.50
3.00	11	Stearic acid	3.00
1.75	12	Colloidal silicon dioxide (Aerosil 200)	1.75
–	13	Alcohol (ethanol 95%)	88.00

[a]Clarithromycin 6.0 mg/tablet is added as an excess to compensate for the water content and assay of the material. The weight of clarithromycin is factored based on potency. The weight of microcrystalline cellulose (Avicel PH 101) is then adjusted to compensate for the factored potency of clarithromycin. Adjust the fill weight and formula for a 500-mg tablet.

Manufacturing Directions

Precautions: Avoid overmixing lubricants, otherwise hardness can be reduced. Process the products in an explosion-proof area, with relative humidity of not more than 50%, and a room temperature of not more than 27°C.

1. Screen, if necessary, through an approximately 710-µm screen, the following: clarithromycin, croscarmellose sodium, microcrystalline cellulose (Avicel PH 101), and silicon dioxide. Blend together in suitable massing equipment.
2. Dissolve povidone in approximately 240 mL of ethanol—a complete solution must be achieved.
3. While mixing the blended powders from step 1, add the povidone solution from step 2.
4. Continue mixing to ensure an even distribution of the solution, and then add extra ethanol until a characteristic granule mass is obtained.
5. If necessary, pass the wet mass through a 3- to 4-mm screen. Dry at approximately 50°C to 55°C until the LOD is not more than 3%.
6. Sift dried granule over a 1.4-mm (approximately) screen. Pass the oversized granules through a 1.7-mm (approximately) screen, using a suitable mill. Alternate screening and milling systems may be used to yield suitable sized granules.
7. Load a portion of the granule from step 6 into a suitable blender. Add microcrystalline cellulose (Avicel PH 102) and croscarmellose sodium, blend, add talc, purify, and blend until uniform.
8. Mix together stearic acid and magnesium stearate with a small portion of granule. If necessary, pass through a 0.5-mm (approximate) screen.
9. Add the steps above, mix, then add the balance of granule. Mix until uniform.
10. Compress tablets to the following parameters: tablet weight 8.5 g/10 tablets ± 3%.
11. Coat using an HPMC coating solution.

Clarithromycin Dispersible Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Clarithromycin base	250.00
22.50	2	Crospovidone	22.50
62.50	3	Croscarmellose sodium	62.50
3.80	4	Polysorbate	3.80
566.20	5	Microcrystalline cellulose	566.20
40.00	6	Aspartame	40.00
20.00	7	Saccharin sodium	20.00
20.00	8	Mint flavor	20.00
5.00	9	Colloidal silica	5.00
10.00	10	Magnesium stearate	10.00

Clarithromycin Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Clarithromycin	500.00
200.00	2	Methocel K100 LV Premium CR Grade	200.00
260.00	3	Lactose monohydrate	260.00
30.00	4	Talc	30.00
	5	Magnesium stearte	

Manufacturing Directions

1. Methocel (K 100 LV) is loaded into a mixer, and dry blended with clarithromycin.
2. The mixture is granulated using water until proper granulation is obtained. The granulation is then dried, sifted, and ground to appropriate size.
3. Talc and magnesium stearate are screened and blended with dry granulation. The granulation is then loaded into hopper and compressed into tablets. The tablets are then coated with an aqueous coating.

Clarithromycin Controlled-Release Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1000.00	1	Clarithromycin	1000.000
25.00	2	Methocel K15 MCR	25.00
12.50	3	Methocel K4 MCR	12.50
12.50	4	Lactose	12.50
20.00	5	Sodium stearyl fumarate	20.00
12.50	6	Magnesium stearate	12.50
10.00	7	Talc	10.00
0.50	8	Colloidal silicon dioxide	0.50

Manufacturing Directions

1. Clarithromycin is blended with the two polymers and lactose and wet granulated with water. The granules are dried, sized, lubricated, and compressed to tablets (1161.5 mg).
2. The tablets thus obtained are optionally film coated.

Clenbuterol Tablets (20 mcg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.02	1	Clenbuterol hydrochloride	0.02
99.00	2	Ludipress	99.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components in a Turbula mixer, and press to tablets with a compression force of 20 kN.
2. Compress into 100-mg tablets, using 8-mm punches.
3. If the content uniformity does not meet the requirements, prepare a premix of clenbuterol hydrochloride with a small part of the Ludipress before mixing with the other components of the tabletting mixture.

Clindamycin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Clindamycin, use clindamycin hydrochloride	22.70
265.00	2	Lactose dihydrate	265.00
33.33	4	Starch (maize)	33.30
2.00	5	Hydroxypropyl cellulose (Klucel EF)	2.00
30.00	6	Calcium lactate. 5H20	30.00
41.00	7	Lactic acid	41.00
128.00	8	Microcrystalline cellulose (Avicel PH 102)	128.00
12.00	9	Kollidon CL	12.00
7.00	10	Aerosil 200	7.00

Manufacturing Directions

1. Clindamycin HCl, lactose, one-half of the cornstarch, HPC, calcium lactate, and lactic acid are granulated in a fluidized-bed granulator.
2. The resulting granules and the remainder of the cornstarch, Kollidon, microcrystalline cellulose, magnesium stearate, and Aerosil are passed through a forced sieve (1.25 mm) and homogenized in a container mixture.
3. The resulting mixture is tabletted on a rotary tabletting machine.

Clobazam Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Clobazam	10.00
135.00	2	Dicalcium phosphate	135.00
7.00	3	Kollidon VA64	7.00
7.00	4	Kollidon CL	7.00
1.50	5	Magnesium stearate	1.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium-compression force (15 kN).
2. Compress into 165-mg tablets, using 8-mm biplanar punches.

Clomifen Citrate Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Clomifen citrate	50.00
100.00	2	Ludipress	100.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, sieve, and press with low-compression force.
2. Compress into 154-mg tablets, using 8-mm biplanar punches.

Clomipramine Hydrochloride Tablets, Buccal (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Clomipramine hydrochloride	10.00
90.00	2	Gelatin	90.00
20.00	3	Glycerin, anhydrous	20.00
10.00	4	Lactose, anhydrous	10.00
20.00	5	Mannitol	20.00

Manufacturing Directions

1. Clomipramine hydrochloride (10 g) and 90 g of gelatin are mixed and pulverized in a mill.
2. After mixing, 20 g of glycerin, 10 g of lactose, and 20 g of mannitol are added, and the components are mixed until uniform.
3. Compress 150 mg to provide a buccal dosage unit. Each buccal unit contains 10 mg of clomipramine hydrochloride.

Clomipramine Hydrochloride Tablets, Effervescent (300 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Clomipramine hydrochloride	300.00
1985.00	2	Sodium bicarbonate	1985.00
1000	3	Citric acid	1000

Manufacturing Directions

1. The components (i.e., clomipramine hydrochloride, sodium bicarbonate, and citric acid, as set forth in the preceding table) are thoroughly mixed.
2. An effervescent tablet is produced by placing the mixture in a die, following with compression with an appropriate punch. Relatively little compression force is used (e.g., about 3000 to about 20000 pounds of force).

Clonazepam Tablets (1 mg/2 mg)

Klonopin, a benzodiazepine, is available as scored tablets with a K-shaped perforation containing 0.5 mgf and 1 or 2 mg of clonazepam, and unscored tablets with a K-shaped perforation containing 1 or 2 mg of clonazepam. Each tablet also contains lactose, magnesium stearate, microcrystalline cellulose, and cornstarch, with the following colorants: 0.5 mg of FD&C Yellow No. 6 Lake; 1 mg of FD&C Blue No. 1 Lake and of FD&C Blue No. 2 Lake.

Clonidine Tablets (0.1 mg/0.2 mg/0.3 mg) Plavix

Plavix for oral administration is available as pink, round, biconvex, engraved film-coated tablets containing 97.875 mg of clopidogrel bisulfate, which is the molar equivalent of 75 mg of clopidogrel base. Each tablet contains anhydrous lactose, hydrogenated castor oil, microcrystalline cellulose, polyethylene glycol 6000, and pregelatinized starch as inactive ingredients. The pink film coating contains ferric oxide (red), hydroxypropyl methylcellulose 2910, polyethylene glycol 6000, and titanium dioxide. The tablets are polished with carnauba wax.

Codeine, Acetaminophen, and Pentobarbital Tablets (15 mg/300 mg/30 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Codeine phosphate, 2.5% excess	15.375
300.00	2	Acetaminophen	300.00
30.00	3	Pentobarbital sodium, use pentobarbital	27.50
40.00	4	Calcium carbonate, precipitated	40.00
58.66	5	Lactose monohydrate	58.66
20.00	6	Povidone K 29–32	20.00
20.00	7	Starch (corn)	20.00
2.00	8	Polyethylene glycol, milled	2.00
0.066	9	Red dye	0.066
0.054	10	Yellow dye	0.054
0.018	11	Scarlet dye	0.018
25.79	14	Polacrillin potassium (Amberlite IRP-88)	25.79
10.40	15	Magnesium steareate	10.40

Manufacturing Directions

1. Mixing
   a. Add codeine phosphate to acetaminophen in the presence of an authorized person.
   b. Pass step a through a micropulverizer fitted with a 6.35-mm aperture or similar screen at high speed, with the hammers forward if the acetaminophen has a bulk density above 0.4 g/cc. After micropulverizing, the bulk density should be checked and should not exceed 0.4 g/cc. Add this to the mixer.
   c. Pass pentobarbital and calcium carbonate through an 840-μm aperture screen, and then add to the mixer.
   d. Add lactose, povidone, cornstarch, and polyethylene G 8000 NF (milled) to the mixer, and mix for 5 minutes.
   e. Dissolve the dyes in water and add alcohol.
   f. Add the dye solution to the powders in the mixer, and mix until the color is evenly dispersed.
   g. Screen the wet granulation through a 9.52-mm aperture screen.
   h. Oven dry for 2 to 3 hours at 43°C, or use a fluid-bed dryer at room temperature for 12 minutes or until the LOD is 1% to 2% (1 hour at 105°C on an Ohaus, Brabender, or equivalent balance).
   i. Mill the dried granulation through a 1.2-mm aperture screen (FitzMill or similar, medium speed, knives forward), and then add to a suitable mixer (V or similar).
   j. Pass the amberlite and magnesium stearate through a 595-μm aperture screen on a suitable shaker (Russel or similar), and add to the mixer (V or similar).
   k. Blend for 30 minutes.
   l. Discharge the blended material into polyethylene-lined containers. Seal and deliver this to the compression area.
2. Compression
   a. Compress on an 11.90-mm standard concave punch.
   b. The weight of 10 tablets is 5.2 g.

Conjugated Estrogens and Medroxyprogeste Tablets, Prempro

Prempro 2.5 mg—Each peach tablet for oral administration contains 0.625 mg conjugated estrogens, 2.5 mg of medroxyprogesterone acetate, and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, and red ferric oxide.

Prempro 5 mg—Each light-blue tablet for oral administration contains 0.625 mg of conjugated estrogens, 5 mg of medroxyprogesterone acetate, and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, and FD&C Blue No. 2.

Premphase—Each maroon Premarin tablet for oral administration contains 0.625 mg of conjugated estrogens and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, titanium dioxide, FD&C Blue No. 2, D&C Red No. 27, FD&C Red No. 40. These tablets comply with USP Drug Release Test 1. Each light-blue tablet for oral administration contains 0.625 mg of conjugated estrogens and 5 mg of medroxyprogesterone acetate and the following inactive ingredients: calcium phosphate tribasic, calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, sucrose, povidone, titanium dioxide, and FD&C Blue No. 2.

Conjugated Estrogens (0.3–2.50 mg) Prematin

Tablets are available in 0.3-, 0.625-, 0.9-, 1.25-, and 2.5-mg strengths of conjugated estrogens. Premarin tablets contain the following inactive ingredients: calcium phosphate tribasic, calcium sulfate anhydrous (white tablet), calcium sulfate, carnauba wax, cellulose, glyceryl monooleate, lactose, magnesium stearate, methylcellulose, pharmaceutical glaze, polyethylene glycol, stearic acid, sucrose, talc, and titanium dioxide. The 0.3-mg tablets also contain D&C Yellow No. 10, FD&C Blue No. 1, FD&C Blue No. 2, FD&C Yellow No. 6. The 0.625-mg tablets also contain FD&C Blue No. 2, D&C Red No. 27, and FD&C Red No. 40. The 0.9-mg tablets also contain D&C Red No. 6, D&C Red No. 7. The 1.25-mg tablets contain black iron oxide, D&C Yellow No. 10, and FD&C Yellow No. 6. The 2.5-mg tablets contain: FD&C Blue No. 2 and D&C Red No. 7.

Coumadin Tablets

Coumadin tablets also contain (all strengths) lactose, starch, and magnesium stearate; 1 mg of D&C Red No. 6; 2 mg of FD&C Blue No. 2 and FD&C Red No. 40; 2 1/2 mg of FD&C Blue No. 1, and D&C Yellow No. 10; 4 mg of FD&C Blue No. 1 Lake; 5 mg of FD&C Yellow No. 6; 7 1/2 mg of D&C Yellow No. 10, and FD&C Yellow No. 6; 10 mg of dye free.

Crospovidone Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1000.00	1	Crospovidone (micronized)	1000.00
150.00	2	Citric acid	150.00
25.00	3	Aerosil® 200	25.00
100.00	4	Sucrose (crystalline)	100.00
1.00	5	Saccharin sodium	1.00
QS	6	Water	QS
5.00	7	Magnesium stearate	5.00
125.00	8	Sodium bicarbonate	125.00
65.00	9	Flavor mixture	65.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with item 6, dry, and pass through a sieve.
2. Mix the dry granules with items 7 to 9, and press with medium-compression force.
3. The dosage may be increased to 2000 mg crospovidone by increasing the tablet weight to 3200 mg.
4. Compress 1590-mg tablets, using 20-mm-diameter biplanar punches.

Cyclobenzaprine Hydrochloride Tablets (10 mg)

Cyclobenzaprine HCl is supplied as 10-mg tablets for oral administration. The inactive ingredients are hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, starch, and titanium dioxide.

Cyclobenzaprine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Cyclobenzaprine	10.00
74.00	2	Lactose anhydrous	74.00
35.00	3	Starch (maize)	35.00
1.00	4	Magnesium stearate	1.00
25.00	5	Starch (maize)	25.00
–	6	Water, purified	30.00 mL

Manufacturing Directions

1. Charge the active ingredient (cyclobenzaprine) and lactose in a suitable mixer.
2. Blend until a uniform mix is obtained.
3. Add item 5 to item 6 to make a paste.
4. Add step 3 into step 2 to form a suitable mass.
5. Add item 3 to step 4, and mix until granules are formed.
6. Screen granules through a suitable milling machine, using a 1/4-in. stainless steel screen.
7. Dry the milled granules in a suitable drying oven until the desired moisture of less than 2% is obtained.
8. Mill the dried granules through a suitable milling machine using a 1/4-in. mesh stainless steel screen, and transfer to a blender.
9. Add the magnesium stearate to the blender after passing through a 250-μm sieve. Then blend for 3 minutes.
10. Compress the tablets.
11. Coat the tablets using an aqueous or nonaqueous coating. (See Appendix.) For example, 2.5 mg of hydroxypropymethylcellulose can be dissolved in 25 mg of deionized water. An aqueous (10 mg) suspension of 1.88 mg of talc, 0.5 mg of titanium dioxide, 0.1 mg of yellow iron oxide, and 0.02 mg of red iron oxide is stirred into this solution. The coating suspension is sprayed on the tablets. The coated tablets are dried overnight at 45°C.

Cyproheptadine Tablets (4 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4.00	1	Cyproheptadine	4.00
194.00	2	Ludipress	194.00
2.00	3	Magnesium stearate	12.00

Manufacturing Directions

1. Pass all ingredients through an 0.8-mm sieve.
2. Mix and press with very low-compression force (4 kN).
3. Compress into 202-mg tablets, using 8-mm biplanar punches. If the content uniformity does not meet the requirements, prepare a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation.

Dapsone Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Dapsone	50.00
80.00	2	Starch (maize)	80.00
50.00	3	Dicalcium phosphate	50.00
20.00	4	Lactose monohydrate	20.00
8.00	5	Starch (maize)	8.00
0.12	6	Methyl paraben	0.12
0.02	7	Propyl paraben	0.03
1.50	8	Talc	1.50
1.00	9	Magnesium stearate	1.00
–	10	Water, purified	QS

Manufacturing Directions

1. Charge items 1 to 4 in a suitable vessel, after passing them through a #40-mesh screen. Mix at medium speed for 15 minutes.
2. In a separate vessel, take a sufficient quantity of item 10, and heat it to 80°C; add items 5 and 6, and dissolve. Allow the mixture to cool to 50°C, and then add item 7. Stir and mix this to obtain a smooth paste.
3. Add the wet mass in step 2 to step 1, and mix well. Pass the wet mass through an 8-mm screen, and collect on paper-lined trays.
4. Dry the wet mass at 50°C overnight to an LOD of not more than 2%.
5. Pass dried granules through an 18-mm sieve, and collect them in a tumble mixer.
6. Pass item 8 through a 500-μm and item 9 through a 250-μm sieve screen, and add to step 5. Blend for 1 minute.
7. Compress into 200-mg tablets, using 8-mm round punches.

Delavirdine Mesylate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Delavirdine mesylate	200.00
198.76	2	Microsrystalline cellulose	198.76
71.29	3	Coarse powder lactose monohydrate spray	71.29
75.00	4	Hydroxypropyl methylcellulose 2910 3 cps	75.00
110.00	5	Croscarmellose sodium Type A	110.00
1.50	6	Colloidal silicon dioxide	1.50
5.00	7	Magnesium stearate	5.00

Manufacturing Directions

1. The above tablets are manufactured by intensely mixing the delavirdine mesylate and the microcrystalline cellulose in a high-shear mixer.
2. Then add and mix the hydroxypropyl methylcellulose, croscarmellose, lactose, and screened colloidal silicon dioxide in a high-shear mixer. Finally add screened magnesium stearate and lubricate in a high-shear mixer. The resulting mixture is compressed and film coated, and polished to give tablets that have about 200 mg of delavirdine mesylate/tablet.

Desloratidine Tablets (5 mg), Clarinex

Clarinex® (desloratadine) tablets are light blue, round, film-coated tablets containing 5 mg of desloratadine, an antihistamine, to be administered orally. The tablet also contains the following excipients: dibasic calcium phosphate dihydrate USP, microcrystalline cellulose NF, cornstarch NF, talc USP, carnauba wax NF, white wax NF, coating material consisting of lactose monohydrate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and FD&C Blue #2 Aluminum Lake.

Desogestrel and Ethinyl Estradiol Tablets (0.15 mg/0.03 mg), Ortho-Cept

Ortho-Cept 21 and Ortho-Cept 28 tablets provide an oral contraceptive regimen of 21 orange, round tablets, each containing 0.15 mg of desogestrel (13-ethyl-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-17-ol) and 0.03 mg of ethinyl estradiol (19-nor-17α-pregna-1,3,5(10)-trien-20-yne-3,17, diol). Inactive ingredients include vitamin E, cornstarch, povidone, stearic acid, colloidal silicon dioxide, lactose, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, talc, and ferric oxide. Ortho-Cept 28 also contains seven green tablets containing the following inactive ingredients: lactose, pregelatinized starch, magnesium stearate, FD&C Blue No. 1 Aluminum Lake, ferric oxide, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, and talc.

Diazepam Tablet (10 mg)

Formulation: Diazepam,10 g; Ludipress,100 to 480 g; magnesium stearate, 0.5 to 2.0 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press with medium compaction force 11 to 490 mg based on label required.

Diazepam Tablets (2 mg/5 mg/10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Diazepam	10.00
70.00	2	Potato starch	70.00
150.00	3	Lactose	150.00
1.50	4	Potato starch, cold swelling	1.50
0.076	5	Polysorbate 80	0.076
48.00	6	Microcrystalline cellulose	48.00
0.75	7	Magnesium stearate	0.75
QS	8	Talc, QS	300.00

Manufacturing Directions

1. Granulation
   a. Weigh and mix for 10 minutes potato starch, lactose, potato starch (cold swelling), and diazepam in a suitable mixer.
   b. Pass the mixture through a FitzMill at highspeed impact forward.
   c. Separately dissolve polysorbate 80 in purified water.
   d. Wet the mixture from step 1b with the solution from step 1c, adding more water if necessary.
   e. Pass the wet mass through a FitzMill sieve #24192, and dry in a drying oven at 35°C for 20 hours.
   f. Pass the dried granulation through a FitzMill.
   g. Separately pass through a FitzMill sieve (0.3-mm screen) the following: microcrystalline cellulose, magnesium stearate, and talc.
   h. Add the granules from step 1f, and mix for 15 minutes.
2. Compression: Compress using round, flat punches with beveled edges and a break line on one side. Theoretical weight of 300 mg (290–310 mg); thickness 3.2 mm (range: 3.1–3.3 mm); diameter 9.5 mm (range 9.3–9.7 mm). For 2-mg and 5-mg tablets, adjust fill weight accordingly; for larger tablet size, adjust proportionally with lactose and starch.

Diclofenac Sodium Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Diclofenac sodium	25.00
85.00	2	Lactose, monohydrate	85.00
10.00	3	Sodium starch glycolate (pH 5.5–7.5)	10.00
3.00	4	Povidone (K 29–32)	3.00
3.00	5	Starch (corn)	3.00
58.00 mL	6	Alcohol isopropyl, anhydrous	58.00 mL
5.00	7	Sodium starch glycolate (pH 5.5–7.5)	5.00
1.50	8	Magnesium stearate	1.50

Manufacturing Directions

1. Granulation
   a. Dry mix together diclofenac sodium, lactose, sodium starch glycolate, and starch in a suitable planetary mixer for 10 to 15 minutes.
   b. Dissolve povidone in 44 mL of alcohol and ensure complete solution.
   c. While mixing, add povidone solution to step 1a, and add the remaining alcohol to obtain suitable mass. Add an extra quantity of alcohol, if required.
   d. Pass the wet mass through a #4 mesh (4.8-mm aperture) screen, and spread on paper-lined oven trays.
   e. Dry the granules at 40°C to an LOD of not more than 2% (3 hours at 60°C under vacuum).
   f. Request samples.
   Note: The balance of manufacturing in the "Granulation" process should be done at not more than 45% relative humidity and at a temperature not exceeding 26.5°C.
   g. Mill the dried granule through a FitzMill fitted with a 1.19-mm aperture screen at slow speed and with knives forward.
   h. Store the material in clean, polyethylene-lined containers that are sealed.
2. Lubrication
   a. Charge one-half of the screened granule from step 1h into a suitable blender. Add sodium starch glycolate and magnesium stearate to the blender, and then add the balance of screened granule from step 1h. Blend for 15 to 20 minutes.
   b. Store in clean, tared polyethylene-lined containers, and seal and weigh for yield.
3. Compression
   a. Compress on a suitable tablet machine equipped with a dedusting unit, using 1/4-in.-diameter concave punches with both sides plain.
   b. The theoretical weight of 10 tablets is 1.325 g (range 1.295–1.355 g), with a thickness of 3.7 to 4.1 mm.
4. Coating: Use a subcoat, an enteric color coat, and a finishing coat. (See Appendix.)

Diclofenac Sodium Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Diclofenac sodium	50.00
85.00	2	Lactose, monohydrate	85.00
15.00	3	Sodium starch glycolate (pH 5.5–7.5)	15.00
5.00	4	Povidone (K 29–32)	5.00
4.00	5	Starch (corn)	5.00
0.073 mL	6	Alcohol isopropyl, anhydrous refined	73.00 mL
7.00	7	Sodium starch glycolate (pH 5.5–7.5)	7.00
2.00	8	Magnesium stearate impalpable powder	2.00

Manufacturing Directions

Follow the manufacturing directions in the previous formulation. The theoretical weight of 10 tablets is 1.68 g (range: 1.64–1.72), with a thickness of 4.60 to 5.0 mm. Apply an enteric coat. (See Appendix.)

Diclofenac Sodium Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Diclofenac sodium	100.00
15.00	2	Eudragit® RSPN, 5% (methyl methacrylate copolymer)	15.00
6.00	3	Dibutyl phthalate (2%)	6.00
176.00	4	Dicalcium phosphate dihydrate	176.00
3.00	5	Magnesium stearate	3.00
–	6	Isopropyl alcohol	QS

Manufacturing Directions

1. Charge items 1, 2, and 4 in a planetary blender, and mix for 10 minutes.
2. In a separate container, add items 3 and 6 until homogenous. Add to step 1 slowly to form loose aggregates of blend.
3. Pass the aggregates through a #8 mesh sieve onto paper-lined trays.
4. Dry the granules in a room with low humidity.
5. Pass the dried granules through a #20-mesh screen into a blending vessel.
6. Add item 5 after passing through a 250-μm sieve to step 5, and blend for 2 minutes.
7. Compress into 300-mg tablets, using a suitable punch.
8. Coat using an enteric coating. (See Appendix.)

Diclofenac Sodium Dispersable Tablets (50 mg)

Formulation: Diclofenac Na, 50.0 mg; Avicel® PH 102, 143.8 mg; Kollidon® CL, 50.0 mg; Aerosil® 200, 5.0 mg; Magnesium stearate, 1.0 mg.

Manufacturing Directions

Mix the ingredients together, pass through a 0.8-mm sieve, and compress into tablets with a force of about 10 kN at 248 mg.

Diclofenac Sodium Tablets (25 mg) Voltaren, Cataflam

Diclofenac potassium is available as Cataflam® immediate-release tablets of 50 mg for oral administration. Cataflam inactive ingredients include calcium phosphate, colloidal silicon dioxide, iron oxides, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, sodium starch glycolate, starch, sucrose, talc, and titanium dioxide.

Diclofenac sodium is available as Voltaren delayed-release (enteric-coated) tablets of 25, 50, and 75 mg for oral administration, as well as Voltaren-XR extended-release tablets of 100 mg. Voltaren inactive ingredients are hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, povidone, propylene glycol, sodium hydroxide, sodium starch glycolate, talc, titanium dioxide, D&C Yellow No. 10 Aluminum Lake (25-mg tablet only), and FD&C Blue No. 1 Aluminum Lake (50-mg tablet only). Voltaren-XR inactive ingredients are cetyl alcohol, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, polyethylene glycol, polysorbate, povidone, silicon dioxide, sucrose, talc, and titanium dioxide.

Diclofenac Sustained-Release Tablets (100 mg)

Formulation: Diclofenac sodium (Ivotec), 100.0 g; Kollidon SR, 100.0 g; silicon dioxide, colloidal, 3.4 g; magnesium stearate, 3.4 g.

Manufacturing Directions

All ingredients are passed through a 0.8-mm sieve, blended for 10 minutes in a Turbula mixer, and then compressed with medium-compression force at 206.40 mg.

Diclofenac Tablets (50 mg)

Formulation: Diclofenac sodium, 50.0 g; Ludipress, 150.0 g; magnesium stearate, 1.5 g; polyethylene glycol 6000, powder, 15.0 g; Kollidon CL, 10.0 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve and press with low-compression force at 226 mg.

Didanosine Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Didanosine	50.00
17.00	2	Microcrystalline cellulose	17.00
2.10	3	Sodium starch glycolate	2.10
0.60	3	Magnesium stearate (for compaction)	0.60
0.40	4	Magnesium stearate (for tabletting)	0.30

Manufacturing Directions

1. Sift items 1 to 4 through a 250-μm mesh, mix well, and dry compress.
2. Pass granules through a large mesh and blend with item 4. Finally, compress into 70-mg tablets, using 8-mm punches.
3. Coat using Eudragit L-30D-55 coating solution. (See Appendix.)

Diethylcarbamazine Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Diethylcarbamazine citrate	102.00
100.00	2	Dicalcium phosphate	100.00
3.50	3	Gelatin	3.50
130.00	4	Lactose monohydrate	130.00
35.00	5	Starch (maize)	35.00
10.00	6	Talc	10.00
3.50	7	Magnesium stearate	3.50
–	8	Water, purified	QS

Manufacturing Directions

1. Sift items 1, 2, and 4 through a 500-μm sieve, and charge them in a suitable blender. Blend for 5 minutes.
2. In a separate vessel, charge items 3 and 5; add sufficient hot item 8 to dissolve and disperse into a smooth slurry.
3. Add step 2 into step 1, make a suitable wet mass, and pass through a 2.38-mm sieve onto paper-lined trays. Dry overnight at 60°C to an LOD of not more than 2.5%.
4. Pass the dried granules through a #16-mesh sieve into a blending vessel.
5. Sift items 6 and 7 through a 250-μm sieve, add to step 4, and blend for 1 minute.
6. Compress into 350-mg tablets, using 9.7-mm punches.

Difenoxin and Atropine Tablets (0.5 mg/0.025 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.50	1	Difenoxin hydrochloride	0.50
0.025	2	Atropine sulfate	0.025
88.00	3	Lactose monohydrate	88.00
23.00	4	Starch (corn)	23.00
2.50	5	Starch (corn)	2.50
5.00	6	Talc	5.00
1.00	7	Magnesium stearate	1.00
–	8	Water, purified	QS

Manufacturing Directions

1. Blending
   a. Prepare a blend of lactose, starch (item 4), and talc.
   b. Blend difenoxin hydrochloride and atropine sulfate with a small quantity of blend from step 1a.
   c. Blend this premix with the remainder of step 1. Pass through a #40-mesh (420-μm aperture or similar) screen.
   d. Slurry the starch (item 5) in 5 mL of cold purified water. Add the slurry to 20 mL of boiling purified water.
   e. Mass blend with starch paste from step 1d, adding more hot purified water, if necessary.
   f. Pass the mass through a #8 mesh (2.38-mm aperture or similar) screen.
   g. Dry the granules at 35°C (95°F) until the LOD is not greater than 5%.
   h. Screen the dried granules through a #20-mesh (840-μm aperture or similar) screen and lubricate with magnesium stearate.
2. Compression: Compress on a rotary tablet machine using 6.35-mm circular punches.

Digoxin Tablets (0.125 mg/0.25 mg), Lanoxin

Lanoxin is supplied as 125-mcg (0.125-mg) or 250-mcg (0.25-mg) tablets for oral administration. Each tablet contains the labeled amount of digoxin and the following inactive ingredients: corn and potato starches, lactose, and magnesium stearate. In addition, the dyes used in the 125-mcg (0.125-mg) tablets are D&C Yellow No. 10 and FD&C Yellow No. 6.

Digoxin Tablets

Manufacturing Directions

1. 12.5 g digoxin and 50.5 g polyvinyl pyrrolidone (MGW: 25000) in 1500 g of an isopropanol–water mixture (7+3) are added to the pot of a planetary agitator of a volume of 20 L.
2. 437 g of amorphous, porous silica is added in portions to this solution while stirring with a blade agitator.
3. After silica has combined with the liquid phase and the batch has taken on a gel type, completely lump-free structure, 4500 g of lactose is added in portions and the batch is mixed vigorously.
4. The pasty mass is then spread evenly on drying trays and dried for 3 hours at 80°C. Thereafter the dry material is passed through a 0.75-mm screen, provided with an addition of 15 wt.% of pelletizing aids, and compacted to tablets in the usual manner.

Dihydroxyaluminum Sodium Carbonate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
31.00	1	Dihydroxyaluminum sodium carbonate (Giulini A 265)	31.00
61.50	2	Sugar	61.50
2.00	3	Magnesium stearate	2.00
15.00	4	Starch	15.00
QS	5	Flavor, sweetener	0.50

Manufacturing Directions

Blend to mix and compress into 110-mg tablets, using 6-mm punch.

Diltiazem Hydrochloride Tablets (60 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Diltiazem hydrochloride	60.00
100.00	2	Lactose monohydrates	100.00
66.00	3	Oil castor hydrogenated (Cutina HR)	66.00
20.00	4	Polyethylene glycol 8000, milled	20.00
0.06 mL	5	Alcohol isopropyl anhydrous	60.00 mL
4.00	6	Magnesium stearate	4.00

Manufacturing Directions

1. Mill castor oil hydrogenated through a #120-mesh (125-μm aperture) screen at medium speed with knives forward.
2. Charge milled castor oil hydrogenated from step 1, lactose (item 2), and diltiazem hydrochloride into a suitable planetary mixer and dry blend for 10 to 15 minutes.
3. Dissolve the polyethylene glycol in the isopropyl alcohol (warm to 40–45°C, if necessary).
4. Gradually add the warm solution from above step 3 to powder blend, and mix until a suitable mass is obtained.
5. Pass the mass through a #4 mesh (4.8-mm aperture) screen, and spread on paper-lined oven trays.
6. Dry the granules at 45°C to 50°C to an LOD of not more than 1% (at 60°C under vacuum for 3 hours). Allow to cool.
7. Mill the dried granule through a #16-mesh (1.19-mm aperture) screen, with knives forward at medium speed. As an alternative, pass the dried granule through a 1.19-mm aperture screen fitted to an oscillating granulator.
8. Charge the screened granule into a suitable blender, add magnesium stearate, and blend for 5 to 10 minutes.
9. Compress on a suitable rotary machine, using 3/8-in. standard concave punches. The theoretical weight of 10 tablets is 250 mg/tablet, with hardness not less than 4 kPa.

Diltiazem Tablets 60 mg Caradizem

Cardizem direct-compression tablets: Each tablet contains 30, 60, 90, or 120 mg of diltiazem HCl. It also contains D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake (60 and 120 mg), or FD&C Blue No. 1 Aluminum Lake (30 and 90 mg), hydroxypropyl methylcellulose, lactose, magnesium stearate, methylparaben, microcrystalline cellulose, silicon dioxide, and other ingredients.

Diltiazem Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Diltiazem	60.00
141.00	2	Ludipress	141.00
5.00	3	Polyethylene glycol 6000 powder	5.00
1.00	4	Aerosil 200	1.00
1.00	5	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, pass through a sieve, and press with low-compression force.
2. Compress into 215-mg tablets, using 8-mm biplanar punches.

Dimenhydrinate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Dimenhydrinate	50.00
245.00	2	Ludipress®	245.00
5.00	3	Magnesium stearate	5.00

Manufacturing Directions

1. Mix all components, sieve, and press with low-compression force.
2. Compress into 300-mg tablets, using 8-mm biplanar punches.

Dimenhydrinate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Dimenhydrinate	50.00
50.00	2	Cellulose (microcrystalline) (Avicel™ PH101)	50.00
125.00	3	Lactose	125.00
2.29	4	Croscarmellose sodium (Ac-Di-Sol, SD-711)	2.29
1.00	5	Fumed silicon dioxide	1.00
0.50	6	Stearic acid	0.50
0.50	7	Magnesium stearate	0.50

Manufacturing Directions

1. Screen items 1, 5, and 6 separately through a 40-mesh sieve.
2. Blend items 1, 2, 4, and 5 in a V-blender for 3 minutes.
3. Add item 3 in the blender, and mix for 17 minutes.
4. Add item 6, and blend for 3 minutes.
5. Add item 7 to the blender, and mix for 5 minutes.
6. Compress using 3/8-in., flat, beveled-edge punches to a hardness of 6 kPa and average tablet weight of 228 mg.

Dimenhydrinate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Dimenhydrinate	100.00
40.00	2	Lactose monohydrate	40.00
40.00	3	Cornstarch	40.00
6.00	4	Kollidon® 90F	6.00
30.00	5	Isopropanol	30.00
14.00	6	Kollidon® CL	14.00
16.00	7	Talc	16.00
2.00	8	Aerosil® 200	2.00
2.00	9	Calcium arachinate	2.00

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with item 5, dry, pass through an 0.8-mm sieve, mix with items 6 to 9, and press with low-compression force.
2. Compress into 210-mg tablets, using 9-mm biconvex punches.

Dimenhydrinate Tablets (50 mg), DC

Formulation: Dimenhydrinate, 50 g; Aerosil 200, 4.0 g; Ludipress, 140 g; Kollidon CL, 2.0 g; magnesium stearate, 1.5 g.

Manufacturing Directions

1. Mix dimenhydrinate with Aerosil 200, add other components, and then sieve.
2. Press with low-compression force at 202 mg.

Diphenhydramine and Psuedoephedrine Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Diphenhydramine Hydrochloride	25.00
60.00	2	Pseudoephedrine Hydrochloride	60.00
415.00	3	Cab-o-sil	415.00
200.00	4	Water	200.00

Manufacturing Directions

1. Diphenhydramine hydrochloride and pseudoephedrine hydrochloride are mixed in the water until thoroughly dissolved.
2. Cab-o-sil M5 (silicon dioxide) is poured into a planetary mixer to which the dissolved drug solution is added and mixed at slow speed.
3. This is continued for 5 minutes until the solution and Cab-o-sil are completely mixed.
4. The entire composition is dried in a forced hot air oven for 7 hours at 50°C.
5. The composition is dried to an LOD of 1.0%.
6. The dried material is then screened through a No. 30 U.S. standard mesh screen and compressed to give average weight of 1.0 g containing 50 mg of diphenhydramine hydrochloride and 120 mg of pseudoephedrine hydrochloride.

Diphenhydramine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Diphenhydramine hydrochloride	25.00
150.00	2	Calcium phosphate (dibasic)	150.00
20.00	3	Starch (StaRX 1500)	20.00
QS	4	Polyvinylpyrrolidone (PVP)	QS
QS	5	Alcohol, USP	QS
75.00	6	Stearic acid (fine powder)	75.00
25.00	7	Cellulose (microcrystalline)	25.00
QS	8	Purified water, USP	QS

Manufacturing Directions

1. In a planetary mixer, charge the diphenhydramine hydrochloride, calcium phosphate dibasic and starch.
2. Mix for 5 to 10 minutes.
3. In a separate mixer, charge polyvinylpyrrolidone, alcohol, and water in a : 1:50:40 ratio.
4. Moisten this mixture with solution from the previous step to granulate.
5. Record the volume used.
6. Pass the wet mass through a #14-mesh screen on dryer trays.
7. Dry the granulation at 120°F to 130°F or use a fluid-bed dryer.
8. Pass the dried granules through a #20-mesh screen.
9. Charge dried granules to twin-shell blender, and add stearic acid (previously passed through #30-mesh screen) and microcrytalline cellulose.
10. Mix for 5 to 7 minutes.
11. Compress into 300-mg tablets, using a rotary press with 5/16-in. standard concave punches.

Diphenoxylate Hydrochloride and Atropine Sulfate Tablets (2.5 mg/0.025 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.50	1	Diphenoxylate hydrochloride	2.50
0.025	2	Atropine sulfate	0.025
11.40	3	Starch (maize)	11.40
54.00	4	Lactose monohydrate	54.00
2.50	5	Starch (maize)	2.50
0.60	6	Magnesium stearate	0.60
QS	7	Water, purified, ca	11.00

Manufacturing Directions

1. Sieve item 5 and disperse into 2.50 g of cold item 7. Then add the balance of item 7 at 70°C and heat to 80°C until completely gelatinized. Prepare a smooth slurry without lumps.
2. Leave the starch paste to cool to 40°C to 50°C.
3. Sieve item 4 and item 3 through a 250-μm sieve. Load items 1 and 2 into the mixer, and mix the items for 5 minutes at medium speed.
4. Add a starch paste cooled to 40°C to 50°C, and mix for 3 minutes at slow speed until a satisfactory mass is obtained. Add extra item 7 if required.
5. Spread the wet granules onto trays, and dry at 55°C for 12 hours.
6. Pass the dried granules through a 1-mm sieve.
7. Sieve item 6 through a 250-μm sieve, add to granules, and mix for 1 minute.
8. Compress into 71-mg tablets, using 5.5-mm punches.

Divalproate Sodium Tablets (125 mg), Depakote

Depakote tablets are supplied in three dosage strengths containing divalproex sodium equivalent to 125, 250, or 500 mg of valproic acid. The inactive ingredients are cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains cornstarch), silica gel, talc, titanium dioxide, and vanillin. In addition, individual tablets contain the following: *125-mg tablets:* FD&C Blue No. 1 and FD&C Red No. 40; *250-mg tablets:* FD&C Yellow No. 6 and iron oxide; and *500-mg tablets*: D&C Red No. 30, FD&C Blue No. 2, and iron oxide.

Divalproate Sodium Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
6.25	1	Povidone K 29–32	6.25
125.00	2	Valproic acid, use divalproex sodium	134.55
25.00	3	Cornstarch	25.00
6.25	4	Povidone K 29–32	6.25
35.00	5	Silicon dioxide	35.00
QS	6	Alcohol SD 3A 200 proof, ca	38 mL
7.50	7	Silicon dioxide	7.50

Manufacturing Directions

Caution: Avoid inhaling or making skin contact with sodium hydrogen divalproate. Wear dust respirator and eye protection during the processing of granulating, lubricating, and compressing sections.

1. Granulation
   a. Dissolve povidone (item 1) in approximately 33 mL of alcohol.
      Caution: Sodium divalproate melts under excessive shear. Ensure adequate lubrication during the milling step.
   b. Cross-feed sodium hydrogen divalproate, pregelatinized starch, povidone (item 4), and approximately one-half of the silicon dioxide (item 5) through a comminuting mill, fitted with a 686-μm aperture screen at high speed, hammers forward.
      Note: To permit easy milling, it is advantageous to premix sodium hydrogen divalproate with one-third of silicon dioxide (item 5) for 5 minutes in a suitable mixer before passing through the comminuting mill.
   c. Charge the milled materials from step 2 and the remaining silicon dioxide (item 5) into a suitable mixer. Blend for 5 to 10 minutes. Add povidone solution (step 1a) to the contents of the mixer to obtain a suitable mass. The materials do not wet easily, but they overmass rapidly. If necessary, add extra alcohol, up to 15 mL. Another method, if using high-shear mixers is to charge the milled materials from step 2 and the

remaining silicon dioxide into the mixer bowl. Blend at fast mixer/fast chopper conditions for 2 minutes. Add the povidone solution (step 1) over a period of 20 to 30 seconds using fast mixer/fast chopper conditions. Discharge from the mixer at a motor current of 35 to 40 amps. If necessary, add extra alcohol, portion wise, up to 8 mL, allowing for sufficient time between additions to ensure that the motor current does not exceed 40 amps.

d. Pass the wet mass through an oscillating granulator fitted with a 4.0-mm aperture screen and spread on paper-lined oven trays. As an alternative, pass the wet mass through a 9.53-mm aperture screen fitted to a comminuting mill, at slow speed, with knives forward, and spread on paper-lined oven trays. Dry at 49°C to an LOD of not more than 2% (3 hours, 60°C, vacuum).
Note: The balance of manufacturing in the "Granulation" process should be done at not more than 45% relative humidity and at temperatures of not more than 30°C.

e. Pass the dried granule through a 1.18-mm or 1.40-mm aperture screen fitted to an oscillating granulator, or screen the dry granules on a 1.4-mm aperture screen fitted to a suitable sieve shaker. Pass coarse granule through either a 1.18-mm or 1.40-mm aperture screen fitted to an oscillating granulator.

2. Lubrication
Note: The balance of manufacturing in the "Lubrication" stage should be done at not more than 40% relative humidity and at not more than 30°C.
   a. Charge one-half of the screened granule from step 1d into a suitable blender. Add silicon dioxide (item 7) via a 1.7-mm aperture screen to the blender followed by the balance of the screened granule from step 1d.
   b. Blend for 20 minutes, ensuring that no pockets or agglomerations of lubricant silicon dioxide remain.
   c. Discharge into tared polythene-lined drums.
3. Compression: Compress into 215-mg tablets, using 6.24 × 11.90-mm punches. For higher-strength 250- and 500-mg tablets, use proportional amounts and larger-sized punches.
Note: The balance of manufacturing in the "Compression" stage must be done at not more than 40% relative humidity and at not more than 26.5°C.
   a. Coating: Apply a PVP subcoat, an enteric opaque methocel coating, and a finishing coat. (See Appendix for details.)

Divalproex Sodium Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Valproic acid, use divalproex sodium, milled	538.20
80.00	2	Hydroxypropyl methylcellulose (Methocel K 15M), CR	80.00
180.00	3	Methyl cellulose (Methocel K100 L), CR	180.00
121.80	4	Lactose, anhydrous	121.80
50.00	5	Microcrystalline cellulose (Avicel PH 101)	50.00
30.00	6	Colloidal silicon dioxide	30.00

Note: Item 3 can be replaced by item 4. Note that this is a once-daily use formulation.

Manufacturing Directions

1. Pass item 1 through a #40-mesh sieve (0.42-mm nominal mesh opening) and charge in a suitable mixing vessel.
2. Pass items 2 to 5 through a 250-μm mesh, add to step 1, and mix for 20 minutes.
3. Add item 6 to step 2, and blend for an additional 5 minutes.
4. Compress into 1000-mg tablets, using a suitable punch.

Doxazosin Mesylate Tablets (1 mg/2 mg/4 mg/8 mg)

Doxazosin mesylate is available as colored tablets for oral use and contains 1 mg (white), 2 mg (yellow), 4 mg (orange), and 8 mg (green) of doxazosin as the free base. The inactive ingredients for all tablets are microcrystalline cellulose, lactose, sodium starch glycolate, magnesium stearate, and sodium lauryl sulfate. The 2-mg tablet contains FD&C Yellow No. 10 and FD&C Yellow No. 6; the 4-mg tablet contains FD&C Yellow No. 6; the 8-mg tablet contains FD&C Blue No. 10 and FD&C Yellow No. 10.

Doxycycline Hydrochloride Tablets (100 mg)

Inert ingredients for the tablet formulation are ethylcellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, talc, titanium dioxide, and FD&C Yellow No. 6 Lake. Inert ingredients for the coated pellets are lactose, NF; microcrystalline cellulose, NF; and povidone, USP. Each shell and band contains FD&C Blue No. 1; FD&C Yellow No. 6, D&C Yellow No. 10; gelatin, NF; silicon dioxide; sodium laurel sulfate, NF; and titanium dioxide, USP.

Doxycycline Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Doxycycline hydrochloride	100.00
40.00	2	Microcrystalline cellulose PH102	40.00
3.00	3	Aerosil 200	3.00
13.00	4	Sodium starch glycolate	13.00
1.75	5	Magnesium stearate	1.75
2.00	6	Talc	2.00

Manufacturing Directions

1. Charge items 1 to 6 in a suitable blender after passing them through a #60 sieve.
2. Mix the items for 10 minutes.
3. Compress into 160-mg tablets, using 12 × 5-mm punches.
4. Coat using HPMC coating. (See Appendix.)

Doxycycline Monohydrate Tablets

Manufacturing Directions

1. Doxycycline monohydrate (105.8 g) and microcrystalline cellulose (45 g) are mixed for 15 minutes in a planetary mixer.
2. The mixture is then granulated with 60 mL of water. After 10 minutes of kneading, the obtained wet mass is passed through a 2-mm sieve and the wet granulation dried at about 40°C until its water content is below 2% by weight.
3. The granulate is then passed through a 0.71-mm sieve and is mixed for 20 minutes with low-substituted hydroxypropylcellulose LHll (18 g), hydroxypropyl methylcellulose 5 cps viscosity(4 g), saccharin (10 g), colloidal silica (0.6 g), and enough lactose to bring the total weight of the mixture to 248 g. Then magnesium stearate (2 g) is added and the mixing is continued for an additional 2 minutes.
4. The resulting mixture is compressed into tablets, each of about 250 mg, about 9-mm diameter and hardness of 70 to 100 N, or into tablets, each of about 125 mg having a hardness of 60 to 90 N. The tablets disintegrate completely in water at room temperature within 30 to 45 seconds.

Efavirenz Tablets

Manufacturing Directions

1. Core tablet: Efavirenz, 950 g; microcrystalline cellulose NF, 380 g; hydroxypropyl cellulose LF NF, 60.8 g; croscarmellose sodium, 95 g; sodium lauryl sulfate, 19 g; lactose hydrous spray dried, 19.8% w/w; magnesium stearate, 1% w/w; water, 1.045 L.
2. Film coating material per tablet: 3.3% by wt of tablet hydroxypropyl cellulose LF NF 8.54 mg (2.5%), hydroxypropyl methylcellulose USP 6CPS 8.54 mg (2.5%), titanium dioxide USP 3.42 mg (1%), and water (94%).
3. Efavirenz (950 g) is blended with microcrystalline cellulose (380 g), sodium lauryl sulfate (19 g), hydroxypropyl cellulose (60.8 g), and croscarmellose sodium (95 g) in a Fielder 10 L high-shear granulator mixer for 4 minutes.
4. At least about 1.1 wt% water per weight of efavirenz (1.045 L) is added to wet granulate the blended mixture over about 6 minutes to about 8 minutes to agglomerate the mixture using an appropriate spray nozzle.
5. The granulated mixture is dried to a moisture content of about 2% to about 5% in a Glatt WST-15 fluid-bed dryer .
6. The dried mixture is milled using a 40 G round screen in a Comil. The milled mixture is blended in a V-blender with lactose for 4 minutes (calculated amount is the amount needed to make the final composition contain 19.8% lactose by weight).
7. The blended mixture is lubricated with magnesium stearate (calculated amount is the amount needed to make the final composition contain 1% magnesium stearate by weight) in the V-blender for 3 minutes.
8. The lubricated mixture is compressed.
9. The compressed tablets are film coated with an aqueous coating suspension that contains 2.5% hydroxypropyl cellulose (HPC); 2.5% hydroxymethylcellulose (HPMC); and 1% titanium dioxide and 94% water by weight percent in a pan coater to a coat weight of about 3.3% per tablet. Note that the coat is the dried form of the suspension.

Eletriptan-Coated Fast-Crumbling Granule Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
98.50	1	Eletpritan (salt)	98.50
4.90	2	AGG sodium croscarmellose	4.90
20.40	3	Ethylcellulose	20.40
4.00	4	Polyoxyethylene glycol 6000	4.00
3.70	5	AGM Sodium croscarmellose precipitated	3.70
1.40	6	Precipitated silica	1.40
3.90	7	Aspartame	3.90
3.50	8	AcDiSol	3.50

Manufacturing Directions

1. A granulation solution is first prepared by dissolving 48 g of ethylcellulose in 273 g of ethyl alcohol.
2. A coating suspension is then prepared by mixing 97 g of ethylcellulose, 28.5 g of polyethylene glycol 6000, 26 g of sodium croscarmellose, 10 g of precipitated silica, and 27.5 g of aspartame in 1900 g of ethyl alcohol, until a homogeneous suspension is obtained.
3. The powder mixture consisting of 700 g of eletriptan and 35 g of Acdisol is then fluidized.
4. Granulation process is then started by spraying the granulation solution for about 15 to 20 minutes at a spraying rate of 25 g/min and a suspension atomization pressure of 0.8 bar.
5. The actual coating is then performed, by spraying the coating suspension for about 1.5 hours at a spraying rate of about 15 to 20 g/min and a suspension spraying pressure of 1.5 bar.
6. The coated granules thus obtained are then formulated as fast-crumbling multiparticulate tablets, the composition of which is as follows:
   a. Coated granules Eletriptan, 136.8 mg (salt) (equivalent to 80 g of base active principle); Mannitol, 575.20 mg; sodium croscarmellose, 24 mg; aspartame 30 mg; mint liquorice, 10 mg; magnesium stearate, 8 mg.
   b. The tablets are manufactured by screening all the excipients, followed by homogenization of the granules coated with the mixture of excipients in a plowshare granulator. The granules obtained are then distributed and shaped on a rotary tabletting machine. The hardness of the tablets obtained is about 30 N.

Enalapril Maleate Tablets (2.5 mg/5 mg/10 mg/20 mg) Vasotec

Enalapril maleate is supplied as 2.5-, 5-, 10-, and 20-mg tablets for oral administration. In addition to the active ingredient enalapril maleate, each tablet contains the following inactive ingredients: lactose, magnesium stearate, starch, and other ingredients. The 2.5-, 10-, and 20-mg tablets also contain iron oxides.

Enalapril Maleate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Enalapril maleate	20.00
10.00	2	Sodium carbonate powder	10.00
146.72	3	Lactose hydrous powder	146.72
22.00	4	Starch (corn)	22.00
1.10	5	Magnesium stearate	1.10
0.050	6	Iron oxide red	0.050
0.130	7	Iron oxide yellow	0.130

Manufacturing Directions

Note: Use goggles, and wear dust protection. Also, process under low-humidity conditions.

1. Granulation: Mix the ingredients with the excipients in a planetary mixer. Pass through a FitzMill equipped with a stainless steel screen, and remix in the planetary mixer. Wet the granulate with starch paste. Pass the wet mass through FitzMill. Dry the granules in hot air, and pass the dried granules through a FitzMill. Collect in polyethylene-lined containers.
2. Lubrication: Transfer the dried, milled granules into the planetary mixer, and magnesium stearate, and mix. Collect in polyethylene-lined drums.
3. Compression: Compress into 200-mg tablets, using round punches.

Enalapril Maleate Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Enalapril maleate	20.00
5.00	2	Sodium carbonate powder	5.00
160.50	3	Lactose hydrous powder	160.50
22.00	4	Starch (corn)	22.00
1.10	5	Magnesium stearate	1.10
0.050	6	Iron oxide red	0.050

Manufacturing Directions

Follow the instructions listed for the 20-mg strength.

Enoxacin Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Enoxacin, use enoxacin sesquihydrate	434.00
80.00	2	Calcium carboxymethyl cellulose	80.00
6.00	3	Hydroxypropylmethyl cellulose	6.00
60.00	4	Cellulose microcrystalline (Avicel PH 101)	60.00
6.00	5	Silicon dioxide colloidal	6.00
14.00	6	Magnesium stearate	14.00
QS	7	Water, purified, ca	200 mL

Manufacturing Directions

1. Granulation
   a. If necessary, mill the enoxacin using a comminuting mill fitted with a 3-mm screen or sift through a 425-μm (40-mesh) screen.
   b. Load the Enoxacin and calcium carboxymethylcellulose into a suitable mixer, and blend for 10 minutes.
   c. Dissolve the hydroxypropyl cellulose in 200 mL of hot (80°C) water and allow to cool to below 40°C.
   d. Add the solution from step 3 to the powder blend from step 2. Mix to produce a satisfactory mass. If necessary, add more purified water.
   e. If necessary, pass the wet mass through a 4-mm screen, and load onto paper-lined trays.
   f. Dry at 55°C to give an LOD of 6.5% to 7.5% (140°C, 2 hours).
   g. Pass the dried granulation through a 1.00- mm screen using a suitable granulator, adding Avicel, silicon dioxide, colloidal, and magnesium stearate, simultaneously.
   h. Blend for 5 minutes in a suitable mixer.
2. Compression: Compress using 16.00 × 8.00 mm ovaloid punches.
3. Coating: Coat using aqueous Methocel* coating. (See Appendix.)

Entacapone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Entacapone	200.00
50.00	2	Microcrystalline Cellulose	50.00
400.00	3	Mannitol	400.00
10.00	4	Magnesium stearate	10.00

Eplerenone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Eplerenone	50.00
71.40	2	Lactose monohydrate	71.40
26.14	3	Microcrystalline cellulose intra granular PH101	26.14
18.00	4	Microcrystalline cellulose extragranular	18.00
5.10	5	Hydroxypropylmethyl cellulose 2910	5.10
8.50	6	Croscarmellose sodium (Acdisol)	8.50
1.70	7	Sodium lauryl sulfate	1.70
1.70	8	Talc	1.70
0.85	9	Magnesium stearate	0.85

Manufacturing Directions

1. Mix and granulate by wet method and compress into 50 mg dose immediate-release tablet (tablet diameter of 9/32 in.') or 25 mg dose immediate-release tablet (tablet diameter of 7/32 in.') using appropriate fill weight.
2. Coat tablets using Opadry White YS-1–18027A at 3% or alternately Opadry Yellow YS-1–12524-A at 4% gain.

Ergotamine Tartrate Fast-Melt Tablets

1. Ergotamine tartrate, 10%; sodium bicarbonate, 27%; citric acid anhydrous, 22%; Avicel PH113, 15%; xylitol, 15%; L-HPC LH-11, 5%; Fujicalin SG, 4%; Crodesta F160, 2%.
2. Dry the above ingredients to significantly reduce the moisture content of each material.
3. Blend for 10 minutes and extruded in a hot melt extruder at 70°C to 100°C to soften and melt the thermal binders (sucrose stearate and xylitol) and to form granules containing the effervescent ingredients.
4. Mix EGT-EGF (20–80 mesh), 55%; microcrystalline cellulose, 26%; Mannitol 10%; AcDiSol, 2.5%; L-HPC LH-11, 2.5%; aspartame, 3%; redberry flavor, 0.4%; magnesium stearate, 0.5%; fumed silicon dioxide, 0.1%.
5. Pass the above granules through a #20 screen and then blend for 5 minutes prior to compression.
6. Ergotamine tartrate tablets are then compressed to a hardness of approximately 1 to 5 kPa and tablets disintegrate in water in approximately 15 to 35 seconds.

Erythromycin and Sulfamethoxazole Tablets

Manufacturing Directions

1. 500 g of sulfamethoxazole and 10 g of a starch derivative are charged into a mass mixer. 10 grams of cornstarch are added along with sufficient water to make a starch paste. This starch paste is used to make a standard granulation tableting, which is dried and sized.
2. Separately, 275 g of erythromycin and 10 g of conventional cellulosic binder are charged into a mass mixer. A solution of 10 g povidone in water is added, and the mixture is granulated. The granulation is dried and sized in similar fashion to the sulfamethoxazole granulation, to yield particles of 10 to 40 mesh. Oversize and undersize particles are recycled.
3. Separately, 80 g of a cellulose phthalate enteric coating polymer, and 8 g of an alkyl citrate plasticizer are dispersed in a sufficient quantity of acetone and ethanol to make a solution. 0.3 g of blue dye lake are added, and the dispersion is stirred to mix.
4. The erythromycin granulation is coated with this solution in a particle coater and the resulting coated particles are sized.
5. Separately, a portion of the sulfamethoxazole granulation is charged into a blender. The dried erythromycin-coated particles sized to 10 to 40 mesh are added, as well as 200 g of microcrystalline cellulose, NF and 4 g of conventional lubricants and glidants. The remainder of the sulfamethoxazole granulation is added and the mixture is blended. This blended material is compressed in a conventional tablet press at applied force of 1500 to 6000 lbs/in.^{2}, into tablets having a weight per 10 tablets of approximately 12 g.

Erythromycin Ethylsuccinate Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Erythromycin, use erythromycin ethylsuccinate, citrate, washed[a]	470.58
200.00	2	Sucrose	200.00
200.00	3	Sodium citrate	200.00
50.00	4	Starch (maize)	50.00
2.50	5	Dye (optional)	2.50
—	6	Water, purified, ca	90.00
40.00	7	Polarcillin potassium (Amberlite IRP-88)	40.00
6.00	8	Magnesium stearate	6.00

[a]Adjust for potency; taken as 850 mcg/g for the amount given.

Manufacturing Directions

Caution: Protect face and hands; relative humidity in the working area should not exceed 50%.

1. Granulation
   a. Pass the following items through a 0.5-mm aperture stainless steel screen: erythromycin ethylsuccinate, sucrose, sodium citrate, starch (maize), and dye (if used). Transfer the screened items to a suitable planetary mixer, and mix for 10 minutes.
   b. While mixing, add purified water to the powders from step 1 until a suitable mass is formed. If necessary, add more purified water to complete the granulation.
   c. Pass the wet mass from step 1b through a suitable granulator fitted with a 2.0-mm aperture stainless steel screen. Collect the granules on paper-lined trays.
   d. Dry the granules in an oven at 50°C until the LOD content is in the range of 1% to 1.5%.
   e. Pass the dried granules through a suitable granulator fitted with a 1.0-mm aperture screen. Collect the granules, and store in securely closed, double polyethylene-lined drums.
2. Lubrication
   a. Place into a suitable blender the dried, screened granules from step 1e.
   b. Pass the amberlite and magnesium stearate through a 0.5-mm aperture stainless steel screen. Add the screened powders to the blender.
   c. Blend for 10 minutes.
   d. Discharge the blended granules into double polyethylene-lined drums. Close securely, and store until ready for compression.
3. Compression: Compress using 9 × 19 mm ovaloid punches. Compress 967 mg. If using dye, compress 969 mg per tablet.
4. Coating: Apply Methocel*, opaque methocel, and Celar glass Methocel* coatings. (See Appendix.)

Erythromycin Particle-Coated Tablets (150 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Cellulose microcrystalline (Avicel PH 101)	150.00
12.00	2	Sodium starch glycolate	12.00
12.00	3	Hydroxypropyl cellulose	12.00
150.00	4	Lactose monohydrate powder	150.00
QS	5	Alcohol SD 3A 200 proof, ca	200 mL
333.00	6	Erythromycin, use erythromycin particle coated*	530.25
1.25	7	Stearic acid	1.25
1.25	8	Wax hydrogenated vegetable (Sterotex K)	1.25
1.25	9	Magnesium stearate powder	1.25
1.25	10	Silicon dioxide	1.25

Note: Adjust weight of erythromycin-coated particles to allow for variable potency: (333 × 1000)/potency = G required for 1000 tablets. Adjust the weight of cellulose and microcrystalline NF (7) to compensate for variable potency of erythromycin. The amount required is 770.75; the factor weight of item 6 is G, required for 1000 tablets.

Manufacturing Directions

Caution: Protect face and hands from erythromycin because some individuals may be sensitive and reactions may occur. Take a shower after excessive exposure during manufacture.

1. Granulating
   a. Charge cellulose microcrystalline (item 1), sodium starch glycolate, hydroxypropyl cellulose, and lactose into a suitable mixer. Mix for approximately 20 minutes.
   b. Granulate by adding approximately 200 mL of alcohol while mixing.
   c. Pass wet granulation through a 5/8-in. band in rotary granulator or a similar granulator.
   d. Spread on paper-lined trays, and dry at 49°C until reaching an LOD of not more than 2% (60°C, 3 hours vacuum).
   e. Pass dried granulation through 1.2-mm aperture screen. Mill oversize material through a 1.2-mm screen, knives forward, medium speed using a FitzMill.
   f. Charge into polyethylene-lined drums.
2. Lubricating
   a. Charge ingredients from step 1f into the blender.
   b. Add erythromycin-coated particles.
   c. Mix and mill approximately 12.5 g of cellulose microcrystalline (item 7), stearic acid, hydrogenated vegetable oil wax, magnesium stearate, and colloidal silicon dioxide through 595-μm aperture screen, knives forward, at high speed, using a FitzMill into a blender.
   d. Charge the balance of the cellulose microcrystalline (item 7) into the blender, and blend for 10 minutes.
   e. Discharge into polyethylene-lined drums.
3. Compression
   a. Compress the product using ovaloid 8.6 × 18.9-mm punches.
   b. Do not grind tablets or rework culls. Use a compressing machine with a force feeder.
   c. The weight of 10 tablets is 11 g, the thickness is 7.7 to 8.6 mm, and the hardness is 18 to 25 kPa.
4. Coating: Use the HPMC clear coating solution. (See Appendix.)

Erythromycin Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Erythromycin, use erythromycin stearate (600 mcg/mg[a])	166.667
91.18	2	Sodium citrate dihydrate powder	91.180
3.287	3	Povidone K 29–32	3.287
11.51	4	Sodium carboxymethylcellulose, high viscosity	11.518
–	5	Alcohol denatured 200 proof	50.800 mL
8.68	6	Pollarcillin potassium (Amberlite IRP-88)	8.684

[a]Adjust for potency.

Manufacturing Directions

See below.

Erythromycin Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Erythromycin, use erythromycin stearate (600 mcg/mg[a])	166.66
100.00	2	Sodium citrate dihydrate powder	100.00
12.80	3	Povidone K 29—32	12.80
14.20	4	Sodium carboxymethylcellulose, high viscosity	14.20
—	5	Alcohol denatured 200 proof	50.80 mL

[a]Adjust for potency.

Manufacturing Directions

1. Granulation
   a. Sift the sodium citrate through a 600-μm aperture or similar screen.
   b. Charge erythromycin stearate, sodium citrate, povidone, starch, and sodium carboxymethylcellulose in a mixer, and mix for 15 minutes.
   c. Gradually add sufficient alcohol, while mixing, to produce a suitable mass.
   d. Dry the granulation at 49°C to less than 1.5% LOD or 7% moisture by Karl Fisher.
   e. Sift the dried granulation through a 1.19-mm aperture screen, or similar, and mill the oversized material through a #2 (1.59-mm aperture, or similar) band on the Hammer mill (FitzMill), or similar, at medium speed, knives forward, for 0 to 30 minutes.
   f. Load the granulation into the blender, add Amberlite IRP-88, if used, and blend for 20 to 30 minutes.
   g. Unload the contents of the blender into polyethylene-lined drums, and deliver to the compressing area.
2. Compression: Compress using 9.5-mm standard concave punches. Fill to appropriate amount.

Erythromycin Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Erythromycin, use erythromycin stearate (630 mcg/mg[a])	794.00
146.00	2	Starch (corn)	146.00
16.00	3	Povidone K 29–32	16.00
104.00	4	Magnesium hydroxide	104.00
—	5	Alcohol SD 3A 200 proof	210–250 mL
26.00	6	Polacrillin potassium (Amberlite IRP-88)	26.00

Note: During the drying step of granulation, starch has a water loss equivalent to approximately 6.2% of its weight. This enables a theoretical reduction in tablet weight of 9 mg. This may, however, be offset by a loss of active ingredient during the manufacturing process.
[a]Do not use erythromycin stearate with a potency less than 610 mcg/mg. Calculate the actual quantity of erythromycin stearate. Do not factor in any ingredient to compensate for erythromycin stearate potency change.

Manufacturing Directions

1. Granulation
   a. Load povidone, cornstarch, magnesium hydroxide, and approximately one-half of erythromycin stearate into a suitable blender, and blend for 10 minutes. Add the balance of the erythromycin stearate, and blend for 15 minutes.
   Note: Proceed to step 1d if only one wet granulation step is necessary.
   b. Empty the blender into tared, polyethylene-lined drums, and weigh for yield.
   c. Divide the blended powder into equal portions for massing. (The size of a massing "part" is predetermined from considering the capacity of the massing equipment.)
   d. Load preblended materials from step 1b into the mixer.
   e. Wet granulation, conventional method: Add 210 mL of alcohol slowly over a period of 10 minutes and mix for 5 minutes. If necessary, add additional alcohol (20–40 mL), and mix until a satisfactory mass is obtained. Do not overmix. Usually 5 minutes of mixing after the final addition of alcohol is sufficient. Record the total amount of alcohol used. Proceed to dry as in step 1g.
   f. Wet granulation, high-speed mixer method:
      i. Load preblended materials from step 1c into the mixer. Or if preblending is not required, load povidone, cornstarch, magnesium hydroxide, and erythromycin stearate into the high-speed mixer, and mix for 3 minutes with the agitator at slow speed and the granulator at fast speed.
      ii. Add 150 mL of alcohol while mixing with the agitator at a slow speed and the granulator at a fast speed over a period of 2 minutes. Continue to mix for another 4 minutes, adding additional alcohol, if necessary, to obtain a satisfactory granulation.
   g. Spread the wet mass onto paper-lined trays. Commence the drying setup immediately after this step has been completed. Do not air dry.

h. Load trays of granulation into a suitable drying oven, and dry at 50°C to 2% to 3.5% LOD, 3 hours in vacuum oven at 60°C, under 5-mm Hg vacuum. Under no circumstances must the Karl Fischer test method be used. Other LOD tests may be used for process control, provided equivalence can be demonstrated to the quoted vacuum oven method.
i. Alternative fluid-bed drying method: Charge granulate into fluid-bed dryer and dry at 40°C to 45°C.

Note: It is important not to dry the granulation below 2%. This loss is obtained after approximately 4 hours drying for oven loads from 70 to 130 kg, depending upon the amount loaded onto trays and the number of trays.

j. Repeat steps 1d through 1h if there is more than one part of blended powder from step 1b.
k. Allow the dried granule to cool, then screen through an 840-μm aperture screen using an oscillating granulator or through a 1.8-mm aperture screen using a comminuting mill with cutters forward at medium speed. Record the total weight of granulation.
l. Request samples.
m. Proceed to "Blending and Lubrication."

2. Lubrication
   a. If Amberlite is lumpy, screen through a 600- μm aperture screen before preblending.
   b. Preblend Amberlite with a small portion of the granule and the blend with approximately one-half of the bulk granule for 5 minutes.
   c. Add the balance of granule, and blend for a further 10 minutes.
   d. Empty the blender into tared, polyethylene-lined drums. Weigh.
3. Slugging (if required): Use a suitable compressing machine with either 19- or 12-mm flat punches.
   a. Compress the material into slugs having the following specifications: For 19 mm, weight is 1.7 to 1.75 g and hardness is 16 to 17 kPa; for 12 mm, weight is 0.8 to 0.85 g and hardness is 14 to 15 kPa.
   b. The slugs should show no signs of lamination, capping, or surface melting and should break with a distinct snap.
   c. Reduce slugs by passing slowly through a 0.107-in. (2.7-mm) perforated screen using cutters at medium speed.
   d. After reduction, lubricate as above.
4. Compression

   Note: Precompression may be used to meet hardness specifications.
5. Coating: Aqueous methocel. (See Appendix.)

Estazolam Tablets (1 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.00	1	Estazolam	1.00
120.65	2	Lactose monohydrate	120.65
8.37	3	Starch (maize)	8.37
3.78	4	Starch (maize)	3.78
QS	5	Water, purified	19.00 mL
1.20	6	Stearic acid	1.20

Manufacturing Directions

Caution: Use a respirator and gloves throughout; shower after exposure.

1. Granulation
   a. Mix starch (item 5) together with approximately 10 mL water in a glass or stainless steel vessel; avoid formation of lumps.
   b. Boil the remaining 18 mL of water, and add it to the mix from step 1a, with continuous stirring until a gel is formed. Further heat may be necessary. A mix temperature of 95°C must be achieved before a gel is formed.
   c. Pass estazolam through a 0.7-mm aperture stainless steel screen.
   d. Pass through a 1.19-mm aperture stainless steel screen lactose, starch (item 3), and hydroxypropylcellulose into a suitable planetary mixer. Add screened estazolam, and mix for 10 minutes.
   e. Add the starch gel from step 1b, and mix for 20 minutes or until a suitable mass is formed.
   f. Pass the wet mass through an oscillating granulator or similar, fitted with a 2.38-mm aperture stainless steel screen. Collect granules on paper-lined trays.
   g. Dry in an oven at 50°C until the LOD is less than 7%.
   h. Pass the dried granules through an oscillating granulator or a similar granulator, fitted with a 1.4-mm aperture stainless steel screen. Collect in a polyethylene-lined drum and close securely.
2. Lubrication
   a. Place the dried granules into a suitable planetary or ribbon filter.
   b. Pass starch (item 7) and magnesium stearate through a 0.25-mm stainless steel screen and mix. Add this blend to the granules, and mix for 5 minutes. Transfer to polyethylene-lined drums.
3. Compression: Compress in a suitable rotary machine using a 7-mm-diameter beveled edged, with weight of 10 tablets at 1.2 g (1.17–1.23 G) and thickness of 2.35 mm ± 0.12 mm.

Estazolam Tablets (2 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.00	1	Estazolam	2.00
79.30	2	Lactose	79.30
24.30	3	Starch (maize), dried	27.10
2.40	4	Hydroxypropylcellulose	2.40
5.00	5	Starch (maize)	5.00
QS	6	Water, purified	28.00 mL
5.70	7	Starch (maize)	5.70
0.30	8	Magnesium stearate	0.30

Manufacturing Directions

See the manufacturing directions for 1-mg formulation of estazolam.

Estradiol Tablets (0.5 mg/1 mg/2 mg), Estrace

Estrace tablets for oral administration contain 0.5, 1, or 2 mg of micronized estradiol per tablet. Estrace 0.5-mg tablets contain the following inactive ingredients: acacia, dibasic calcium phosphate, lactose, magnesium stearate, colloidal silicon dioxide, starch (corn), and talc. Estrace 1-mg tablets contain the following inactive ingredients: acacia, D&C Red No. 27 Aluminum Lake, dibasic calcium phosphate, FD&C Blue No. 1 Aluminum Lake, lactose, magnesium stearate, colloidal silicon dioxide, starch (corn), and talc. Estrace 2-mg tablets contain the following inactive ingredients: acacia, dibasic calcium phosphate, FD&C Blue No. 1 Aluminum Lake, FD&C Yellow No. 5 (tartrazine) (Aluminum Lake), lactose, magnesium stearate, colloidal silicon dioxide, starch (corn), and talc.

Estradiol Vaginal Tablets (25.8 mcg)

Bill of Materials			
Scale (mg/tablet)	item	Material Name	Quantity/1000 Tablets (g)
25.8 mcg	1	Estradiol hemihydrate equivalent to Estradiol 25 mcg	0.0258
101.974	2	Lactose Spray Dried	101.974
15.00	3	Maize starch	15.00
2.00	4	Hypromellose	2.00
1.00	5	Magnesium stearate	1.00
2.60	6	Hypromellose	2.60
0.50	7	Polyethylene glycol 4000	0.50
–	8	Water, purified	30.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 3, and 4 through 0.5-mm sieve and collect in a stainless steel container and mix well.
4. Add 5% (=2.5 g) powder from step 1 to step 3 and mix well.
5. Add 10% (=5 g) powder from step 1 to step 4 and mix well.
6. Add 15% (=7.6 g) powder from step 1 to step 5 and mix well.
7. Transfer step 6 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 5 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 120-mg tablets, using a suitable punch (6 mm, round).
13. Charge item 8 in a stainless steel vessel. Add item 6 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hypromellose.
14. Add item 7 to step 13 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Check that coating dispersion is clear and lump free.
15. Load core tablets from step 12 in coating pan and apply coating dispersion from step 14 to get 1.5% to 1.8% weight gain.

Estropipate Tablets (0.626 mg/1.25 mg/2.25 mg/5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.626	1	Estropipate, 25% excess	0.769
157.02	2	Lactose monohydrate	157.02
1.00	3	Yellow dye	1.00
0.007	4	Yellow dye	0.007
1.00	5	Dibasic potassium phosphate, anhydrous	1.00
1.20	6	TRIS (tromethamine)	1.20
7.00	7	Hydroxypropyl cellulose	7.00
10.00	8	Sodium starch glycolate	10.00
40.00	9	Cellulose microcrystalline	40.00
QS	10	Water, purified	QS
QS	11	Alcohol SD 3A 200 proof	QS
0.50	12	Colloidal silicon dioxide	0.50
1.25	13	Magnesium stearate	1.25
1.25	14	Wax, hydrogenated vegetable oil (Sterotex K)	1.5

Note: For 1.25-, 2.25-, and 5.0-mg tablets, adjust with item 2 and modify dyes.

Manufacturing Directions

1. Granulation
   a. Charge lactose cellulose microcrystalline, hydroxypropyl cellulose, dyes, or dye into mixer, and blend powders. If necessary, screen or mill powders to break up agglomerates. A portion of the cellulose microcrystalline may be added at the lubrication step.
   b. Dissolve the dibasic potassium phosphate in purified water. Use this solution to granulate powders in step 1a.
   c. Size wet granulation, dry, and pass through screen and mill.
   d. Dissolve tromethamine and estropipate in water or alcohol.
   e. Charge granulation from step 1c and sodium starch glycolate into mixer, and mass with step 1d. Size wet granulation and dry. Pass the dried granulation through screen and mill.
2. Lubrication
   a. Charge the portion of the dried granulation into the blender.
   b. Screen colloidal silicon dioxide, magnesium stearate, and hydrogenated vegetable oil wax, and charge into blender.
   c. Charge remainder of dried granulation into blender and blend.
3. Compression: Compress using a rotary machine using oval tooling. The theoretical weight is 221 mg.

Ethambutol Tablets (400 mg)

Formulation: Ethambutol, 400 g; Sorbitol, crystalline, 200 g; Kollidon VA 64, 20 g; Kollidon CL, 10 g; magnesium stearate, 10 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press with medium/high-compression force at 620 mg.

Ethambutol Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Ethambutol hydrochloride	400.000
5.60	2	Silicon dioxide colloidal	5.600
68.00	3	Starch (corn) NF[a]	76.800
33.50	4	Mannitol	33.600
22.40	5	Starch (corn)	22.400
11.20	6	Corn oil hydrogenated	11.200
8.00	7	Magnesium stearate	8.000
11.20	8	Talc powder	11.200
QS	9	Water, purified	80.000

[a]The quantity of starch (corn) is based on a moisture content of 13% w/w. If the moisture content varies outside this range of 12.5% to 13.5%, then the amount used should be factored accordingly.

Manufacturing Directions

1. Massing
   a. Mix starch (item 5) with approximately 27.3 mL of purified water (item 9) in a glass or stainless steel vessel, avoiding the formation of lumps.
   b. Boil the remaining 52.8 mL of purified water (item 9), and add the mix from step 1a with continuous stirring until a gel is formed. Further heat may be necessary.
   Note: A mix temperature greater than 95°C must be exceeded before a gel is formed.
   c. Mill the ethambutol through a 1.59-mm aperture screen at medium speed with knives forward, then charge into a suitable mixer.
   d. Pass silicon dioxide, starch (corn) (item 3), and mannitol through a 1.00-mm aperture stainless steel screen and add to the mixer. Mix at 60 rpm for 10 minutes.
   e. Pass the mixed powders from step 1d through a 1-mm aperture stainless steel screen and return to the mixer.
   f. Add, in one charge, the starch gel from step 1b at 70°C to 80°C, and mix for 5 minutes at 60 rpm.
   g. Stop the mixer and inspect the mass. Add the extra 6.88 mL of purified water (item 10) at 50°C to complete the granulation while mixing. Mix for a further 5 minutes at 60 rpm.
2. Drying/granulation: Proceed to step 2a or 2b.
   a. Oven drying
      i. Pass the wet mass through an A granulator fitted with a 4.76-mm aperture stainless steel screen. Collect the granules on paper-lined trays.
      ii. Dry the granules in a hot-air oven at 50°C, turning over the granules every half hour. After 1 hour of drying, pass the granules through an A granulator fitted with a 2.38-mm aperture stainless steel screen. Collect the granules on paper-lined trays, and return to the hot-air oven at 50°C.
   b. Fluid-bed drying
      i. Pass the wet mass through an A granulator fitted with a 4.76-mm aperture stainless steel screen into the fluid-bed dryer bowl.
      ii. Dry the granules in the fluid-bed dryer at 50°C for 30 minutes, turning over after 15 minutes. Then, pass the granules through a granulator fitted with a 2.38-mm aperture stainless steel screen, and return to the fluid-bed dryer bowl with the air inlet and outlet fully open. Proceed to step 3.
   c. Continue drying the granules while turning them over every 30 minutes until the LOD is between 1.5% and 2%.
   d. Pass the dried granules through an A granulator fitted with a 1-mm aperture stainless steel screen. Collect the granules in a polyethylene-lined drum, and close securely.
   e. Request samples.
3. Lubrication
   a. Place the dried granules from step 2d in a suitable blender.
   b. Add oil castor hydrogenated, magnesium stearate, and talc via a 0.6-mm aperture stainless steel screen, and mix for 25 minutes.
   c. Transfer to a polyethylene-lined drum, and close securely until ready for compression.
4. Compression: Compress on a suitable tablet machine using ovaloid punches that are 15.5 × 7.7 mm or 14.6 × 7.8 mm, where the weight of 10 tablets is 5.6 g, hardness is more than 5 kPa, and the disintegration time is not more than 15 minutes. If using a coating, move to the next step.
5. Coating: Use an HPMC methylene chloride coating. (See Appendix.)

Ethambutol Tablets (800 mg)

Bill of Materials			
Scale (mg/tablet)	item	Material Name	Quantity/1000 Tablets (g)
800.00	1	Ethambutol	800.00
200.00	2	Dicalcium phosphate (Di-Tab)	100.00
30.00	3	Kollidon 30	30.00
–	4	Isopropyl alcohol	QS
50.00	5	Kollidon CL	50.00
15.00	6	Magnesium stearate	15.00

Manufacturing Directions

1. Granulate the mixture of items 1 and 2 with a solution of items 3 and 4. Dry, pass through a 0.8-mm sieve, add items 5 and 6, and press with high-compression force.
2. Compress into 1.112-g tablets, using 20-mm oblong punches.

Etophylline and Theophylline Tablets (100 mg/22 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Etophylline powder (Knoll)	101.00
22.00	2	Theophylline, anhydrous	23.00
53.00	3	Ludipress	53.00
1.00	4	Magnesium stearate	1.00
2.00	5	Aerosil 200	2.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press into tablets with low-compression force.
2. Compress into 175-mg tablets, using 8-mm biplanar punches. To enhance the flowability of the tabletting mixture, the amount of Aerosil 200 can be increased.

Etophylline and Theophylline Tablets (100 mg/22 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Etophylline powder (Knoll)	100.00
22.00	2	Theophylline, anhydrous	23.00
50.00	3	Starch (maize)	50.00
3.00	4	Kollidon VA 64	3.00
4.00	5	Kollidon VA 64	4.00
–	6	Water, purified, ca	35.00
1.00	7	Magnesium stearate	1.00
5.00	8	Talc	5.00

Manufacturing Directions

1. Granulate a mixture of items 1 to 4 with solution of items 5 and 6. Pass through a 0.8-mm sieve, dry, mix with items 7 and 8, pass through a 0.5-mm sieve, and press with medium-compression force.
2. Compress into 183-mg tablets, using 8-mm biplanar punches.

Ezetimibe and Simvastatin Tablets (10 mg/40 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Ezetimibe	10.00
40.00	2	Simvastatin	40.00
94.92	3	Lactose Monohydrate	94.92
40.00	4	Microcrystalline cellulose (Avicel PH102)	40.00
2.00	5	Hydroxylpropylmethyl cellulose	2.00
0.04	6	Butylated hydroxyanisole	0.04
3.00	7	Citric acid monohydrate	3.00
0.04	8	Propyl gallate	0.04
8.00	9	Croscarmellose sodium	8.00
2.00	10	Magnesium stearate	2.00
–	11	Water, purified	20.00
–	12	Ethanol 95%	10.00
4.00	13	Hydroxylpropylmethyl cellulose	4.00
–	14	Water, purified	35.00

Manufacturing Directions

1. Dissolve item 7 in half of item 11 (10 g) in a stainless steel container.
2. Dissolve item 5 in the mixture of remaining half quantity of item 11 and half quantity of item 12 (5 g) and add to step 1 and mix well.
3. Dissolve items 6 and 8 one by one in the remaining half quantity of item 12 in another stainless steel container.
4. Mix step 3 with step 2.
5. Pass items 3, 1, and 2 through 0.5-mm sieve and mix well.
6. Charge step 5 in a granulator.
7. Knead step 6 with solution of step 4 for 5 to 10 minutes until a loose, moist mass is obtained.
8. Granulate the moist mass using a centrifugal granulator with a 7-mm sieve.
9. Spread step over paper-lined trays, and dry at 45°C to 50°C for 8 hours (the relative humidity over the granules should be 20–35%).
10. Pass the dried granules through a 1.25-mm sieve granulator.
11. Transfer the granules to a tumbler.
12. Pass 9 through 0.5-mm sieve and add to step 11 and mix for 15 minutes.
13. Pass item 10 through 0.250-mm sieve and add to step 12.
14. Mix step 13 for 2 minutes.
15. Compress into 200-mg tablets, using a suitable punch (8.5 mm, round).
16. Charge item 14 in a stainless steel vessel. Add item 13 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hydroxylpropylmethyl cellulose.
17. Load core tablets from step 15 in coating pan and apply coating dispersion from step 16 to get 1.5% to 1.8% weight gain.

Ezetimibe and Simvastatin Tablets (10 mg/80 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Ezetimibe	10.00
80.00	2	Simvastatin	80.00
127.38	3	Lactose monohydrate	127.38
60.00	4	Microcrystalline cellulose (Avicel PH102)	60.00
3.00	5	Hydroxylpropylmethyl cellulose	3.00
0.06	6	Butylated hydroxyanisole	0.06
4.50	7	Citric acid monohydrate	4.50
0.06	8	Propyl gallate	0.06
12.00	9	Croscarmellose sodium	12.00
3.00	10	Magnesium stearate	3.00
–	11	Water, purified	30.00
–	12	Ethanol 95%	15.00
6.00	13	Hydroxylpropylmethyl cellulose	6.00
–	14	Water, purified	50.00

Manufacturing Directions

1. Dissolve item 7 in half quantity of item 11 (15 g) in a stainless steel container.
2. Dissolve item 5 in the mixture of remaining half quantity of item 11 and half quantity of item 12 (7.5 g) and add to step 1 and mix well.
3. Dissolve items 6 and 8 one by one in the remaining half quantity of item 12 in another stainless steel container.
4. Mix step 3 with step 2.
5. Pass items 3, 1, and 2 through 0.5-mm sieve and mix well.
6. Charge step 5 in a granulator.
7. Knead step 6 with solution of step 4 for 5 to 10 minutes until a loose, moist mass is obtained.
8. Granulate the moist mass using a centrifugal granulator with a 7-mm sieve.
9. Spread step over paper-lined trays, and dry at 45°C to 50°C for 8 hours (the relative humidity over the granules should be 20–35%).
10. Pass the dried granules through a 1.25-mm sieve granulator.
11. Transfer the granules to a tumbler.
12. Pass item 9 through 0.5-mm sieve and add to step 11 and mix for 15 minutes.
13. Pass item 10 through 0.250-mm sieve and add to step 12.
14. Mix step 13 for 2 minutes.
15. Compress into 300-mg tablets, using a suitable punch (11.0 mm × 8.5 mm, modified oval).
16. Charge item 14 in a stainless steel vessel. Add item 13 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hydroxylpropylmethyl cellulose.
17. Load core tablets from step 15 in coating pan and apply coating dispersion from step 16 to get 1.5% to 1.8% weight gain.

Ezetimibe Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000Tablets (g)
10.00	1	Ezetimibe	10.00
62.70	2	Lactose spray dried	62.70
20.00	3	Microcrystalline cellulose (Avicel PH102)	20.00
3.00	4	Povidone K30	3.00
1.00	5	Sodium lauryl sulfate	1.00
2.50	6	Croscarmellose sodium	2.50
0.80	7	Magnesium stearate	0.80

Manufacturing Directions

1. Pass item 2 through 1-mm sieve and collect in a tumbler.
2. Pass items 1, 4, and 5 through 0.5-mm sieve and collect in a stainless steel container and mix well for 5 minutes.
3. Transfer step 2 to step 1.
4. Pass item 6 and item 3 through 0.5-mm sieve and add to step 1.
5. Mix step 1 for 20 minutes using tumbler.
6. Pass item 7 through 0.250-mm sieve and add to step 5.
7. Mix step 6 for 2 minutes.
8. Compress into 100-mg tablets, using a suitable punch (5.0 mm × 5.5 mm, oval)

Famciclovir Tablets (125 mg/250 mg)

Bill of Materials			
Scale (mg/tablet)	item	Material Name	Quantity/1000 Tablets (g)
125.00	1	Famciclovir	125.00
165.00	2	Microcrystalline cellulose (Avicel) QS	165.00
4.00	3	Sodium starch glycolate (Primojel®)	4.00
0.50	4	Magnesium stearate	0.50

Manufacturing Directions

1. Sift Famciclovir, Avicel, and sodium starch glycolate through a 250-μm sieve into a mixer.
2. Mix for 5 minutes.
3. Sift magnesium stearate through a 250-μm sieve and add to step 1. Blend for 3 minutes.
4. Compress 295 mg in a suitable punch. For 250-mg strength, compress 590 mg.
5. Coat using a hypermellose coating. (See Appendix.)

Famotidine Tablets (20 mg), Pepcid

Each tablet for oral administration contains either 20 or 40 mg of famotidine. The inactive ingredients are hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide. Each Pepcid RPD orally disintegrating tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: aspartame, mint flavor, gelatin, mannitol, red ferric oxide, and xanthan gum.

Famotidine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Famotidine	20.00
80.00	2	Microcrystalline cellulose (Avicel PH 102)	80.00
67.60	3	Pregelatinized starch (Starch 1500)	67.60
2.00	4	Povidone (PVP K-25)	2.00
–	5	Alcohol (ethanol 95%)	36.67
22.80	6	Microcrystalline cellulose (Avicel PH 102)	22.80
8.16	7	Pregelatinized starch (starch 1500)	8.16
2.00	8	Glyceryl behenate	2.00
2.41	9	Talc (fine powder)	2.41

Manufacturing Directions

1. Preparation of binding solution: Dissolve item 4 in item 5 to make a clear solution by using a stirrer at medium speed in a stainless steel container.
2. Dry mixing: Load items 1 to 3 into a mixer. Mix for 5 minutes with a mixer and chopper at low speed.
3. Wet massing
   a. Add the binding solution at a rate of 8.3 g/min to the dry powder in the mixer, while mixing at low speed. Mix and chop for a further 2 to 3 minutes at low speed.
   b. Check for a satisfactory wet mass. Add additional ethanol 95% if required to get a satisfactory wet mass.
4. Drying
   a. Spread the granules onto stainless steel trays to a thickness of one-quarter of the tray thickness. Load the trays on the trolley.
   b. Load the trolleys to the oven. Keep the doors open. Start the air circulation, heaters off, for 2 hours.
   c. Start the heaters of the dryer. Close the doors. Set the temperature at 55°C for 6 hours.
   d. Check the moisture contents of the dried granules (limit: not more than 3.5%). Dry further, if required, to get a moisture content of 3.5%.
5. Grinding: Pass the dried granules through a sifter using a 1250-μm sieve. Pass the retained granules through a granulator equipped with a 1.0-mm sieve.
6. Lubrication
   a. Pass items 6 and 7 through a 500-μm sieve using a sifter. Collect in a stainless steel container.
   b. Load the sized granules from step 5a along with sieved powder from step 6a into the blender. Blend for 3 minutes.
   c. Mix items 8 and 9 in a polythene bag for 1 minute. Pass this mixture through a 250-μm sieve into the sifter. Collect in a polythene bag. Add 3 to 5 g of granules from step 6b to it, and mix manually for 1 minute. Add this mixture to step 6b, and mix for 1 minute.
   d. Unload in stainless steel drums.
7. Compression: Compress the granules using a rotary tabletting machine. The dimension is 7.1 ± 0.1 mm concave plain. The weight of 10 tablets is 2.05 g ± 2%.
8. Tablet coating: Coat the tablet using an HPMC coating. (See Appendix.)

Famotidine Tablets (40 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
40.00	1	Famotidine	40.00
70.50	2	Microcrystalline cellulose (Avicel PH 102)	70.50
67.60	3	Pregelatinized starch (Starch 1500)	67.60
0.09	4	Ferric oxide (iron oxide red)	0.09
2.50	5	Povidone (PVP K-25)	2.50
—	6	Alcohol (ethanol 95%)	36.67
11.16	7	Microcrystalline cellulose (Avicel PH 102)	11.16
8.66	8	Pregelatinized starch (Starch 1500)	8.66
2.00	9	Glyceryl behenate	2.00
2.41	10	Talc (Fine powder)	2.41

Manufacturing Directions

See the manufacturing directions for the 20-mg formulation.

Fenoprofen Calcium Tablets

Manufacturing Directions

1. Mixture A: A Diosna mixer is charged with 17.5 kg of fenoprofen calcium, 2.64 kg of lactose, 1.75 kg of starch powder, and 656 g of pregelatinized starch through a #10-mesh screen. The mixture is blended for 5 minutes using a low-speed mixer and low-speed chopper settings.
2. While continuing to mix as described above, 4373 mL of a 15% wt/v aqueous povidone solution is added slowly.
3. The mixture is then agitated using a high-speed mixer and high-speed chopper settings for 3 minutes. During this time, purified water is added to the mixture in a quantity sufficient to produce a satisfactory granulation.
4. The granulation is then wet sieved through a #6 screen onto paper-lined trays. The granulation is dried at 110°F for 16 hours. The dried granulation is milled at 1400 rpm with a FitzMill into a clean, polyethylene lined drum yielding 22.32 kg of mixture A. The mill employed a 2AA plate with knives forward.
5. Mixture B: To a Diosna mixer is added 26.25 kg of fenoprofen calcium, 3.965 kg of lactose, 2.625 kg of starch powder, and 984.5 g of pregelatinized starch. The mixture is blended for 5 minutes using a low-speed mixer and low-speed chopper settings. While continuing to mix as described above, 6563 mL of a 15% wt/v aqueous povidone solution containing 495 g of Opaspray Butterscotch L-2701 (Manufactured by Colorcon, Inc.) is added slowly. The mixture is then agitated using a high-speed mixer and high-speed chopper settings for 3 minutes. During this time, purified water is added in a quantity sufficient to produce a satisfactory granulation. The wet granulation is sieved using a #6 screen onto paper-lined trays. The granulation is dried at 110°F for 16 hours.
6. A third mixture, mixture C, is prepared in the same manner as mixture B. After drying, this mixture is combined with mixture B and milled at 1400 rpm with a FitzMill into a clean polyethylene lined drum yielding 68.03 kg of mixture BC. The mill employed a 2AA plate with knives forward.
7. A ribbon mixer is charged with 11.6 kg of mixture A and 35.3 kg of mixture BC. To this mixture is added 1.5 kg of cellulose with sodium carboxymethylcellulose-591 (Avicel RC-591, FMC Corporation) and 120 g of sodium lauryl sulfate through a #30-mesh screen. The mixture is blended for 10 minutes. To the mixture is added 250 g of magnesium stearate and 500 g of stearic acid powder through a #30-mesh screen. Mixing is continued for an additional 5 minutes after which the granulation is discharged into a clean polyethylene lined drum, yielding 49.20 kg of material.
8. This is then compressed on a Manisty Express Tabletting Machine using appropriate tooling.
9. The resulting tablets are coated in a 48 in. Accela Cota with an aqueous film coating mixture consisting of hydroxypropyl methylcellulose 7% w/w, polyethylene glycol 2% w/w, propylene glycol 3% w/w, and benzyl alcohol 1% w/w. The tablets are then placed on paper-lined trays to dry.
10. The tablets prepared by the preceding method had the following per tablet unit formula: fenoprofen calcium, 700.0 mg; lactose, 105.7; starch powder, 70.0; pregelatinized starch, 26.25; povidone, 26.25; opaspray butterscotch, 9.9; cellulose with sodium CMC-591, 30.0; sodium lauryl sulfate, 2.4; magnesium stearate, 5.0; stearic acid powder, 10.0; clear film coat (theory) 19.32.

Ferrous Fumarate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Ferrous fumarate	200
295.00	2	Ludipress®	295
5.00	3	Magnesium stearate	5

Manufacturing Directions

1. Mix all components, and pass through an 0.8-mm sieve.
2. Press with low-compression force.
3. Compress into 509-mg tablets, using 12-mm biplanar punches.

Ferrous Sulfate, Manganese Sulfate, and Copper Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
65.00	1	Anhydrous ferrous sulfate	65.00
3.50	2	Manganese sulfate	3.50
0.16	3	Copper sulfate	0.16
70.00	4	Ludipress®	70.00
10.00	5	Kollidon® 30	10.00
2.00	6	Magnesium stearate	2.00
3.00	7	Aerosil® 200	3.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with high-compression force.
2. Compress into 149-mg tablets, using 8-mm biplanar punches.

Ferrous Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Anhydrous ferrous sulfate	203.00
185.00	2	Ludipress®	185.00
15.00	3	Kollidon® VA 64	15.00
4.00	4	Magnesium stearate	4.00
4.00	5	Talc	4.00
3.00	6	Aerosil® 200	3.00

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press to tablets with medium-compression force.
2. Compress into 413-mg tablets, using 8-mm biplanar punches.

Fexofenadine and Pseudoephedrine Tablets (10 mg/240 mg), Allegra

Allegra-D® (fexofenadine HCl and pseudoephedrine HCl) extended-release tablets for oral administration contain 60 mg of fexofenadine HCl for immediate-release and 120 mg of pseudoephedrine HCl for extended release. Tablets also contain the following excipients: microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, carnauba wax, stearic acid, silicon dioxide, hydroxypropyl methylcellulose, and polyethylene glycol.

Fexofenadine and Pseudoephedrine Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
240.00	1	Pseudoephedrine sulfate	240.00
15.00	2	Microcrystalline cellulose (Avicel PH 101)	15.00
200.00	3	Xanthan gum Keltrol TF	200.00
80.00	4	Sodium alginate keltone HVCR	80.00
53.00	5	Calcium carbonate	53.00
6.00	6	Magnesium stearate	6.00
6.00	7	Aerosil 200	6.00
10.00	8	Fexofenadine	10.00
95.00	9	Lactose monohydrate	95.00
66.50	10	Microcrystalline cellulose (Avicel PH 101)	66.50
1.00	11	Yellow FD&C No. 10	1.00
20.00	12	Starch (maize)	20.00
6.00	13	Starch (maize)	6.00
1.50	14	Magnesium stearate	1.50
–	15	Water, purified	60.00

Manufacturing Directions

1. Charge pseudoephedrine sulfate, microcrystalline cellulose, xanthan gum, sodium alginate, calcium carbonate, and one-half of the lubricants in a suitable mixer, after sieving through a #44 sieve.
2. Pass the blend through a roll compactor.
3. Sieve the compact through a #22 sieve to obtain granules.
4. Mix the granules with the remaining lubricants (items 6 and 7), and compress into tablets (600 mg) to form the first tablet layer.
5. Charge items 8 to 12 after passing through a #100 sieve in a suitable mixer. Blend for 10 minutes.
6. Charge item 13 in a separate vessel, and make a paste (10%) using item 14.
7. Add step 6 into step 5, and granulate.
8. Dry the granules, and blend the sifted item 14.
9. Compress into 200-mg tablets (the second layer).
10. Use appropriate tabletting equipment for bilayer tabletting or core tabletting.

Fexofenadine Tablets (30 mg/60 mg/180 mg) Allegra

Each tablet contains 30, 60, or 180 mg of fexofenadine hydrochloride (depending on the dosage strength) and the following excipients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The aqueous tablet film coating is made from hydroxypropyl methylcellulose, iron oxide blends, polyethylene glycol, povidone, silicone dioxide, and titanium dioxide.

Finasteride Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Finasteride	5.00
56.70	2	Lactose monohydrate	56.70
5.00	3	Starch 1500 (pregelatinized starch)	5.00
20.00	4	Avicel PH 102 (microcrystalline cellulose)	20.00
27.00	5	Maize starch	27.00
5.50	6	Primojel (sodium starch glycolate)	5.50
0.60	7	Magnesium stearate	0.60
3.50	8	Hypromellose (hydroxypropyl methylcellulose)	3.50
0.60	9	Talc, fine powder, extra pure	0.60
0.60	10	Titanium dioxide	0.60
–	11	Purified water	QS
0.20	12	Disperse blue E132	0.20
0.10	13	Triacetin	0.10
–	14	Ethanol 95%	QS
–	15	Purified water	QS

Manufacturing Directions

1. Make a slurry of starch paste in purified water.
2. Mix finasteride, maize starch, and Primojel.
3. Add lactose monohydrate with step 2, and pass through a 0.5-mm sieve.
4. Knead the mixed powder from steps 2 and 3 with starch paste to make a suitable wet mass. Pass the wet mass through a #8 sieve onto drying trays.
5. Dry the granules for approximately 3.5 hours at 55°C to get the desired LOD of 2.5%.
6. Grind the dried granules from step 5, and blend with magnesium stearate, previously sieved (250 mm) in a drum blender. Blend for 2 minutes.
7. Lubricate the granules.
8. Compress into 120-mg tablets, using a suitable punch.
9. Disperse hypromellose and triacetin in purified water and ethanol. Keep it overnight. Disperse talc, titanium dioxide, and colorant, and homogenize.
10. Coat the core tablets with the coating dispersion in step 9. (See Appendix.)

Fluconazole Tablets (50 mg/100 mg/200 mg), Diflucan

Diflucan tablets: These tablets contain 50, 100, or 200 mg of fluconazole and the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, povidone, croscarmellose sodium, FD&C Red No. 40 Aluminum Lake dye, and magnesium stearate.

Fluoxetine Tablets (20 mg)

Formulation: Fluoxetine HCl (BASF), 22.4 g; Ludipress, 176.0 g; magnesium stearate, 1.6 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press to tablets with low-compression force at 205 mg.

Fluoxetine Hydrochloride Tablets (10 mg/20 mg/40 mg), Prozac

Each Prozac® pulvule contains fluoxetine hydrochloride equivalent to 10 mg (32.3 mcmol), 20 mg (64.7 mcmol), or 40 mg (129.3 mmol) of fluoxetine. The pulvules also contain starch, gelatin, silicone, titanium dioxide, iron dioxide, and other inactive ingredients. The 10- and 20-mg pulvules also contain FD&C Blue No. 1, and the 40-mg pulvule also contains FD&C Blue No. 1 and FD&C Yellow No. 6.

Each Prozac tablet contains fluoxetine HCl equivalent to 10 mg (32.3 mmol) of fluoxetine. The tablets also contain microcrystalline cellulose, magnesium stearate, crospovidone, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and yellow iron oxide. In addition to the preceding ingredients, the 10-mg tablet contains FD&C Blue No. 1 Aluminum Lake and polysorbate 80.

Fluoxetine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Fluoxetine, use paroxetine hydrochloride	11.45
20.00	2	Microcrystalline cellulose	20.00
64.05	3	Lactose	64.05
4.00	4	Sodium starch glycolate	4.00
0.50	5	Magnesium stearate	0.50

Manufacturing Directions

1. Charge items 1 to 4 in a suitable blender, after passing through a 250-mm sieve.
2. Mix for 20 minutes.
3. Add item 5 after passing through a 250-μm mesh, and blend for 1 minute.
4. Compress.
5. Coat using HPMC coating, adding 6% to 10% tablet weight.
6. For a controlled-release formulation, use 5% to 12% of tablet core weight) %w/w of Eudragit RS 100 and 86.0; dibutyl phthalate 10.0; talc 4.0; FD&C Yellow No. 6 0.01; and triacetin 10.

Fluoxetine Hydrochloride Tablets (12.5 mg/25.0 mg), Controlled-Release Bilayer

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Fluoxetine, use paroxetine hydrochloride	28.59
15.00	2	Methocel K4M	15.00
62.00	3	Lactose monohydrate	62.00
3.00	4	Polyvinyl pyrrolidone	3.00
1.00	5	Magnesium stearate	1.00
1.00	6	Syloid 244	1.00
15.04	7	Compritol 888	15.04
29.32	8	Lactose monohydrate	29.32
4.00	9	Polyvinyl pyrrolidone	4.00
1.52	10	Magnesium stearate	1.52
–	11	Water, purified	QS
29.32	12	Methocel E5	29.32
0.08	13	Iron oxide	0.08

Manufacturing Directions

1. Two layers are made (items 1–6 and items 7–10, using item 11 as necessary for wet granulation).
2. Compress tablets on a Manesty triple-layer press.
3. Coat using items 12 and 13 on a Manesty triple-layer press.
4. Adjust item 3 for 12.5-mg strength.

Fluoxetine Hydrochloride Fast-Melt Tablets

Manufacturing Directions

1. Mix fluoxetine hydrochloride, 18%; sodium bicarbonate, 26%; citric acid anhydrous, 26%; microcrystalline cellulose, 4%; anhydrous lactose, 13%; xylitol, 10%; and Crodesta F160, 3%.
2. Dry above ingredients at an elevated temperature to significantly reduce the moisture content of each material.
3. Blend for 5 to 10 minutes and extruded in a hot melt extruder at approximately 70°C to 100°C to soften and melt the thermal binders (sucrose stearate and xylitol) and to form granules containing the effervescent ingredients.
4. Mix FLX-EFG (20–80 mesh), 50%; anhydrous lactose, 31%; microcrystalline cellulose, 10%; L-HPC LH-11, 5%; aspartame, 3%; redberry flavor, 0.4%; magnesium stearate, 0.5%; fumed silicon dioxide, 0.1%.
5. Screen the above granules and blend for 5 minutes prior to compression.
6. Fluoxethine HCl tablets are then compressed to a hardness of approximately 1 to 5 kPa (depending upon the dose of the active) and tablets disintegrate in water in approximately 15 to 40 seconds.

Fluvoxamine Maleate Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Fluvoxamine maleate	50.00
96.00	2	Mannitol	96.00
39.00	3	Maize starch	39.00
12.00	4	Pregelatinized starch (Starch 1500)	12.00
0.60	5	Colloidal silicone dioxide (Aerosil 200)	0.60
1.50	6	Sodium stearyl fumarate	1.50
QS	7	Purified water	QS

Manufacturing Directions

1. Make a slurry of starch paste in purified water.
2. Sift mannitol, fluvoxamine maleate, and the remaining part of maize starch through a 0.5-mm stainless steel sieve.
3. Knead the powder mix from step 2 with starch paste to get the desired wet mass. Then pass the mass through a #8 mesh to drying trays.
4. Dry at 50°C for 24 hours to reach an LOD of not more than 2%.
5. Pass the dried granules through a #16 mesh into a blending vessel.
6. Pass Starch 1500, Aerosil 200, and sodium stearyl fumarate through a 0.25-mm sieve into step 5. Blend for 2 minutes.
7. Compress into 200-mg tablets, using 12-mm punches.
8. Apply Eudragit L 100–55 coating. (See Appendix.)

Folic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Folic acid[a]	5.24
12.00	2	Maize starch (dried)[b]	12.00
5.26	3	Cellulose (microcrystalline) (Avicel™ PH102)	5.26
20.00	4	Cellulose (microcrystalline) (Avicel™ PH102)	20.00
1.50	5	Colloidal silicon dioxide (Aerosil® 200)	1.50
66.00	6	Lactose (spray-dried)[c]	66.00
2.50	7	Talc (fine powder)	2.50
2.50	8	Stearic acid (fine powder)	2.50

[a]Extra folic acid is added (0.08 mg/tablet) to compensate water (water NMT 8.0%).
[b]LOD: NMT 4.5% when dried at 120°C for 4 hours.
[c]Meets the USP NF, except particle size distribution, as follows: min 98%, 250 μm; 30% to 60%, 100 μm; max. 15%, 45 μm.

Manufacturing Directions

1. Folic acid must be protected from exposure to direct light.
2. Sift items 1 to 3 through a FitzMill (impact forward, high speed), and collect in a stainless steel drum.
3. Load the material into a blender, and mix for 3 minutes.
4. Sift items 4 to 8 through a 500-μm sieve using a sifter, and collect in a stainless steel drum.
5. Load this sieved material into a blender.
6. Mix for 5 minutes.
7. Unload the lubricated powder into a stainless steel drum. Check for small lumps or globules in the powder mix.
8. If required, pass the entire mass through a 500-μm sieve using a sifter, and mix for 1 minute in a blender.
9. Compress into 1.15-g tablets (hardness, 3–7 kPa), using 7-mm round flat punches.
10. For 1-mg tablets, compensate with lactose and compress as above.

Folic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Folic acid	5.00
195.00	2	Ludipress®	195.00
1.50	3	Magnesium stearate	1.50

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press into tablets using medium-compression force.
2. If the content uniformity does not meet the requirements, prepare a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation.
3. Compress into 213-mg tablets, using 8-mm biplanar punches.

Fosinopril Tablets (20 mg), Monopril

Monopril is available for oral administration as 10-, 20-, and 40-mg tablets. Inactive ingredients include lactose, microcrystalline cellulose, crospovidone, povidone, and sodium stearyl fumarate.

Fosinopril Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Fosinopril sodium	20.00
134.50	2	Lactose monohydrate	134.50
40.00	3	Microcrystalline cellulose (Avicel PH 102)	40.00
7.00	4	Crospovidone	7.00
4.50	5	Povidone	4.50
4.00	6	Sodium stearyl fumarate	4.00
–	7	Alcohol	QS

Note: For 10- and 40-mg strength, adjust with item 2.

Manufacturing Directions

1. Charge items 1 and 2 in a suitable mixer, after sifting, and mix for 20 minutes.
2. In a separate vessel, charge item 5 with a suitable quantity of item 7, and make a binder solution.
3. Add step 2 into step 1 to make a wet mass.
4. Dry the mass at 45°C to 70°C in a tray oven or a fluid-bed dryer, until the LOD is less than 3%.
5. Pass the dried granules through a hammer mill fitted with 0.03- to 0.07-in. screen.
6. Transfer screened granules into a suitable blender, add items 3 and 4, and blend for 1 to 3 minutes.
7. Compress into 200-mg tablets.

Fucidine Tablets (125 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
125.00	1	Fucidine	125.00
63.00	2	Dicalcium phosphate (Di-Tab)	63.00
2.50	3	Kollidon 90C	2.50
–	4	Isopropyl alcohol	30 mL
6.20	5	Kollidon CL	6.20
1.30	6	Aerosil 200	1.30
3.00	7	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate the mixture of items 1 and 2 with a solution of items 3 and 4. Dry and then pass the mixture through a 0.8-mm sieve.
2. Add the mixture of items 5 and 6, and press with low-compression force.
3. Compress into 200-mg tablets, using 9-mm punches. To accelerate the disintegration, the amount of Kollidon 90F should be reduced and Kollidon CL should be applied in intra- and extragranular forms.

Furazolidone Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Furazolidone	104.00
40.00	2	Lactose monohydrate	40.00
40.00	3	Dicalcium phosphate	30.00
2.00	4	Gelatin	2.00
2.00	5	Talc	2.00
2.00	6	Magnesium stearate	2.00
20.00	7	Starch (maize)	10.00
QS	9	Water, purified	QS

Manufacturing Directions

1. Sift items 1 to 3 through a 250-mm sieve, and charge into a suitable mixing vessel. Mix the items for 5 minutes.
2. Separately, charge a sufficient quantity of item 9. Add item 4, and dissolve it at 50°C. Add item 7, and mix until a smooth slurry is formed.
3. Add step 2 into step 1, and mix to form a wet mass suitable for granulation. Pass the mass through the sieve onto paper-lined trays, and dry at 60°C overnight to reach an LOD of not more than 2%.
4. Pass the dried granules through 1.19-mm mesh into a suitable blending vessel.
5. Sift items 5 and 6 through a 500-mm sieve, and blend for 2 minutes.
6. Compress into 200-mg tablets, using 8.3-mm punches.

Furosemide Tablets (40 mg), Lasix

Lasix is a diuretic that is an anthranilic acid derivative. Lasix for oral administration contains furosemide as the active ingredient. It also contains the following inactive ingredients: lactose, magnesium stearate, starch, and talc.

Furosemide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
40.00	1	Furosemide	40.00
158.00	2	Ludipress	158.00
2.00	3	Magnesium stearate	3.00

Manufacturing Directions

1. Mix all components, pass through 0.8-mm sieve, and press with low-compression force.
2. Compress into 205-mg tablets, using 8-mm biplanar punches.

Furosemide Tablets (40 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
40.00	1	Furosemide	40.00
83.10	2	Starch (maize)	83.10
30.00	3	Lactose monohydrate	30.00
1.00	4	Colloidal silicon dioxide (Aerosil 200)	1.00
14.00	5	Starch (maize)	14.00
2.00	6	Talc (fine powder)	2.00
20.00	7	Starch 1500 (pregelatinized starch)	20.00
1.60	8	Stearic acid	1.60
8.00	9	Starch (maize, dried)	8.00
0.30	10	Magnesium stearate	0.30
–	11	Purified water	70.00

Manufacturing Directions

Note: Avoid overmixing lubricants, otherwise hardness can be reduced.

1. Preparing starch paste: Make a smooth slurry of item 5 in 14 g of item 11 (25–30°C). Transfer the slurry into 56 g of item 11 (80–90°C) preheated in a steam jacket vessel under continuous stirring to get a translucent paste. Cool to 45°C to 50°C.
2. Sieving and dry mixing: Sift items 1, 3, 2, and 4 through a stainless steel 630-mm sieve in sifter. Load into mixer. Mix for 5 minutes at low speed.
3. Kneading: Knead the powder mix in the mixer with starch paste at low mixer speed for 3 minutes. Scrape sides and blades. Mix and chop at low speed for 3 minutes. Check the end point of granulation. If required, add more purified water to separate the granules, freeing big lumps.
4. Drying
   a. Unload the wet mass in stainless steel trays for drying. Dry the wet mass in an oven at 55°C for 10 hours. After 2 hours of drying, scrape the semidried granules to break lumps for uniform drying.
   b. Check the LOD. The LOD limit is 2% to 2.5%.
   c. If required, dry further at 55°C to meet the LOD limit.
   d. Transfer the dried granules to stainless steel drums.
5. Grinding and lubricating
   a. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect in stainless steel drums. Load the granules into the blender.
   b. Sift items 7 and 9 through a 500-µm sieve, using a sifter, and add it into the blender. Mix for 2 minutes.
   c. Sift items 6, 8, and 10 through a 500-µm sieve. Add 2 to 4 g of granules from bulk (step 5a).
   d. Mix in a polythene bag for 1 minute, and add to blender. Blend the mixture for 1 minute.
   e. Unload in stainless steel drums.
6. Compression: Check temperature and humidity before starting compression. As a limit, the temperature should not exceed 27°C, and the recommended relative humidity is 55% to 60%. Compress the granules using a rotary tabletting machine. The diameter should be 8.0-mm round punches.

Furosemide Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Furosemide	200.00
388.00	2	Ludipress	388.00
6.00	3	Magnesium stearate	6.00
6.00	4	Aerosil 200	6.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress into 618-mg tablets, using 12-mm biplanar punches.

Gabapentin Tablets (600 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
600.00	1	Gabapentin (10–125 mm)	600.00
24.00	2	Hydroxypropyl cellulose 75–150 cps (Klucel LF)	24.00
39.00	3	Corpovidone sodium (polyplasdone XL)	39.00
12.00	4	Calcium stearate	12.00
—	5	Alcohol	QS

Note: Compress 675 mg; for 800 mg, compress 900 mg.

Manufacturing Directions

1. Prepare a 7.5% solution of item 2 in item 5 by slowly adding item 2 to item 5 and mixing for 60 minutes at room temperature, until a clear homogenous solution is obtained
2. Charge item 1 in a fluid-bed dryer, and apply the solution in step 1 to granulate.
3. The process air volume is set to 100 cfm, and gabapentin is fluidized. When the product temperature reaches about 25°C to 28°C, the binder solution is applied. This solution is introduced through a pneumatically atomized nozzle positioned in the expansion chamber of the fluid-bed processor. The fluidized gabapentin particles are thus coated with the binder solution. While spraying, the process air volume is increased until the product temperature is stabilized between 12°C and 25°C. Once all the binder solution is applied, the process air volume is set to 150 cfm and the temperature to about 35°C to dry the coated particles. Drying is complete when the LOD, determined by a Computerized Moisture Analyzer Balance, is not more than 0.75%.
4. Pass the spray-coated particles through a comminuting mill.
5. Charge the sized particles in a V-blender with items 3 and 4. Blend these materials for 5 minutes.
6. Compress at a pressure of 12 to 14 kN. The hardness range of the 600-mg tablets is 13.3 to 14.9 kPa, with an average hardness of 14.2 kPa.
7. Optionally, coat the tablets with an aqueous dispersion such as an Opadry. (See Appendix.)

Galanthamine Hydrobromide Tablets (1 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.00	1	Galanthamine hydrobromide	1.00
32.00	2	Calcium phosphate	3.20
5.00	3	Lactose	5.00
15.00	4	Microcrystalline cellulose	15.00
0.70	5	Talc	0.70
0.70	6	Magnesium stearate	0.70

Note: For 5-mg strength, fill a proportionate amount or adjust with item 2.

Manufacturing Directions

1. Pass items 1 to 4 through a 250-μm sieve, and charge in a blending vessel. Mix the materials for 10 minutes.
2. Pass items 5 and 6 through a 250-μm sieve, and add to step 1. Blend this mixture for 1 minute.
3. Compress.

Garlic Extract + Thyme Extract Tablets Cores with Vitamin C (300 mg + 25 mg + 100 mg)

Formulation: Garlic extract, granulated (Aflopa), 300 g; thyme extract, powder (Aflopa), 25 g; ascorbic acid, crystalline (BASF), 100 g; Kollidon CL, 14 g; Ludipress, 268 g; magnesium stearate, 7 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press to tablets with medium-compression force at 714 mg.

Garlic Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
95.00	1	Calcium phosphate, dibasic	95.00
94.00	2	Lactose monohydrate	94.00
9.00	3	Kollidon® 30	9.00
25.00	4	Water	25.00
100.00	5	Dried garlic powder	100.00
2.00	6	Magnesium stearate	2.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 3 and 4, pass through an 0.8-mm sieve, add items 5 and 6, and press with low-compression force.
2. Compress into 312-mg tablets, using 9-mm biconvex punches.

Gemfibrozil Tablets (600 mg)

It is available in tablet form for oral administration. Each tablet contains 600 mg of gemfibrozil. Each tablet also contains calcium stearate; candelilla wax FCC; microcrystalline cellulose; hydroxypropyl cellulose; hydroxypropyl methylcellulose, USP; methylparaben, NF; Opaspray white; polyethylene glycol; polysorbate 80; propylparaben; colloidal silicon dioxide; and pregelatinized starch.

Gemfibrozil Tablets

Bill of Materials			
Scale (mg/tablet)	item	Material Name	Quantity/1000 Tablets (g)
600.00	1	Gemfibrozil	600.00
120.00	2	Microcrystalline cellulose (Avicel PH 101)	120.00
40.00	3	Gelatin	40.00
2.00	4	Diotilan	2.00
16.00	5	Calcium stearate	16.00
54.00	6	Sodium carboxymethyl starch	54.00
24.00	7	Talc	24.00
8.00	8	Silicon dioxide colloidal	8.00
9.50	9	Hydroxypropylmethyl cellulose	9.50
4.00	10	Polyethylene glycol 4000	4.00
0.50	11	Simethicone	0.50
2.00	12	Titanium dioxide	2.00
–	13	Water, purified	QS
–	14	Alcohol	QS

Manufacturing Directions

1. Charge the gemfibrozil and microcrystalline cellulose in a suitable whirlpool mixer and homogenize.
2. Prepare an aqueous solution of item 3 and add to step 1.
3. Prepare an ethanolic solution of item 4, add to step 1, and granulate.
4. Dry the granules. Screen the granules through a 0.8-mm sieve screen, return to the mixer, and homogenize with the components of the external layer (calcium stearate, sodium carboxymethyl starch, talc, colloidal silicic acid).
5. Compress the homogenized mixture into oval biconvex tablets weighing 864 mg.
6. Coat the tablets to a final weight of 880 mg, using items 9 to 12. (See Appendix for details.)

Ginkgo Extract Tablets (40 mg)

Formulation: Ginkgo biloba extract, dry powder, 240 g; (Biogen) Aerosil 200, 1 g; Kollidon CL, 4 g; Ludipress, 203 g; magnesium stearate, 2 g.

Manufacturing Directions

Mix the Ginkgo extract with Aerosil 200, add the other components, pass through a 0.8-mm sieve, and press to tablets with low-compression force at 254 mg.

Glibenclamide Tablets (2.5 mg)

Bill of Materials			
Scale (mg/tablet)	item	Material Name	Quantity/1000 Tablets (g)
2.50	1	Glibenclamide, micro (4.8% excess)	2.62
80.88	2	Lactose monohydrate	80.88
50.00	3	Starch (maize)	50.00
1.00	4	Colloidal silicon dioxide (Aerosil 200)	1.00
11.00	5	Starch (maize)	11.00
10.00	6	Starch (maize, dried)	10.00
3.00	7	Talc (fine powder)	3.00
0.50	8	Magnesium stearate	0.50
1.00	9	Colloidal silicon dioxide (Aerosil 200)	1.00
–	10	Purified water	55.00

Manufacturing Directions

Note: Glibenclamide is an oral hypoglycemic agent. During the processing of the batch, the person involved may take a glass full of 5% glucose solution, if required.

1. Preparing the binder
   a. Make a slurry of item 5 in 15 g of item 10 (40–45°C) in a stainless steel container. Check that it is free of lumps.
   b. Charge this slurry into 40 g of item 10 heated to 95°C into the vessel. Stir until there is complete gelatinization.
   c. Cool to 50°C.
2. Dry mixing: Load items 1 to 4 into the mixer (Diosna P 250). Mix and chop for 5 minutes at high speed.
3. Kneading
   a. Add starch paste to the mixer. Mix for 2 minutes, with the mixer at low speed and the chopper at high speed.
   b. Scrape the sides and blades. Mix and chop at low speed for 2 minutes. If required, add item 10.
   c. If required for breaking bigger lumps, pass the wet mass through a FitzMill, using sieve #24205 at medium speed, with knives forward.
4. Drying
   a. Spread the wet granules onto the trays. Load the trolleys onto the dryer. Dry the granules at 55°C for 10 hours or up to the moisture content limit. Scoop the granules after 4 hours of drying. Then rotate the trays—put the upper trays down and the down trays up—for uniform drying.
   b. Check the moisture content. Limit: not more than 2.5%.
5. Grinding: Pass the dried granules through a 1-mm sieve. Collect in a stainless steel drum and load in a blender.
6. Lubricating: Mix items 6, 7, and 9 in a polythene bag. Pass through a 250-μm sieve, using a sifter. Collect in a polythene bag. Add to the granules in the blender (step 5a). Mix this mixture for 5 minutes.
7. Pass item 8 through a 250-μm sieve. Collect in a polythene bag. Mix 2 g of granules with this, and add it to the blender in step 5a. Mix for 1 minute. Unload lubricated granules in a stainless steel drum.
8. Compressing: Compress the granules using a rotary tabletting machine. Toolings should be of length 10 mm × 5 mm. The weight of 10 tablets should be 1.6 g ± 3%.

Glibenclamide Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Glibenclamide, micro	5.00
78.50	2	Lactose monohydrate	78.50
50.00	3	Starch (maize)	50.00
1.00	4	Colloidal silicon dioxide (Aerosil 200)	1.00
10.00	5	Starch (maize)	10.00
11.00	6	Starch (maize, dried)[a]	11.00
3.00	7	Talc (fine powder)	3.00
0.50	8	Magnesium stearate	0.50
1.00	9	Colloidal silicon dioxide (Aerosil 200)	1.00
–	10	Purified water	55.00

[a]LOD: Not more than 4.5% when dried at 120°C for 4 hours.

Manufacturing Directions

Follow the manufacturing directions provided in the previous formulation.

Gliclazide Tablets (80 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
80.00	1	Gliclazide[a]	80.00
30.00	2	Starch (maize)	30.00
40.00	3	Lactose monohydrate	40.00
23.00	4	Dicalcium phosphate	23.00
4.00	5	Starch maize	40.00
1.80	6	Gelatin	1.80
0.06	7	Propyl paraben	0.06
0.06	8	Methyl paraben	0.06
1.00	9	Talc	1.00
1.00	10	Magnesium stearate	1.00
1.00	11	Sodium croscarmellose	1.00
1.00	12	Aerosil 200	1.00
1.00	13	Sodium starch glycolate	1.00
–	14	Water, purified, ca	50 mL

[a]Untapped bulk density of 0.69 to 0.70.

Manufacturing Directions

1. Screen items 1 to 4 through a 250-µm sieve.
2. Charge items 1 to 4 in a suitable vessel, and mix for 30 minutes.
3. In a separate vessel, heat item 14 to boiling, and add to it items 7 and 8 at 90°C to dissolve. Add item 6, and stir and mix to dissolve completely. Then allow the mixture to cool to room temperature.
4. Add item 5 to step 3, and stir and mix to obtain a lump-free slurry. Stop heating, and mix for another 5 minutes.
5. Add the slurry in step 4 to step 2. Stir at a high speed for 30 minutes to obtain a uniform wet mass.
6. Pass the wet mass through an 8-mm size sieve, and dry the mass in a fluid-bed dryer for 50 minutes at 50°C.
7. Pass the dried granules through #20 mesh (grind larger size), and transfer to a tumbler.
8. Sift items 11 to 13 through a 500-µm sieve, and sift item 10 through a 250-µm sieve. Then add these items to step 7, and blend for 10 minutes.
9. Compress into 180-mg tablets, using 3-mm punches.

Glimepiride Tablets (1 mg/2 mg), Amaryl

Amaryl® tablets contain the active ingredient glimepiride and the following inactive ingredients: lactose (hydrous), sodium starch glycolate, povidone, microcrystalline cellulose, and magnesium stearate. In addition, Amaryl 1-mg tablets contain ferric oxide red. Amaryl 2-mg tablets contain ferric oxide yellow and FD&C Blue No. 2 Aluminum Lake. Amaryl 4-mg tablets contain FD&C Blue No. 2 Aluminum Lake.

Glimepiride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.00	1	Glimepiride	2.00
109.90	2	Lactose monohydrate	109.90
35.00	3	Avicel PH 102 (microcrystalline cellulose PH 102)	35.00
8.00	4	Primojel (sodium starch glycolate)	8.00
0.75	5	Iron oxide yellow	0.75
0.85	6	Dispersed FD&C Blue No. 2	0.85
3.00	7	Polyvinyl pyrrolidone K-30 (PVP K-30)	3.00
0.50	8	Magnesium stearate	0.50
QS	9	Purified water	QS

Manufacturing Directions

1. Dissolve color in water and homogenize it. Then make a binding solution with PVP K-30.
2. Mix glimepiride with Primojel, iron oxide yellow, and dispersed blue E 132 (FD&C Blue No. 2), and pass through a 0.710-mm sieve.
3. Mix Avicel PH 102 with powder from step 2, and pass through a 0.710-mm sieve.
4. Mix lactose monohydrate with powder from step 3, and pass through a 0.710-mm sieve.
5. Knead the powder with binding solution to get the desired granules.
6. Dry the granules at 60°C for 12 hours to obtain an LOD of not more than 3%.
7. Pass the dried granules in a Frewitt granulator using a 1.25-mm sieve.
8. Compress into 160-mg tablets, using 12-mm punches. For 1-mg and 3-mg strengths, compress the same weight and adjust with lactose.

Glipizide Tablets (5 mg), Glucotrol

Immediate-release tablets—Each immediate-release tablet for oral administration contains glipizide, 5 or 10 mg, and the following inactive ingredients: cornstarch, anhydrous lactose, microcrystalline cellulose, colloidal silicon dioxide, and stearic acid.

Extended-release tablets—Inert ingredients in the formulations are as follows: polyethylene oxide, hydroxypropyl methylcellulose, magnesium stearate, sodium chloride, red ferric oxide, cellulose acetate, polyethylene glycol, and Opadry white and black ink. Glucotrol XL extended-release tablets are similar in appearance to conventional tablets. Each tablet, however, consists of an osmotically active drug core surrounded by a semipermeable membrane.

The core is divided into two layers: an "active" layer containing the drug and a "push" layer containing pharmacologically inert (but osmotically active) components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the drug layer, resulting in the release of drug through a small, laser-drilled orifice in the membrane on the drug side of the tablet. The Glucotrol XL extended-release tablet is designed to provide a controlled rate of delivery of glipizide into the GI lumen, which is independent of pH or GI motility. The function of the Glucotrol XL extended-release tablet depends upon the existence of an osmotic gradient between the contents of the bilayer core and fluid in the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant and then gradually falls to zero. The biologically inert components of the tablet remain intact during drug GI transit and are eliminated in the feces as an insoluble shell.

Glipizide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Glipizide, 10% excess	6.00
43.00	2	Starch (maize)	43.00
50.00	3	Lactose monohydrate	50.00
28.00	4	Dicalcium phosphate	28.00
2.00	5	Gelatin	2.00
0.075	6	Propyl paraben	0.075
0.075	7	Methyl paraben	0.075
2.00	8	Magnesium stearate	2.00
2.00	9	Sodium starch glycolate	2.00
–	10	Water, purified, ca	50 mL

Manufacturing Directions

1. Pass items 1 to 4 through a 250-μm sieve, and charge in a suitable blender. Mix these items for 30 minutes.
2. In a separate vessel, charge item 10 and bring to boil by heating. Add items 6 and 7, and stir to dissolve at 90°C. Allow to cool to 50°C.
3. Add items 4 and 5 to step 2. Stir and mix vigorously at 50°C to obtain a smooth paste without lumps. Allow the mixture to cool to room temperature.
4. Transfer step 3 to step 1, and mix to obtain a wet mass.
5. Transfer the wet mass onto trays, and dry in an oven at 60°C overnight to an LOD of not more than 2.5%.
6. Pass dried granules through #20 mesh, and collect in a tumble blender.
7. Pass item 9 through a 500-μm sieve and item 8 through a 250-μm sieve. Add to step 8. Blend for 2 minutes.
8. Compress into 120-mg tablets, using 6-mm punches.

Glipizide Tablets CR (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Xanthan gum	20.00
30.00	2	Locust bean gum	30.00
108.00	3	Dextrose	108.00
8.30	4	Surelease®	8.30
–	5	Water, purified	–
5.00	6	Glipizide	5.00
3.30	7	Sodium stearyl fumarate	3.30
43.70	8	Dextrose powder, anhydrous	43.70

Manufacturing Directions

1. Charge items 1 to 3 in a mixer, and mix at high speed for 3 minutes using a chopper blade.
2. In a separate vessel, add and mix item 4 with item 5, and spray the mixture gradually into step 1 while mixing at high speed to provide even distribution and to produce a suitable wet mass.
3. Dry the wet mass in a fluid-bed dryer to an LOD of less than 10% (preferably less than 5%).
4. Pass the dried granules through a 20-mesh screen, and transfer them to a mixing vessel (V-blender). Blend for 10 minutes.
5. Add items 6 and 8 to step 4 after passing through a 250-μm sieve. Blend the mixture for 15 minutes.
6. Add item 7, and blend for 3 minutes.
7. Compress into 220-mg tablets, using a suitable punch at 5-kPa hardness.

Glyburide and Metformin Tablets (250 mg/500 mg; 1.25 mg/2.50 mg), Glucovance

The glyburide used in Glucovance has a particle size distribution of 25%, with an undersize value not more than 6 mm, a 50% undersize value not more than 7 to 10 mm, and a 75% undersize value not more than 21 μm. Glucovance is available for oral administration in tablets containing 1.25 mg glyburide with 250 mg metformin hydrochloride, 2.5 mg glyburide with 500 mg metformin hydrochloride, and 5 mg glyburide with 500 mg metformin hydrochloride. In addition, each tablet contains the following inactive ingredients: microcrystalline cellulose, povidone, croscarmellose sodium, and magnesium stearate. The tablets are film coated, which provides color differentiation.

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Metformin hydrochloride	250.00
1.25	2	Glyburide	1.25
7.00	3	Croscarmellose sodium	7.00
10.00	4	Povidone	10.00
28.25	5	Microcrystalline cellulose (Avicel PH 101)	28.25
2.25	6	Magnesium stearate	2.25
—	7	Water, purified	QS

Note: For 2.5/500 strength, increase the fill volume to double.

Manufacturing Directions

1. Charge croscarmellose sodium and glyburide in a suitable blender, and blend for 10 minutes.
2. In a separate vessel, charge metformin hydrochloride and magnesium stearate (99.5%:0.5% w/w) using high shear force.
3. In a separate container, add item 4 and an appropriate quantity of item 7 (1:10 ratio) to make paste.
4. Add the paste in step 3 to steps 1 and 2 combined and mixed prior to the addition of the paste.
5. Granulate using a high-shear mixer. Dry the granules in a fluid-bed dryer at approximately 60°C to achieve a moisture content of not more than 2%.
6. Size the dried granules with a screening mill, and mix with the microcrystalline cellulose using a tumble mixer.
7. Incorporate magnesium stearate as a lubricant, using a tumble mixer (step 6) to produce the final compression blend.
8. Compress 300 mg for 250/1.25 and 600 mg for 500/2.5 tablets.
9. Coat the tablets using an HPMC-based film-coating system, until the required amount of film coat is applied. The typical level of a film coat applied to the tablets is 2% w/w. (See Appendix for details.)

Glyburide Tablets (5 mg), Micronase

Micronase® tablets (standard glyburide)—mmase tablets contain glyburide, which is an oral blood-glucose-lowering drug of the sulfonylurea class. Glyburide is a white, crystalline compound, formulated as mmase tablets of 1.25-, 2.5-, and 5-mg strengths for oral administration. The inactive ingredients of the compound are colloidal silicon dioxide, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, sodium alginate, and talc. In addition, the 2.5-mg tablet contains aluminum oxide and FD&C Red No. 40. The 5-mg tablet contains aluminum oxide and FD&C Blue No. 1.

Glynase® PresTab® tablets (micronized glyburide)—Glynase PresTab tablets contain micronized (smaller particle size) glyburide, which is an oral blood-glucose-lowering drug of the sulfonylurea class. Glyburide is a white, crystalline compound, formulated as Glynase PresTab tablets of 1.5-, 3-, and 6-mg strengths for oral administration. The inactive ingredients of the compound are colloidal silicon dioxide, cornstarch, lactose, and magnesium stearate. In addition, the 3-mg strength contains FD&C Blue No. 1 Aluminum Lake, and the 6-mg tablet contains D&C Yellow No. 10 Aluminum Lake.

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Glyburide, micronized (ca 5 m^2/g)	5.25
140.00	2	Lactose spray dried (foremost spray-dried lactose #315 or #316)	140.00
28.60	3	Starch (maize)	28.60
0.75	4	Magnesium stearate	0.75

Manufacturing Directions

1. Charge items 1 to 3 in a suitable mixing vessel. Mix for 20 minutes, until a homogenous mixture is reached.
2. Sift item 4 through a 250-μm mesh and add to step 1. Blend slowly for 2 minutes.
3. Compress into ca 175-mg tablets, using a suitable punch.

Griseofulvin Tablets (125 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
125.00	1	Griseofulvin, micronized	125.00
250.00	2	Ludipress	250.00
10.00	3	Polyethylene glycol 6000 powder	10.00
19.00	4	Aerosil 200	19.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, and mix.
2. Press with low-compression force, applying a vibrating hopper.
3. Compress into 367-mg tablets, using 12-mm biplanar punches.
4. The flowability of the tabletting mixture can be increased by adding higher amounts of Ludipress and Aerosil 200.

Griseofulvin Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Griseofulvin	500.00
100.00	2	Kollidon VA 64	100.00
–	3	Dimethylformamide	7500.00
75.00	4	Kollidon CL	75.00
75.00	5	Lactose monohydrate	75.00
5.00	6	Magnesium stearate	5.00
5.00	7	Aerosil 200	5.00

Manufacturing Directions

1. Dissolve the mixture of items 1 and 2 in item 3.
2. Evaporate to dryness.
3. Pass the obtained coprecipitate through a 0.5-mm sieve.
4. Mix with items 4 to 7 and press with low-compression force.
5. Compress into 751-mg tablets, using 12-mm biplanar punches.

Guaifenesin Tablets

Manufacturing Directions

1. Inner tablet: Guaifenesin, 175.0 mg; microcrystalline cellulose, 35.1 mg; crosspovidone, 35.0 mg; polyvinylpyrrolidone, 7.3 mg; talc, 2.3 mg; zinc stearate, 2.3 mg. Total 257.0 mg.
2. Outer Tablet: Guaifenesin, 425.0 mg; hydroxypropyl-methylcellulose K4M, 139.9 mg; stearic acid, 30.0 mg; zinc stearate, 5.4 mg. Total 600.3 mg.
3. The inner tablet is made by oscillating guaifenesin and half of the polyvinylpyrrolidone through a 30-mesh screen.
4. The blend is then transferred to a pharmaceutical-grade blender and mixed until it is of uniform consistency.
5. It is then granulated with polyvinylpyrrolidone that had been previously dissolved in a sufficient amount of purified water to make a solution of about 8% to about 12% of polyvinylpyrrolidone.
6. This mixture is discharged and dried in a forced air oven at 40°C until the water content is less than 1%.
7. The dried granulation is then oscillated through a 12-mesh screen and returned to the blender.
8. The remaining polyvinylpyrrolidone, microcrystalline cellulose, and talc are added to this dried granulation and mixed until it is of uniform consistency.
9. Finally, zinc stearate is added and the mixture is mixed until it is of uniform consistency.
10. This mixture is then compressed into inner tablets, using a standard tabletting press.
11. The outer tablet is made by first passing guaifenesin through an oscillator equipped with a 30-mesh screen.
12. After this step, guaifenesin is transferred to a blender and hydroxypropyl methylcellulose K4M and stearic acid are added to it. It is mixed until uniform.
13. Zinc stearate is added and the mixture is blended until uniform.
14. The mixture of ingredients that comprise the outer tablet is compressed around the already formed inner tablet, on a standard compression coating tablet press.

Guaifenesin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Percent (w/w) ((w/w)Quantity/1000 Tablets (g)
69.77	1	Guaifenesin USP	69.77
16.00	2	Starch 1500	16.00
9.48	3	Microcrystalline Cellulose NF	9.48
4.00	4	Starch 1500	4.00
0.50	5	Stearic Acid NF	0.50
0.25	6	Magnesium stearate	0.25
100.00	7	Total	100.00

Manufacturing Directions

1. Granulation: items 1 and 2 are preblended for 2 minutes prior to granulating with water to appropriate moisture.
2. Wet mass for 3 minutes.
3. Size the granulation.
4. Lubricant passed through a 60-mesh screen prior to blending.
5. Colloidal silicon dioxide is passed through a 30-mesh screen along with the MCC.
6. All the ingredients except the lubricant are blended for 10 minutes.

Heparin Tablets*

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.08	1	Heparin (low molecular weight)	0.08
0.40	2	Water	0.40
0.92	3	Monoglyceride	0.92
1.24	4	CPL-Galactolipid	1.24
1.40	5	Palm kernel stearin	1.40

*Other proportions may include heparin 0.18, 0.21 and proportionally increased excipients. Lipid materials Trade name and source Galactolipids from oats (CPL-Galactolipid; Lipid Technologies Provider AB, Karlshamn, Sweden) Medium chain monoglyceride (Akoline MCM; Karlshamns AB, Karlshamn Sweden) Palmkernel stearin (fraction of palmkernel oil; Karlshamns AB, Karlshamn Sweden) Heparin (low molecular weight; Calbiochem, p. no. 375097 Hydrogenated cotton seed oil (Akofine NF; Karlshamns AB, Karlshamn Sweden)

Manufacturing Directions

1. The ingredients are blended and the mixture melted by heating to a temperature of 60°C and stirred at this temperature for 5 hours when all heparin had dissolved.
2. Aliquots (0.24 g) of the melted phase are cast in a mould covered with hydrogenated triglyceride (Akofine NF) powder. The mould is cooled in a freezer and the tablets recovered.

Herbal Hemorrhoid Tablets

Manufacturing Directions

1. Initially genera Glycyrrhizae Radix, Rhei Rhizoma, Ephedrae Herba, Moutan Radicis Cortex, Menthae Herba, Pinelliae Rhizoma, Pasoniae Radix, Acontii Tuber, Corni Fructus, Gypsum, Ginseng Radix and Pelladendri Radix, respectively, are washed with water to remove sand, clay, dust and the like.
2. These natural substances are cleaned and dried to a moisture content of approximately 5%.
3. 168 g of Glycyrrhizae Radix, 104 g of Rhei Rhizoma, 104 g of Ephedrae Herba, 168 g of Moutan Radicis Cortex, 104 g of Menthae Herba, 168 g of Pinelliae Rhizoma, 56 g of Pasoniae Radix, 56 g of Acontii Tuber, 56 g of Corni Fructus, 168 g of Ginseng Radix, and 104 g of Pelladendri Radix are cut into a particle size of about 1 cm and mixed together.
4. To the mixture mentioned above are added, 104 g of Testidinis Carapax, 56 g of Natrii Sulfas, 168 g of Gypsum, 56 g of Cinnabaris, and 256 g of Talcum.
5. Thereafter, this mixture is placed in an extractor having an aromatic vapor collector.
6. 12 L of water is added to approximately 2 kg of the mixture in the extractor.
7. The mixture in the extractor is heated up to about 80°C for 1 hour and then extracted.
8. The aqueous mixture is filtered first in a centrifugal separator and is then filtered again in a microfilter.
9. The aromatic vapor distilled from the aqueous mixture is condensed and added as an aromatic liquid to the filtrate.
10. The filtrate is evaporated through an automatic vacuum evaporator to a moisture content of about 30% to produce an extract that is useful as an antihemorrhoidal composition in extract form.
11. At this time, the concentrated liquid is dried through a dry sprayer to produce a granulated formulation, a tablet formulation, a pill formulation, an ointment formulation, or the like, for use as an antihemorrhoid medicine.

Horsetail Extract Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
450.00	1	Horsetail extract (powder)	456.00
14.00	2	Kollidon® VA 64	14.00
5.00	3	Lutrol F 68	5.00
QS	4	Isopropanol	~120.00
14.00 g	5	Kollidon® CL	14.00
QS	6	Magnesium stearate	QS

Manufacturing Directions

1. Granulate the extract (item 1) with solution of items 2 to 4, then dry, pass through an 0.8-mm sieve, mix with items 5 and 6 and press with high-compression force.
2. Compress into 489-mg tablets, using 12-mm biplanar punches.

Hydrochlorothiazide and Potassium Chloride (50 mg/300 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Hydrochlorothiazide	50.00
300.00	2	Potassium chloride	300.00
15.00	3	Kollidon CL	15.00
2.00	4	Aerosil 200	2.00
2.00	5	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve. Mix the components, and press.
2. Compress into 369-mg tablets, using 9-mm punches.

Hydrochlorothiazide Fast-Melt Tablets

Manufacturing Directions

1. Mix hydrochlorothiazide, 20%; sodium bicarbonate, 25%; citric acid anhydrous, 25%; Avicel PH113, 18%; xylitol, 10%; Crodesta F160, 2%.
2. Dry at elevated temperatures to significantly reduce the moisture content of each material.
3. Blend for 10 minutes and extrude in a hot melt extruder at 70°C to 100°C to soften and melt the thermal binders (sucrose stearate and xylitol) and to form granules containing the effervescent ingredients.
4. Mix HYD-EFG (30–60 mesh), 50%; microcrystalline cellulose, 31%; anhydrous lactose, 10%; AcDiSol, 2.5%; L-HPC LH-11, 2.5%; aspartame, 3%; redberry flavor, 0.4%; magnesium stearate, 0.5%; Cab-O-Sil M5P 0.1%.
5. The above granules are then screened and blended with the ingredients for 5 minutes prior to compression.
6. Hydrochlorothiazide tablets are then compressed to a hardness of approximately 1 to 3 kPa and tablets disintegrate in water in approximately 15 to 35 seconds.

Hydrochlorothiazide Tablets (50 mg)

Hydrochlorothiazide is supplied as 25-, 50-, and 100-mg tablets for oral use. Each tablet contains the following inactive ingredients: calcium phosphate, FD&C Yellow No. 6, gelatin, lactose, magnesium stearate, starch, and talc.

Hydrochlorothiazide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Hydrochlorothiazide	50.00
280.00	2	Ludipress	280.00
2.00	3	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all components, and pass through a 0.8-mm sieve.
2. Compress with a low-compression force. Compress into 328-mg tablets, using 8-mm punches.

Hydrochlorothiazide Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Hydrochlorothiazide	50.00
422.00	2	Lactose monohydrate	422.00
8.00	3	Kollidon 90F	8.00
—	4	2-Propanol	38 mL
15.00	5	Kollidon CI	15.00
2.00	6	Magnesium stearate	2.00

Manufacturing Directions

1. Granulate the mixture of items 1 and 2 with item 2, Pass through a 0.8-mm sieve, add items 5 and 6, and press with low-compression force.
2. Compress into 495-mg tablets, using 12-mm biplanar punches.

Hydrochlorothiazide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Hydrochlorothiazide	50.00
64.76	2	Dicalcium phosphate	64.76
64.76	3	Lactose	64.76
20.00	4	Starch 1500	20.00
0.50	5	Magnesium stearate	0.50

Manufacturing Directions

1. All the materials (except magnesium stearate) are blended for 15 minutes.
2. Magnesium stearate is then added and blended for 5 additional minutes.
3. Compress 200 mg tablets; for 25.00-mg strength, compress 100 mg.

Hydrocodone and Acetaminophen Tablets (5.0 mg/500 mg; 7.50 mg/750 mg)

Each tablet contains hydrocodone bitartrate (5 mg) and acetaminophen (500 mg). Other ingredients include colloidal silicon dioxide, cornstarch, croscarmellose sodium, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, povidone, and stearic acid. Each extra-strength tablet contains hydrocodone bitartrate (7.5 mg) and acetaminophen (750 mg). Other ingredients include colloidal silicon dioxide, cornstarch, croscarmellose sodium, magnesium stearate, povidone, and stearic acid.

Hydrocodone and Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
750.00	1	Acetaminophen powder	750.00
7.50	2	Hydrocodone bitartrate	7.50
12.00	3	Colloidal silicon dioxide	12.00
154.40	4	Microcrystalline cellulose	154.40
64.00	5	Croscarmellose sodium	64.00
26.00	6	Hydroxypropyl methylcellulose	26.00
124.80	7	Starch (maize)	124.80
4.00	8	Magnesium stearate	4.00
–	9	Water, purified	QS

Note: For 500 mg item 1 and 5.0 mg item 2 formulation, adjust fill volume.

Manufacturing Directions

1. Pass hydrocodone bitartrate through a #20 mesh. Pass acetaminophen and colloidal silicon dioxide (50%) through a Frewitt SG Turbo Sieve equipped with a 1.0-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-lined collecting drum at speed setting 5 (approximately 1030 rpm).
2. Pass microcrystalline cellulose (50%), croscarmellose sodium (50%), cornstarch (66%), and hydroxypropyl methylcellulose through the Turbo Sieve at the same settings as in step 1. Charge the screened powders into a Lodige MGT-600 mixer, and mix for 5 minutes with the plow speed at approximately 103 rpm and no choppers.
3. Add water to the mixer over a 10-minute period, using a stainless steel transfer container with a valve, while mixing with the plows at about 103 rpm and the choppers at slow speed.
4. Mix the wet mass for another 15 minutes, until a wattmeter reading of 15 to 16 MkW is reached.
5. Dry the material. Preheat a Glatt fluid-bed dryer by running it for 2.5 minutes at 60°C inlet air temperature at 3500 m^3/h. Set the exhaust blower bypass speed at about 40%, the filter shaking interval for about 2 minutes, and the filter shaking duration for 5 seconds. Transfer the material in the dryer for drying. Decrease the inlet air to 2500 m^3/h and the inlet air temperature to 55°C after 30 minutes. Dry the material until an LOD of less than 0.5% is reached.
6. Pass the dried granulation through a FitzMill using a #20 mesh wire screen with knives forward, at medium speed.
7. Pass the remaining microcrystalline cellulose and the colloidal silicon dioxide through a Frewitt SG Turbo Sieve equipped with a 1-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-lined collecting drum. The speed setting is at approximately 1030 rpm.
8. Add magnesium stearate, and mix for 3 minutes.
9. Compress using a 13/32-in. round tooling.

Hydrocodone and Ibuprofen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Ibuprofen	400.00
15.00	2	Hydrocodone bitartrate	15.00
12.00	3	Colloidal silicon dioxide	12.00
154.40	4	Microcrystalline cellulose	154.40
64.00	5	Croscarmellose sodium	64.00
26.00	6	Hydroxypropyl methylcellulose	26.00
124.80	7	Starch (maize)	124.80
4.00	8	Magnesium stearate	4.00
–	9	Water, purified	QS

Manufacturing Directions

1. Pass hydrocodone bitartrate through a #20 mesh. Pass ibuprofen and colloidal silicon dioxide (50%) through a Frewitt SG Turbo Sieve equipped with a 1.0-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-lined collecting drum at speed setting 5 (approximately 1030 rpm).
2. Pass microcrystalline cellulose (50%), croscarmellose sodium (50%), cornstarch (66%), and hydroxypropyl methylcellulose through the Turbo Sieve at the same settings as in step 1. Charge screened powders into a Lodige MGT-600 mixer, and mix for 5 minutes with the plow speed at approximately 103 rpm and no choppers.
3. Add water to the mixer over a 10-min period, using a stainless steel transfer container with a valve while mixing with the plows at about 103 rpm and the choppers at slow speed.
4. Mix the wet mass for another 15 minutes until a wattmeter reading of 15 to 16 MkW is reached.
5. Dry the material using a preheated Glatt fluid-bed dryer; preheat by running the dryer for 2.5 minutes at 60°C inlet air temperature at 3500 m^3/h. Set the exhaust blower bypass speed at about 40%, the filter shaking interval for about 2 minutes, and the filter shaking duration for 5 seconds. Transfer the material in the dryer for drying. Decrease the inlet air to 2500 m^3/h and the inlet air temperature to 55°C after 30 minutes. Dry the material until an LOD of less than 0.5% is reached.
6. Pass the dried granulation through a FitzMill using a #20 mesh wire screen, with knives forward, at medium speed.
7. Pass the remaining microcrystalline cellulose and the colloidal silicon dioxide through a Frewitt SG Turbo Sieve equipped with a 1-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-lined collecting drum. The speed setting is at approximately 1030 rpm.
8. Add magnesium stearate, and mix for 3 minutes.
9. Compress using a 13/32-in. round tooling.

Hydromorphone Hydrochloride Fast-Melt Tablets

Manufacturing Directions

1. Mix hydromorphine hydrochloride 15%, sodium bicarbonate 28%, citric acid anhydrous 24%, microcrystalline cellulose 10%, anhydrous lactose 11%, xylitol 10%, sucrose stearate 2%.
2. Mix the above ingredients and dry at elevated temperatures to significantly reduce the moisture content of the material.
3. Blend for 10 minutes and extruded in a hot melt extruder at 70°C to 100°C to soften and melt the thermal binders (sucrose stearate and xylitol) and to form granules containing the effervescent ingredients.
4. Mix HDM-EGF (30–60 mesh), 50%; microcrystalline cellulose, 18%; anhydrous lactose, 18%; cross povidone, 5%; L-HPC LH-11, 5%; aspartame, 3.25%; natural orange powder, 0.15%; magnesium stearate, 0.45%; fumed silicon dioxide, 0.15%.
5. Screen the above granules and blend for 5 minutes prior to compression.
6. Hydromorphone tablets are compressed to a hardness of approximately 1 to 5 kPa (depending upon the dose of the active) and tablets disintegrate in water in approximately 15 to 35 seconds.

Hydroxyzine Tablets

Inert ingredients for the tablets are acacia, carnauba wax, dibasic calcium phosphate, gelatin, lactose, magnesium stearate, precipitated calcium carbonate, shellac, sucrose, talc, and white wax. The 10-mg tablets also contain sodium hydroxide, starch, titanium dioxide, and FD&C Yellow No. 6 Lake. The 25-mg tablets also contain starch and velo dark green. The 50-mg tablets also contain starch and velo yellow. The 100-mg tablets also contain alginic acid, FD&C Blue No. 1, polyethylene glycol, and FD&C Red No. 3.

Hyoscine Butylbromide Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.000	1	Hyoscine butyl bromide	10.000
16.500	2	Lactose monohydrate	16.500
28.000	3	Lactose monohydrate, dense	28.000
17.930	4	Starch (maize)	19.720
2.240	5	Povidone (PVP K-30)	2.240
–	6	Purified water	5.080
0.400	7	Magnesium stearate	0.400
2.740	8	Pregelatinized starch (Starch 1500)	2.740

Manufacturing Directions

Caution: Hyoscine butylbromide is a potent smooth muscle relaxant. Inhalation can produce toxic effects. Strictly adhere to the usage of mask, gloves, and goggles.

1. Preparation of binding solution: Dissolve item 5 in item 6 by stirring to make a clear solution. Use the stirrer at medium speed in a stainless steel container.
2. Dry mixing: Check to see if hyoscine butyl bromide is in fine powder form. If not, pass through a 630-μm sieve using a sifter. Load items 1, 2, 4, and 3 into the mixer, and mix for 5 minutes with the mixer and chopper at low speed.
3. Wet massing
   a. Add the binding solution to the dry powder in the mixer while mixing at low speed. When the addition is over, mix and chop for a further 2 minutes at high speed.
   b. Scrape the lid and blade, and check for a satisfactory wet mass. Add more item 6 if required to get a satisfactory wet mass.
4. Drying
   a. Spread the granules onto stainless steel trays to a thickness of one-third of the tray thickness, and load the trays on the trolley.
   b. Load the trolleys into the oven. Dry at 60°C for 16 hours. Turn the granules after 3 to 4 hours so as to ensure uniform drying of the granules.
   c. Check the moisture content of the dried granules, keeping in mind the limit of 1.0% to 1.5%.
5. Grinding: Pass the dried granules through a granulator equipped with a 1.0-mm sieve.
6. Lubricating
   a. Mix items 7 and 8 in a polythene bag, and pass through a 250-μm sieve using a sifter. Collect the material in a stainless steel container.
   b. Load the sized granules from step 5a along with sieved powder from step 6a into the drum mixer. Mix these items for 3 minutes.
   c. Unload into stainless steel drums.
7. Compression: Compress the granules using a rotary tabletting machine (with dies and punches: 6 mm, concave, plain punches with fill weights of 780 mg).
8. Coating: Sugar coat the tablets. (See Appendix.)

Ibuprofen and Domperidone Maleate Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Ibuprofen	200.00
7.50	2	Domperidone maleate	7.50
750.00	3	Sucrose	750.00
50.00	4	Sorbitol	50.00
1.12	5	Silica fumed	1.12
6.75	6	Stearic acid	6.75

Manufacturing Directions

1. Combine items 1 to 6 to form a homogeneous blend.
2. Compress by direct compression to form a chewable tablet containing 200 mg of ibuprofen and 7.5 mg of domperidone maleate.
3. Compression weight approximately 1015 mg per tablet.

Ibuprofen and Domperidone Maleate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Ibuprofen	200.00
5.00	2	Domperidone maleate	5.00
20.00	3	Microcrystalline cellulose	20.00
30.00	4	Croscarmellose sodium	30.00
2.00	5	Magnesium stearate	2.00
2.00	6	Hydrogenated cottonseed oil	2.00
60.00	7	Tricalcium phosphate	60.00
10.00	8	Hydroxypropyl cellulose	10.00
10.00	9	Hydroxypropylmethyl cellulose	10.00
112.00	10	Sorbitol	112.00

Manufacturing Directions

1. Ibuprofen, domperidone maleate, tricalcium phosphate, hydroxypropyl cellulose, croscarmellose sodium, and microcrystalline cellulose are sieved and blended to form a homogeneous mixture
2. The mixture is granulated to a suitable end point with water and dried.
3. The dried granules are blended with magnesium stearate
4. The lubricated granules are compressed to form tablet cores each containing 200 mg of ibuprofen and 5 mg of domperidone or each containing 400 mg of ibuprofen and 10 mg of domperidone.
5. The tablet cores are coated with a conventional film coating.

Ibuprofen and Domperidone Sustained-Release Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Ibuprofen	400.00
20.00	2	Domperidone maleate	20.00
100.00	3	Xanthan gum	100.00
12.00	4	Hydroxypropyl methylcellulose	12.00
6.00	5	Stearic acid	6.00
2.00	6	Colloidal silicon dioxide	2.00

Manufacturing Directions

1. Granulate the hydroxypropyl methylcellulose and ibuprofen with approximately 20% of the total content of xanthan gum using water as the granulating agent.
2. The ibuprofen granule is combined with the remainder of the xanthan gum and the other ingredients and compressed into tablets containing 400 mg of ibuprofen and 20 mg of domperidone.

Ibuprofen and Hydrocodone Bitartarate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Ibuprofen	200.00
7.52	2	Hydrocodone Bitartarate	7.52
6.00	3	Colloidal silicon dioxide	6.00
77.20	4	Microcrystalline cellulose	77.20
32.00	5	Sodium croscarmellose	32.00
13.00	6	Hydroxypropyl methylcellulose	13.00
62.40	7	Corn startch	62.40
2.00	8	Magnesium stearate	2.00

Manufacturing Directions

1. Hydrocodone bitartrate is passed through a #20 mesh handscreen.
2. Ibuprofen (50%) and colloidal silicon dioxide (0.75%) are passed through a Frewitt SG Turbo Sieve equipped with a 1.0-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-line collecting drum at speed setting 5 (approximately 1030 rpm).
3. Microcrystalline cellulose (9.5%), croscarmellose sodium (4.0%), cornstarch (10.6%), and hydroxypropyl methylcellulose (3.3%) are passed through the turbosieve at the same settings.
4. The screened powders are introduced into a Lodige MGT-600 mixer and mixed for 5 minutes with plow speed at approximately 103 rpm and NO choppers.
5. Water is added to the mixer over a 10-minute period using a stainless steel transfer container with a valve while mixing with plows at about 103 rpm and choppers at slow speed.
6. The wet material is mixed for another 15 minutes until a Wattmeter of 15 to 16 kW is reached.
7. To dry the material, a Glatt fluid-bed dryer is preheated by running it for 2.5 minutes at 60°C, with inlet air temperature at 3500 m^3/h. The exhaust blower bypass speed is set at about 40%, the filter shaking interval for about 2 minutes, and the filter shaking duration is for 5 seconds. The material is placed in the dryer for drying. The inlet air is decreased to 2500 m^3/h and the inlet air temperature to 55°C. after 30 minutes. The material is dried until an LOD of less than 0.5% is reached.
8. The dried granulation is passed through a FitzMill using a #20 mesh wire screen 1536-0200 with knives forward at medium speed.
9. The remaining microcrystalline cellulose and the colloidal silicon dioxide is passed, alternatively, through a Frewitt SG Turbo Sieve equipped with a 10-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-lined collecting drum. The speed setting is set at approximately 1030 rpm.
10. The milled granulation, the remaining croscarmellose, the screened colloidal silicon dioxide, the microcrystalline cellulose, and the cornstarch are introduced into a Littleford FKM-3000 mixer through a chute and mixed for 3 minutes at fast speed.
11. Magnesium stearate is passed through a Frewitt Turbo Sieve equipped with a 1.0-mm round-hold screen, an angle bar, a cloth skirt and a polyethylene line collecting drum. The speed setting is at about 1030 rpm.
12. Magnesium stearate is then added to the mixture and mixed for 3 minutes at fast speed. The final blend is discharged through a cloth sleeve into tared totes with inserts with minimum jogging.
13. The composition is compressed into tablets by using a Kilian TX-32 tablet press and 13/32 in. round tooling and filmed coated.

Ibuprofen Chewable Tablets

Manufacturing Directions

1. PVAP and PVP-K90, equivalent to a 2:1 weight ratio, are dissolved in minimum volumes of an aqueous ammonium hydroxide solution (28% v/v) and water, respectively, and then mixed.
2. To the resulting mixture, ibuprofen, equal to the amount of PVAP used, is dissolved and then 0.1N HCl solution is added drop wise until the pH of the solution is 1.0.
3. The white solid precipitate is filtered, washed with water, and then vacuum dried.
4. The entrapped granules containing 39.06% ibuprofen are used in the preparation of tablets.
5. Appropriate amounts of the granules and the cherry vehicle, corresponding to 200 mg of ibuprofen per 668 mg of tablet, are accurately weighed and then mixed and tablets compressed.

Ibuprofen Coated Fast-Crumbling Granule Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Ibuprofen	200.00
16.00	2	Sodium croscarmellose (AGG)	16.00
27.50	3	Aspartame	27.50
12.20	4	Precipitated silica	12.20
35.00	5	Ethylcellulose	35.00
8.00	6	Hypermellose	8.00
1.33	7	Sodium (AGM) croscarmellose	1.33
	8	Pharmacoat 606	

Manufacturing Directions

1. A suspension is obtained by mixing ethylcellulose, 80% precipitated silica, and 30% aspartame in ethyl alcohol, until a homogeneous suspension is obtained.
2. The powder mixture consisting of ibuprofen, item 7, 70% aspartame, and 20% precipitated silica is then fluidized.
3. Granulation is then started by spraying the mixture for about 15 to 20 minutes at a spraying rate of 25 g/min and a suspension atomization pressure of 0.8 bar.
4. The actual coating is then performed by spraying the remainder of the mixture over about 1.5 hours at a spraying rate of 15 to 20 g/min and a suspension atomization pressure of 1.5 bar.
5. 15% of the mixture is sprayed during the granulation step, and the remainder to 100% is sprayed during the coating step.
6. The granules obtained are then formulated as fast-crumbling multiparticulate tablets, with the following composition: coated granules, 300 mg; Mannitol, 344 mg; sodium croscarmellose, 21 mg; precipitated silica, 7 mg; aspartame, 20 mg; mint flavoring, 4 mg; magnesium stearate, 4 mg.

Ibuprofen Fast-Dissolve Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
121.90	1	Ibuprofen coated	121.90
11.00	2	Citric acid	11.00
3.90	3	Magnasweet 135	3.90
6.50	4	Aspartame	6.50
7.80	5	Cherry flavor	7.80
39.00	6	Croscarmellose sodium	39.00
1.95	7	Silicon dioxide	1.95
3.25	8	Magnesium stearate	3.25
457.90	9	Fast-dissolving granulation (see below)	457.90

Manufacturing Directions

1. Fast-dissolving granulation is made by combining 400 g of melted PEG 900 with fructose powder (100 g) in a planetary mixer (low-shear mixer) and mixed until granules are formed.
2. The granulations are allowed to cool, and then screened.
3. Ingredients are screened, and then mixed in a V-blender.
4. Tablets are compressed (653.7 mg) at 600 lb (about 2.7 kN).
5. The tablets have hardness of 0.2 to 0.5 kPa and disintegrate in less than 15 seconds.

Ibuprofen Sustained-Release Bi-Layer Tablet

Manufacturing Directions

1. Immediate-release layer composition
   a. Part I: Ibuprofen USP 160.0 mg; microcrystalline cellulose NF, 32.0 mg; (Avicel PH 101) starch NF, 32.0 mg; pregelatinized starch NF, 16.0 mg; (Starch 1500) sodium starch glycolate NF, 6.4 mg.
   b. Part II: Hydroxypropyl methylcellulose, 1.6 mg; 2910 USP (Methocel E-5) Purified Water USP q.s.
   c. Part III: Sodium starch glycolate NF, 1.6 mg (Explotab); colloidal silicon dioxide NF, 0.8 mg. Total 250.4 mg.
   d. Weigh the components of Part I and preblend them in a high-shear mixer (fielder: impeller speed of approximately 118 RPM for 3 minutes).
   e. Prepare the granulating agent (Part II) by dissolving hydroxypropyl methylcellulose 2910 USP into purified water USP (a ratio of 3.2 g of hydroxypropyl methylcellulose to 200 g water).
   f. Deliver the granulating agent to the powders of Part I, in the high-shear mixer.
   g. Granulate the mixture for 20 minutes (fielder: impeller speed of approximately 118 rpm).
   h. Remove the completed wet granulation from the high-shear mixer and load into the product bowl of a fluid-bed apparatus (e.g., Aeromatic or Glatt).
   i. With an inlet air temperature of approximately 60°C, dry the granulation to a moisture level of 0.5% to 1.1% as determined by loss on drying (e.g. Computrac). The wet granulation can also be dried on trays in drying ovens.
   j. Sieve the dried granulation (e.g. Glatt Quick Sieve: Stator No. 3, Screen No. 1.5 mm, 1000 rpm). Other machines such as a Fitzpatrick Comminution Mill can also be used.
   k. Blend the sieved and dried granulation with the powders of Part III using a suitable mixer such as a twin-shell, ribbon, or planetary mixer.
2. Sustained-release layer
   a. Povidone USP, 14.7 mg (Plasdone K 29/32); alcohol USP 1:1 mixture q.s. purified water USP
   b. Part III: Pregelatinized starch NF, 8.0 mg (Starch 1500 LM); microcrystalline cellulose NF, 7.3 mg (Avicel PH 101); magnesium stearate NF, 5.0 mg; colloidal silicon dioxide, NF 5.0 mg (Cab-O-Sil). Total = 523.3 mg; total tablet weight = 773.7 mg.
   c. Weigh the components of Part I and preblend them in a high-shear mixer (fielder: impeller speed of approximately 250 Rpm for 1 minute).
   d. Prepare the granulating agent (Part II) by dissolving the Povidone USP in a 1:1 mixture of alcohol USP and purified water USP (a ratio of 12.25 g of povidone to 100 g of alcohol/water).
   e. Spray the granulating agent at a rate of 600 mL/min onto Part I in the high-shear mixer.
   f. Granulate the mixture for 1 minute after the addition of Part II (fielder: impeller speed of approximately 250 rpm).
   g. Remove the completed wet granulation from the high-shear mixer and load it into the product bowl of a fluid-bed apparatus (e.g., Aeromatic or Glatt).
   h. With an inlet air temperature of approximately 60°C, dry the granulation to a moisture level of 0.3% to 0.8% as determined by loss on drying (e.g., Computrac).
   i. The wet granulation can also be dried on trays in drying ovens.
   j. Sieve the dried granulation (Fitzpatrick Comminution Mill, Model D6: medium speed, knives forward, 0.093 screen). Other machines such as Glatt Quick Sieve can also be used.
   k. Blend the sieved and dried granulation with the powders of Part III by using a suitable mixer such as a twin-shell, ribbon, or planetary mixer.
3. Compression of tablets or caplets
   a. Load the granulation of the immediate-release layer into one hopper and the granulation of the sustained-release layer into the second hopper of a bilayer tabletting machine (e.g., Stokes Versapress).
   b. Compress tablets using 0.749 × 0.281 × 0.060 extra deep concave capsule shaped tooling. (Tablet tooling of other shapes such as oval or round can also be used).
   c. The sustained-release layer has a target weight of 523.3 mg and the immediate-release layer has a target weight of 250.4 mg. Ideal tablet hardness immediately after compression is 11 to 12 kPa.

Ibuprofen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Ibuprofen	200.00
88.00	2	Maize starch	88.00
30.00	3	Maize starch	30.00
12.80	4	Maize starch (dried)[a]	12.80
1.60	5	Stearic acid (fine powder)	1.60
–	6	Purified water	144.00

[a]Loss on drying: NMT 4.5% when dried at 120°C for 4 hours.

Manufacturing Directions

1. Pass item 3 through a 250-μm sieve using a sifter.
2. Prepare a slurry of item 3 with 10.67 g of cold item 6 (25–30°C) in a stainless steel container.
3. Pour the slurry into a vessel containing 37.33 g of hot item 6 (70–90°C).
4. Heat to 80°C to 90°C and mix until mixture swells and becomes translucent.
5. Cool to 50°C.

6. Check weight (theoretical weight, 58.00 g). If required, adjust with hot purified water. Record the quantity of extra water added.
7. Pass items 1 and 2 through sifter using 250-μm sieve.
8. Load it into a mixer (if required, grind item 1 through a 1-mm sieve).
9. Mix the powder for 15 minutes at high speed.
10. Add binding solution to the dry powder in the mixer and mix for 15 minutes at high speed. Check for satisfactory wet mass.
11. Pass the wet mass through a FitzMill using sieve 24207, knives forward, and medium speed.
12. Collect and spread the granules onto the trays, one third the thickness of the tray.
13. Load the trolleys into the oven and dry the granules at 55°C for 36 hours.
14. After 12 hours of drying, stir the granules in the trays and change the position of the trays for uniform drying.
15. Check the moisture of the dried granules. The limit NMT is 2.5%. Dry further if required to obtain moisture content of 2.5%.
16. Check the weight of dried granules (theoretical weight = 318.00 g).
17. Pass the dried granules through a 1.5-mm sieve using a granulator. Collect in a stainless steel drum and add it to the blender.
18. Pass items 4 and 5 through a 250-μm sieve using a sifter.
19. Add the sieved material to the granules in a blender and mix for 5 minutes.
20. Compress into 330-mg tablets, using 10-mm convex punches at 4 to 9 kPa.
21. Coat the tablets using one of the polyvinylpyrrolidone (PVP) coating solutions provided in the Appendix or use the following sugar-coating formulation:

Bill of Materials: Sugar Coating			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
7.06	1	Sandrac varnish (WMR)	7.06
3.33	2	Povidone (PVP K-25)	3.33
1.86	3	Povidone (PVP K-25)	1.86
175.85	4	Sucrose	175.85
0.16	5	Titanium dioxide	0.16
1.20	6	Polishing emulsion*	1.20
1.33	7	Talc (fine powder)	1.33
–	8	Purified water	87.10

*See appendix for polishing emulsion formulation.

22. Load the tablets into the pan.
23. Start the tablets rolling with the exhaust on and air supply off.
24. Pour the item 1 solution onto the rolling tablets and allow the tablets to roll, using hand agitation if required, permitting the solution to spread well over the tablet bed.
25. Permit the tablets to roll until tack develops, at which point item 7 should be quickly sprinkled over the tablets.
26. Allow to roll freely for 2 minutes at 45°C.
27. Do not roll too long, as the seal may be worn from the tablet edges.
28. After 2 minutes of rolling, jog the tablets every 1 minute over a period of 15 minutes with exhaust and drying air on at 45°C.
29. Continue jogging for a further 15 minutes. Jog every 3 minutes with exhaust and drying air temperature on at 45°C.
30. Dissolve 2.40 g of item 2 in 28.80 g of item 8.
31. Apply a half quantity of it to the tablets over 5 minutes; allow to dry and apply the remainder over a 15-minute period.
32. Heat 11.52 g of item 8 to boiling, dissolve 26.88 g of item 4, and cool down to 25°C.
33. Check weight (theoretical weight, 38.40 g). If less, adjust weight to 38.40 g with purified water.
34. Apply sugar coat over a 30-minute period.
35. Dry the tablets in the coating pan at 30°C, jogging every 1 hour for 6 hours.
36. Heat 72.0 g of item 8 in mixer to boiling.
37. Dissolve 168.0 g of item 4 and then cool to 25°C.
38. Filter the syrup through a 180-μm stainless steel sieve.
39. Dissolve item 3 in 3.68 g of item 8.
40. Dissolve 4.53 g of item 4 in item 6.
41. Disperse item 5 in about 10.67 g of sugar syrup from the previous step and homogenize.
42. Mix these steps with sugar syrup. Check for evenness of the dispersion.
43. Apply sugar coating.

Bill of Materials: Polishing Coat			
Scale (mg/tablet)	Item	Material Name	Quantity/kg (g)
28.75	1	Bee's wax, bleached (white bee's wax)	28.75
70.00	2	Polyethylene glycol (PEG-6000)	70.00
57.50	3	Carnauba wax	57.50
125.00	4	Talc (fine powder)	125.00
718.75	5	Ethanol, 95%	718.75

44. Melt items 1 to 3 in a steam-heated vessel by gentle heating to 70°C or in a stainless steel container on a hotplate heater.
45. Add item 4 to the vessel or stainless steel container and stir manually.
46. Add item 5 to the vessel or stainless steel container and stir manually.
47. Pass the mixture through a homogenizer.
48. Store the polishing emulsion in a closed container at room temperature.
49. Apply gloss solution.
50. Add item 6 without air to the tablet bed carefully to get a uniform distribution while rolling.
51. After 5 minutes of distribution, turn on the cold air and roll further until a shine appears.
52. Once the desired polish appears, stop rolling the pan.
53. Dry the tablets in the pan at 30°C for 30 minutes. Final tablet weight should be 480 mg.

Ibuprofen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
115.00	1	Lactose	115.00
11.30	2	Povidone	11.30
QS	3	Water, purified	QS
23.00	4	Starch (maize)	23.00
40.00	5	Starch pregelatinized	40.00
11.00	6	French chalk	11.30
1.10	7	Magnesium stearate	1.10
6.80	8	Explotab	6.80
400.00	9	Ibuprofen	400.00

Manufacturing Directions

1. Granulation
   a. Charge the following into a planetary mixer: ibuprofen, starch pregelatinized, and polyvinylpyrrolidone. Mix all for 15 minutes.
   b. Pass the powder through a #40-mesh screen.
   c. Add a sufficient quantity of purified water to form a desirable mass.
   d. Pass the mass through #40 mesh on a dryer tray.
   e. Dry the granules in a fluid-bed dryer or use a fan-forced oven at 50°C to 60°C for 24 hours to dry granules to an LOD of not more than 1%.
   f. Pass the granules through a #40 sieve mesh.
2. Blending
   a. Charge the granules in a planetary mixer. Add maize starch, French chalk (item 6), magnesium stearate, and Explotab, and mix for 20 minutes.
3. Compressing: Compress using a rotary press in round punches. The average weight is 610 mg (± 5%).
4. Coating: Apply a sugar coating. (See Appendix.)

Ibuprofen Tablets (400 mg), Motrin

Ibuprofen, a nonsteroidal antiinflammatory agent, is available in 400-,600-, and 800-mg tablets for oral administration. The inactive ingredients are carnauba wax, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, and titanium dioxide.

Ibuprofen Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Ibuprofen	400.00
43.70	2	Starch (maize)	48.45
18.00	3	Povidone (PVP K-30)	18.00
105.00	4	Starch (maize)	108.13
40.00	5	Starch (maize, dried)	40.00
4.00	6	Colloidal silicon dioxide (Aerosil 200)	4.00
3.45	7	Colloidal silicon dioxide (Aerosil 200)	3.45
1.50	8	Stearic acid	1.50
4.50	9	Magnesium stearate	4.50
–	10	Purified water	163.97

Manufacturing Directions

1. Preparing the paste
   a. Pass item 2 through a sifter using a 630-μm sieve. Prepare a slurry of item 2, with 51.78 g of item 10 (30°C). Pour the slurry into a vessel containing 112.19 g of item 10 (70°C). Heat to 80°C to 90°C, and mix until the material swells and becomes translucent.
   b. Cool to 50°C. Check the weight. The theoretical weight is 212.43 g.
   c. If required, adjust with item 10 (70°C). Record the quantity of extra water added.
2. Mixing: Load items 1, 4, and 3 to the mixer. Mix for 5 minutes at high speed.
3. Wet massing:
   a. Add two-thirds of the starch paste quantity (preparing the paste, step 1b) to the dry powder in the mixer (Diosna). Mix for 4 minutes at low speed. Scrape the sides and blades.
   b. Add the remaining quantity, and mix for 3 minutes at low speed. Scrape the sides and blades.
   c. Mix and chop for a further 2 minutes. Check for a satisfactory wet mass. If required, add additional purified water to obtain a satisfactory wet mass.
4. Drying
   a. Dry the granules in a fluid-bed dryer at 55°C for 3 hours. Keep just enough air pressure in order to bounce the granules. After 1 hour of drying, scrape the semidried granules to break the lumps for uniform drying. Unload in a stainless steel drum. Keep overnight for curing.
   b. Check the moisture content of the dried granules. The limit is not more than 2.5%
5. Grinding: Pass the granules through a 1.25-mm sieve using a granulator. Collect the granules in a stainless steel drum, and add to the blender.
6. Lubricating
   a. Mix items 6 and 8 in a stainless steel drum, and pass through a 500-μm sieve using a sifter. Collect in a stainless steel drum, and add to the blender.
   b. Pass items 5 and 9 through a 250-μm sieve in a sifter. Collect the sieved items in a stainless steel drum, and add to the blender. Mix the materials for 2 minutes.
   c. Unload the result in stainless steel drums.
7. Compressing
   a. Compress the tablets after slugging.
   b. Check the temperature and humidity before starting slugging and compression.
   c. The recommended relative humidity is 45% to 55% at temperatures 25°C to 27°C.
8. Slugging: Slug the granules using a rotary tabletting machine with 16-mm punches.
9. Grinding: Grind the slugs through a 6.0-mm sieve followed by a 1.25-mm sieve. Keep 5.40 g of the granules aside. Load the rest of the ground granules in a blender.
10. Sift 5.4 g of the ground granules from step 9 through a 630-μm sieve using a sifter. Add the retained granules to the blender.
11. Add item 7 into the sieved granules from step 10. Mix in a polythene bag. Sift through a 630-μm sieve using a sifter. Add to the blender, and mix for 2 minutes.
12. Compress the granules using a rotary tabletting machine (12.7-mm concave punches; compress 620 mg).
13. Tablet coating: Coat using Opadry and HPMC coatings. (See Appendix.)

Ibuprofen Tablets (400 mg)

Formulations: Ibuprofen (Francis), 400 g; Aerosil 200, 4 g; Ludipress, 342 g; Kollidon CL, 8 g; magnesium stearate, 8 g.

Manufacturing Directions

1. Pass ibuprofen and magnesium stearate through a 200-μm sieve.
2. Mix with the other components and press with medium-compression force at 752 mg.

Ibuprofen Tablets (600 mg)

Formulations: Ibuprofen 50 (BASF), 600 g; Aerosil 200, 9 g; Avicel PH 200, 108 g; Kollidon VA 64, 50 g; Kollidon CL, 27 g; Macrogol 6000 powder, 6 g.

Manufacturing Directions

1. Mix ibuprofen with Aerosil 200, and add the other components.
2. Press with low-compression force at 793 mg.

Ibuprofen Tablets (600 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
600.00	1	Ibuprofen	600.00
129.80	2	Starch (maize)	144.22
1.15	3	Colloidal silicon dioxide (Aerosil 200)	1.15
70.00	4	Starch (maize)	70.00
5.00	5	Colloidal silicon dioxide (Aerosil 200)	5.00
8.07	6	Stearic acid	8.07
41.15	7	Pregelatinized starch (Starch 1500)	41.15
10.00	8	Magnesium stearate	10.00
–	9	Purified water	469.00

Manufacturing Directions

See the manufacturing directions for 400-mg strength tablet.

Imipramine Tablets (25 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Imipramine hydrochloride	26.00
1.40	2	Polyvinyl pyrroidone	1.40
1.40	3	Magnesium stearate	1.40
1.40	4	Talc	1.40
50.00	5	Lactose monohydrate	50.00
50.00	6	Dicalcium phosphate	50.00
14.00	7	Starch (maize)	14.00
–	8	Isopropyl alcohol, ca	20 mL

Manufacturing Directions

1. Sift through a 250-μm sieve, and charge items 1 and 5 to 7 in a suitable mixing vessel. Mix the items for 10 minutes.
2. In a separate vessel, charge item 2 and a suitable quantity of item 8 to dissolve it.
3. Add step 2 into step 1, and make a suitable wet mass; pass through a 2.38-mm sieve and dry in a dehumidified room overnight.
4. Pass the dried granules through #18 mesh into a blending vessel.
5. Sift items 3 and 4 through a 250-μm sieve, and add to step 4. Blend for 1 minute.
6. Compress into 140-mg tablets, using 7.2-mm punches.

Indomethacin Sustained-Release Tablets (75 mg)

Formulation: Indomethacin (Synopharm), 75 g; Kollidon SR, 125 g; Ludipress LCE, 100 g; silicon dioxide, colloidal, 1.5 g; magnesium stearate, 1.5 g.

Manufacturing Directions

All ingredients are passed through a 0.8-mm sieve, blended for 10 minutes in a mixer, and then compressed with medium-compression force at 303 mg.

Indomethacin Tablets (50 mg), DC

Formulation: Indomethacin, 50 g; Ludipress, 227 g; Kollidon CL, 20 g; magnesium stearate, 3 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press with medium-compression force at 303 mg.

Indomethacin Tablets (100 mg)

Formulation: Indomethacin, 100 g; Ludipress, 397 g; magnesium stearate, 3 g.

Manufacturing Directions

1. Mix all components, and pass through a 0.8-mm sieve.
2. Press with low-compression force at 500 mg.
3. If the flowability of indomethacin is not good, it should be mixed with a low percentage of Aerosil 200.

Inosin Tablets

Bill of Materials			
Scale (g/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Inosin (Ribaxin, Russia)	200.00
51.00	2	Lactose monohydrate	51.00
6.00	3	Kollidon® 90F	6.00
QS	4	Isopropanol	60.00 mL
10.00	5	Kollidon® CL	10.00
3.00	6	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with the solvent mixture of items 4.
2. Dry and pass through an 0.8-mm sieve, add items 5 and 6, and press with low-compression force.
3. Compress into 270-mg tablets, using 9-mm biconvex punches.

Irbesartan Tablets (75 mg/150 mg/300 mg), Avapro

Avapro is available for oral administration in unscored tablets containing 75, 150, or 300 mg of irbesartan. Inactive ingredients include lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, poloxamer 188, silicon dioxide, and magnesium stearate.

Irbesartan Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Irbesartan[a]	75.00
15.38	2	Lactose monohydrate	15.38
22.50	3	Microcrystalline cellulose (Avicel PH 101)	22.50
22.50	4	Pregelatinized starch	22.50
7.50	5	Croscarmellose sodium	7.50
4.50	6	Poloxamer 188 (Pluronic F 68)	4.50
1.12	7	Silicon dioxide colloidal	1.12
1.50	8	Magnesium stearate	1.50
–	9	Water, purified[b]	QS

[a]Use different fill weights for 150-mg and 300-mg strength tablets.
[b]The tablets are prepared by a wet granulation process wherein the total amount of water employed (by weight) is up to 50% of the total solids weight.

Manufacturing Directions

1. Charge irbesartan, lactose, pregelatinized starch, and a portion (one-half) of croscarmellose sodium in a mixer. Mix the materials for 20 minutes.
2. Pass the powder blend in step 1 through sizing equipment (cone mill or oscillator), and mix in a mixer.
3. Dissolve poloxamer 188 in purified water (25% of the weight of total solids), and use it to wet granulate (with the further addition of water in an amount up to 25% of the weight of total solids, as needed) the mixed powder in step 2.
4. Dry the granules (tray or fluid-bed dryer) until the LOD is 2% or less.
5. Pass the dried granules through a screen, or mill them to obtain the proper size (1–3 mm).
6. Mix the sized granules with silicon dioxide, microcrystalline cellulose, and the remaining croscarmellose sodium in a mixer.
7. Add and mix for 1 minute magnesium stearate.
8. Compress 150 mg for 75-mg strength, 300 mg for 150-mg strength, and 600 mg for 300-mg strength.

Iron (Polymer-Coated Particle) Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Elemental iron; use ferrous sulfate polymer-coated particles (233 mg iron per g ferrous sulfate)	450.60
200.00	2	Cellulose microcrystalline	200.00
254.40	3	Lactose monohydrate	254.40
36.00	4	Sodium starch glycolate	36.00
9.00	5	Magnesium stearate	9.00

Note: Factor in potency of ferrous sulfate polymer-coated particles.
Adjust with item 3. Item 1 is prepared by first granulating ferrous sulfate using alcohol and water, drying, and sieving particles over 1200 μm in size. Regranulate smaller particles. Apply enteric (HPMC) coating to the granules in a fluid-bed dryer.

Manufacturing Directions

1. Charge a suitable mixer/blender with microcrystalline cellulose and disperse the ferrous sulfate polymer-coated powder.
2. To this mix, add about half the lactose (item 3) and blend for 5 minutes.
3. Pass the sodium starch glycolate through a 500-μm sieve, followed by about half of the remaining lactose.
4. Add to the mix.
5. Blend for a further 5 minutes.
6. Pass the magnesium stearate (item 5) through a 500-μm sieve, followed by the remaining lactose.
7. Add to the previous mix.
8. Blend for a further 5 minutes.
9. Compress into 950-mg tablets at 8 to 14 kpi, using 8 × 16 mm punches; 16 mm punches; do not rework tablets.
10. Coat the tablets using a HPMC coating solution. (See Appendix.)

Isoniazid Tablets (100 mg)

Bill of Materials			
Scale (mg/Tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Isoniazid	105.00
2.00	2	Starch maize	2.00
1.25	3	Gelatin	1.25
1.25	4	Magnesium stearate	1.25
1.25	5	Talc	1.25
–	6	Water, purified	QS

Manufacturing Directions

1. Sift item 1 through a 250-μm sieve into a blending vessel.
2. In a separate vessel, charge item 3 and a suitable quantity of item 6, heat to 50°C, and dissolve item 3. Then add item 2 into step 1, and form a smooth slurry.
3. Add step 2 and form a suitable wet mass.
4. Pass the wet mass through a 2.38-mm sieve onto paper-lined trays, and dry at 60°C for 8 hours to an LOD of not more than 2.5%. Transfer the wet mass to a suitable blending vessel.
5. Sift items 4 and 5 through a 500-μm sieve, and add to step 4. Blend these materials for 1 minute.
6. Compress into 125-mg tablets, using 7.3-mm punches.

Isosorbide Dinitrate Tablets (5 mg) Indur

Each Ismo tablet contains 20 mg of isosorbide mononitrate. The inactive ingredients in each tablet are D&C Yellow No. 10 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 20, povidone, silicon dioxide, sodium starch glycolate, titanium dioxide, and hydroxypropyl cellulose.

Imdur tablets contain 30, 60, or 120 mg of isosorbide mononitrate in an extended-release formulation. The inactive ingredients are aluminum silicate, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, paraffin wax, polyethylene glycol, titanium dioxide, and trace amounts of ethanol.

Isosorbide Dinitrate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Isosorbide dinitrate (40% in Lactose)	13.15
25.00	2	Microcrystalline cellulose (Avicel PH 102)	25.00
58.60	3	Lactose (spray dried)	58.60
0.75	4	Magnesium stearate	0.75
2.50	5	Starch (maize, dried)	2.50

Manufacturing Directions

Note: Protect the product from heat and moisture. Heat and moisture affect the potency of isosorbide.

1. Dry mixing and sieving
   a. Mix items 1 to 3 in a suitable stainless steel drum. Pass these materials through a 630-μm sieve using a sifter. Collect in a stainless steel drum.
   b. Load the powders into the drum blender.
2. Mixing
   a. Mix items 4 and 5 in a bag. Pass the material through 250-μm sieve. Collect in a bag.
   b. Take about 1.25 g powder from step 1b and add to step 2a. Mix manually, and transfer to step 1b.
3. Mix for 5 minutes using a drum blender.
4. Check and record the weight of the granules. The theoretical weight of the granules is 100.0 g.
5. Compression: Compress into 100 mg of the granules using a rotary tabletting machine with 6-mm punches.

Isosorbide Dinitrate Tablets (5 mg)

Formulation: Isosorbide dinitrate + lactose (4 + 6), 12.5 g; lactose monohydrate, 152.1 g; Kollidon 30, 5.4 g; Kollidon CL, 9.0 g; magnesium stearate, 1.0 g.

Manufacturing Directions

1. Mix all components, and pass through a 0.8-mm sieve.
2. Press with low-compression force at 184 mg.

Isosorbide Dinitrate Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Isosorbide dinitrate (40% in lactose)	26.30
50.00	2	Microcrystalline Cellulose (Avicel PH 102)	50.00
117.20	3	Lactose (spray dried)	117.20
1.50	4	Magnesium Stearate	1.50
5.00	5	Starch (maize, dried)	5.00

Manufacturing Directions

See the manufacturing directions for the 5-mg formulation.

Isovaleramide Sustained-Release Tablets

Manufacturing Directions

1. Preparation of the tablet core
   a. Active drug (e.g., Isovaleramide; NPS 1776; Oread, Lawrence, Kans.; cGMP grade) is dispersed by passage through a #30-mesh screen.
   b. Drug, xanthan gum (e.g., XANTURAL; Monsanto, St. Louis, MO; NF grade) and lactose (e.g. monohydrate form, spray dried,: Oread, Palo Alto,CA; NF grade) are mixed into a 1-L glass jar and blended in a mixer for 4 minutes at 96 rpm.
   c. Magnesium stearate (e.g. Oread, Palo Alto,CA; NF grade) is added and the mixture blended for 1 minute.
   d. The final blend is compressed into caplets by using 0.32 in. × 0.75-in. × 0.060-in. tooling to a target weight of 800 mg, target hardness of 8 kPa, and target thickness of 0.25 in.
2. Coating of the tablet cores
   a. Hydroxypropyl methylcellulose (HPMC; e.g., Dow Chemical Co., Midland, MI; NF grade) solution is prepared by adding HPMC slowly to purified water heated to approximately 80°C. The solution is allowed to cool to room temperature by placing vessel in a cold water bath. Additional water is added to prepare the final requisite amount of HPMC solution.
   b. AQUACOAT ECD/dibutyl sebecate mixture is prepared by adding dibutyl sebacate (DBS: e.g., Morflex Inc., Greenboro, NC; NF grade) to AQUACOAT ECD (e.g., FMC Pharmaceutical Division, Philadelphia, PA) while mixing. Mixing is continued for a minimum of 30 minutes.
   c. The HPMC solution is added slowly to the AQUACOAT ECD/DBS mixture.
   d. The core tablets are loaded into a coating apparatus (Vector LCDS 3 coater) fitted with a 1.3-L coating pan and warmed until an outlet temperature of 40°C is reached.
   e. The tablets are spray coated until the planned theoretical weight gain (based on core tablet weight) is achieved; however, after curing, the actual coating solids applied are less than the theoretical value (e.g., 8% or 15% theoretical can be 5% and 12% coat, respectively after curing). Thus, extra spray may need to be added to account for the loss upon curing. Conditions for coating are as follows: Inlet temperature, 70°C; outlet temperature, 40°C to 43°C; spray rate, 4 5 g/min; pan speed, 14 rpm; fluidizing air, 30 40 scfm; atomization air pressure 26 psi.
   f. Spraying is stopped when the requisite amount of coating suspension is applied. The tablets are dried for approximately 5 minutes in the coating pan. The inlet temperature is adjusted during drying to keep outlet temperature below 45°C.
   g. The tablets are cured in an oven at 60°C for 18 hours.

Kaolin–Pectin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
QS	1	Distilled purified water	300 mL
50.00	2	Cornstarch	50.00
50.00	3	Povidone (K-29–32)	50.00
QS	4	Distilled purified water	0.50 L
630.00	5	Hydrated aluminum–magnesium silicate	630.00
100.00	6	Kaolin (powder)	100.00
50.00	7	Pectin	50.00
80.00	8	Cornstarch	80.00
80.00	9	Sodium lauryl sulfate	7.00
10.00	10	Magnesium stearate	10.00

Manufacturing Directions

1. Heat purified water (item 1) to 75°C to 80°C, and add cornstarch (item 2) with continuous stirring until a translucent paste is formed; use this paste within 1 hour.
2. Dissolve Povidone in purified water (item 4) in a separate container. Ensure that dissolution is complete.
3. Charge the following into a suitable planetary mixer: hydrated aluminum–magnesium silicate, kaolin, and pectin.
4. Mix for 5 minutes.
5. Add freshly prepared starch paste from the first step and the Povidone solution to the powder blend from the third step; mix until a mass of suitable consistency is obtained.
6. Add extra purified water, if needed.
7. Spread the wet mass on paper-lined trays and dry in the oven at 50°C for 2 hours.
8. Pass the semidried mass through a 4.8-mm (4-mesh) screen by hand or by using a suitable granulator, and load the granule mass onto paper-lined trays.
9. Dry in the oven at 50°C until the moisture content is between 10.0% and 15.0%.
10. Pass the dried granules through a 1.0-mm (18-mesh) screen on a comminuting mill at medium speed, knives forward, into clean, tared, polyethylene-lined drums; seal and weigh.
11. Transfer the dried granules to a suitable blender.
12. Screen the following items through a 595-μm (30-mesh) screen, and add to the blender: cornstarch (item 8), sodium lauryl sulfate, and magnesium stearate.
13. Blend for 5 to 10 minutes.
14. Compress on a suitable compression machine using 1/2- in. round standard concave punches, upper punch with logo, and lower punch with a bisect line.
15. Compress into 977-mg tablets at 10 to 18 kpi.
16. Coat using an aqueous methocel coating and polish as desired.

Ketotifen Tablets (1 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.00	1	Ketotifen, use ketotifen fumarate DC	1.38
1.90	2	Magnesium stearate	1.90
32.50	3	Maize starch	32.50
154.20	4	Calcium hydrogen phosphate anhydrous	154.20
QS	5	Water purified	QS

Manufacturing Directions

1. Granulation
   a. Make a 10% paste with maize starch using a sufficient quantity of purified water and one-half the quantity of maize starch.
   b. Add calcium hydrogen phosphate anhydrous with one-half the quantity of the starch paste.
   c. Add one-half the quantity of maize starch with ketotifen; mix in a planetary mixer.
   d. Add mixture from step 1b to 1c, and mix for 5 minutes. Add the balance of the maize starch powder, and mix for another 10 minutes.
   e. Pass the wet mass through a #20-mesh screen over lined trays and dry at 95°C until an LOD of not more than 3% is achieved.
2. Lubrication: Mix dry granules with magnesium stearate for 3 minutes.
3. Compression: Compress using round, flat, beveled edge, scored punch with the logo on one side; diameter is 7 mm, weight is 190 mg.

Khellin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Khellin	25
124.0	2	Ludipress®	124
1.00	3	Magnesium stearate	1

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix intensively, and press.
2. Compress into 150-mg tablets, using 8-mm biplanar punches.

Labetalol Tablets (50 mg)

Formulation: Labetalol, fine powder (Joy Sun), 50.0 g; Ludipress, 98.4 g; Aerosil 200, 0.8 g; Magnesium stearate, 0.8 g.

Manufacturing Directions

1. Mix all components, and sieve through a 0.8-mm screen.
2. Press with low-compression force at 150 mg.

Lamotrigine Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Lamotrigine, 3% excess	103.00
48.00	2	Avicel PH 102	48.00
111.00	3	Lactose monohydrate	111.00
7.00	4	Primojel	7.00
7.00	5	PVP K30	7.00
1.00	6	Iron oxide yellow	1.00
12.00	7	Avicel PH 102	12.00
8.00	8	Primojel	8.00
1.50	9	Magnesium stearate	1.50
1.50	10	Iron oxide yellow	1.50
–	11	Water purified, ca	75 mL

Manufacturing Directions

1. Charge items 1 to 4 after sifting through a 500-μm sieve into a suitable mixer.
2. In a separate vessel, charge items 5, 6 and 11; dissolve and homogenize for 5 minutes at medium speed.
3. Add step 2 to step 1, and knead for 1 to 2 minutes; mix until a suitable mass is obtained.
4. Dry granules on trays at 55°C for 12 hours to and LOD of 0.8%.
5. Grind the dried granules through 1.25-mm sieve.
6. Transfer step 5 to a blender, and add items 7 to 9 after passing them through a 500-μm sieve. Blend for 2 minutes.
7. Compress into 300-mg tablets, using 9.5-mm round punches.

Lansoprazole Tablets (10 mg or 20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Lansoprazole	10.00
200.00	2	Calcium glycerophosphate	200.00
400.00	3	Sodium bicarbonate	400.00
12.00	4	Croscarmellose sodium	12.00
3.00	5	Pregelatinized starch	3.00

Lansaprazole Enteric-Coated Tablet

1. Core material non-pareil cores, 400 g; lansoprazole, 400 g; hydroxypropyl methylcellulose, 80 g; sodium lauryl sulfate, 3 g; water purified 1360 g.
2. Separating layer core material (step 1 above), 100 g; hydroxypropyl methylcellulose, 9 g; polyethyleneglycol 6000, 1 g; talc, 18 g; ethanol 95%, 250 g; water purified, 250 g.
3. Enteric coating layer sub-coated pellets (step 2 above), 100 g; hydroxypropyl methylcellulose phthalate, 40 g; acetyltributyl citrate, 8 g; cetanol, 2 g; ethanol 95%, 162 g; acetone, 378 g. Suspension layering is performed in a Wurster equipped fluid-bed apparatus.
4. Lansoprazole is sprayed onto inert non-pareil cores from a water suspension containing lansoprazole, the dissolved binder, and the wetting agent.
5. The prepared core material is coating layered with a separating layer in the same equipment by spraying a suspension of talc in a HPMC/PEG solution. PEG is added to act as a plasticizer for the HPMC.
6. Enteric coating layer is applied in the same equipment by spraying the enteric coating polymer solution (including additives according to above) onto the pellets (layered with a separating layer). The obtained enteric coating layered pellets are mixed with prepared granules and other component as described in example 1, and compressed into effervescent

Lansoprazole Tablets (10 mg or 20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Lansoprazole	10.00
175.00	2	Calcium glycerophosphate	175.00
175.00	3	Calcium lactate	175.00
250.00	4	Sodium bicarbonate	250.00
20.00	5	Polyethylene glycol 6000	20.00
12.00	6	Croscarmellose sodium	12.00
3.00	7	Peppermint flavor	3.00
1.00	8	Magnesium silicate	1.00
1.00	9	Magnesium stearate	1.00

Lansoprazole Tablets Chewable (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Lansoprazole	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
250.00	4	Sodium bicarbonate	250.00
0.50	5	Aspartame calcium	0.50
12.00	6	Silicon dioxide colloidal	12.00
15.00	7	Starch (maize)	15.00
12.00	8	Croscarmellose sodium	12.00
10.00	9	Dextrose, anhydrous	10.00
3.00	10	Peppermint flavor	3.00
3.00	11	Maltodextrin	3.00
3.00	12	Mannitol	3.00
3.00	13	Pregelatinized starch	3.00

Manufacturing Directions

1. Pass all ingredients through a 250-μm mesh, and blend in a suitable blender.
2. Compress into 672-mg tablets, using 15-mm biplanar punches. For 20-mg tablets, increase the quantity of item 1, and compress an additional 10 mg.

Lansoprazole Tablets, Rapid Dissolution (20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Lansoprazole	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
500.00	4	Sodium bicarbonate	500.00
50.00	5	Calcium hydroxide	50.00
12.00	6	Croscarmellose sodium	12.00

Levamisole Hydrochloride Tablets (40 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
40.00	1	Levamisole hydrochloride, with excess	47.40
10.00	2	Starch (maize)	10.00
20.00	3	Lactose monohydrate	20.00
10.00	4	Sodium starch glycolate	10.00
30.60	5	Starch (maize)	30.60
1.00	6	Magnesium stearate	1.00
5.00	7	Talc	5.00
1.00	8	Aerosil 200	1.00
–	9	Water, purified, ca	50 mL

Manufacturing Directions

1. Sift items 1 to 4 through a 250-μm sieve, and charge in a suitable mixer. Mix the items for 15 minutes.
2. In a separate vessel, charge item 5, mix with hot item 9, and form a smooth slurry.
3. Add step 2 into step 1, and mix the items to achieve a lump-free mass.
4. Pass the wet mass through a #8 sieve onto paper-lined trays.
5. Dry the granules at 50°C overnight to reach an LOD of no more than 2%. Transfer to a blender.
6. Pass items 6 to 8 through a 250-μm sieve, add to step 5, and blend for 2 minutes.
7. Compress into 125-mg tablets, using 7-mm punches.
8. Coat tablets with an HPMC methylene chloride coating. (See Appendix.)

Levamisole Tablets (150 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Levamisole hydrochloride	150.00
300.00	2	Ludipress	300.00
4.00	3	Magnesium stearate	4.00

Manufacturing Directions

1. Mix all components, pass the mixture through a 0.8-mm sieve.
2. Press with low-compression force.
3. Compress into 458-mg tablets, using 12-mm biplanar punches.

Levofloxacin Tablets (250 mg) Levaquin

Levaquin tablets are available as film-coated tablets and contain the following active ingredients: *250 mg (as expressed in the anhydrous form):* hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80, and synthetic red iron oxide; *500 mg (as expressed in the anhydrous form):* hydroxypropyl methylcellulose, crospovidone, microcrystalline cellulose, magnesium stearate, polyethylene glycol, titanium dioxide, polysorbate 80, and synthetic red and yellow iron oxides.

Levothyroxine Sodium Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.05	1	Levothyroxine sodium	0.05
10.00	2	Citric acid anhydrous	10.00
1.00	3	Magnesium citrate	1.00
89.00	4	Ludipress	89.00

Manufacturing Directions

1. Prepare a premix of items 1 and 2. Add items 3 and 4, and pass the mixture through a 0.8-mm sieve.
2. Mix and press with low-compression force.
3. Compress into 101-mg tablets, using 6-mm biplanar punches. Item 2 may be omitted and compensated with item 4. If the content uniformity of formulation No. 1 does not meet the requirements, add a small part of the Ludipress and item 3 mixture, and the mixture of items 1 and 2. The function of citric acid in formulation No. 2 is to stabilize the active ingredient.

Levothyroxine Tablets

The inactive ingredients in synthroid tablets are acacia, confectioner's sugar (contains cornstarch), lactose, magnesium stearate, povidone, and talc. The following are the color additives by tablet strength: *25 mcg:* FD&C Yellow No. 6; *50 mcg:* none; *75 mcg:* FD&C Red No. 40 and FD&C Blue No. 2; *88 mcg:* FD&C Blue No. 1, FD&C Yellow No. 6, and D&C Yellow No. 10; *100 mcg:* D&C Yellow No. 10, FD&C Yellow No. 6; *112 mcg:* D&C Red No. 27 and 30; *125 mcg:* FD&C Yellow No. 6, FD&C Red No. 40, FD&C Blue No. 1; *150 mcg:* FD&C Blue No. 2; *175 mcg:* FD&C Blue No. 1, D&C Red No. 27 and 30; *200 mcg:* FD&C Red No. 40, *300 mcg:* D&C Yellow No. 10, FD&C Yellow No. 6, and FD&C Blue No. 1.

Levothyroxine Tablets (50 mcg) Synthroid

The inactive ingredients in synthroid tablets are as follows: acacia, confectioner's sugar (contains cornstarch), lactose, magnesium stearate, povidone, and talc. The following are the color additives by tablet strength: *25 mcg:* FD&C Yellow No. 6; *50 mcg:* none; *75 mcg:* FD&C Red No. 40 and FD&C Blue No. 2; *88 mcg:* FD&C Blue No. 1, FD&C Yellow No. 6, and D&C Yellow No. 10; *100 mcg:* D&C Yellow No.10, FD&C Yellow No. 6; *112 mcg:* D&C Red No. 27 and 30; *125 mcg:* FD&C Yellow No. 6, FD&C Red No. 40, and FD&C Blue No. 1; *150 mcg:* FD&C Blue No. 2; *175 mcg:* FD&C Blue No. 1 and D&C Red No. 27 and 30; *200 mcg:* FD&C Red No. 40; and *300 mcg:* D&C Yellow No. 10, FD&C Yellow No. 6, and FD&C Blue No. 1.

Levothyroxine Tablets (0.025 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.025	1	Levothyroxine	0.025
11.42	2	Prosolv SMCC 50	11.42
104.29	3	Prosolv SMCC 90	104.29
6.14	4	Sodium starch glycolate	6.14
0.86	5	Magnesium stearate	0.86
0.28	6	FD&C Yellow No. 6	0.28

Manufacturing Directions

1. Add items 1 and 2 in a suitable blender. Blend the items for 10 minutes, and pass through #60 mesh.
2. In a separate container, take 50% of item 3 and item 6, and blend for 10 minutes.
3. Add the balance of item 3 to step 1, and blend for 1 minute.
4. Add step 3 into step 1, and mix.
5. Add items 4 and 5, one at a time, and blend.
6. Compress into 123-mg tablets.

Levothyroxine Sodium Fast-Melt Tablets

Manufacturing Directions

1. Mix levothyroxine sodium, 30%; sodium bicarbonate, 24%; citric acid, anhydrous, 24%; anhydrous lactose, 10%; xylitol, 10%; and sucrose stearate, 2%.
2. Dry the above ingredients at elevated temperatures to significantly reduce the moisture content of each material.
3. Blend for 10 minutes and extruded in a hot melt extruder at 70°C to 100°C to soften and melt the thermal binders (sucrose stearate and xylitol) and to form granules containing the effervescent ingredients.
4. Mix LS-EGF (20–80 mesh), 55%; microcrystalline cellulose, 26%; Mannitol, 10%; cross povidone, 5%; aspartame, 3%; redberry flavor, 0.4%; magnesium stearate, 0.5%; and fumed silicon dioxide, 0.1%.
5. Blend for approximately 5 minutes prior to compression.
6. Levothyroxine sodium tablets are then compressed to a hardness of approximately 1 to 5 kPa (depending upon the dose of the drug) and tablets disintegrate in water in approximately 15 to 35 seconds.

Linezolid Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Linezolid	400.00
40.00	2	Starch (maize)	40.00
78.40	3	Microcrystalline cellulose PH 101	78.40
8.00	4	Hydroxypropyl cellulose	8.00
28.00	5	Sodium starch glycolate	28.00
5.60	6	Magnesium stearate	5.60

Manufacturing Directions

Mix all ingredients, and compress into 560-mg tablets, using 12-mm biplanar punches.

Lisinopril and Hydrochlorothiazide Tablets (10/12.50)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000Tablets (g)
10.00	1	Lisinopril	10.00
12.50	2	Hydrochlorothiazide	12.50
68.20	3	Dibasic calcium phosphate Anhydrous, DC Grade	68.20
30.00	4	Mannitol	30.00
6.50	5	Starch 1500	6.50
0.50	6	Yellow ferric oxide	0.50
1.00	7	Red ferric oxide	1.00
1.30	8	Magnesium stearate	1.30

Manufacturing Directions

1. Pass item 3 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 2, 5, 6, and 7 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 15% (= 5.20 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity from step 4 into step 2.
6. Pass item 4 through 0.7-mm sieve and charge in step 2.
7. Transfer the remaining half quantity of step 4 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 8 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 130-mg tablets, using a suitable punch (5.0 mm × 6.0 mm, oval).

Lisinopril and Hydrochlorothiazide Tablets (20/12.5)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Lisinopril	20.00
12.50	2	Hydrochlorothiazide	12.50
73.50	3	Dibasic calcium phosphate Anhydrous, DC Grade	73.50
35.00	4	Mannitol	35.00
7.50	5	Starch 1500	7.50
1.50	6	Magnesium stearate	1.50

Manufacturing Directions

1. Pass item 3 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 2, and 5 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 15% (=5.5 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity from step 4 into step 2.
6. Pass item 4 through 0.7-mm sieve and charge in step 2.
7. Transfer the remaining half quantity of step 4 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 6 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 150-mg tablets, using a suitable punch (6.5 mm, round).

Lisinopril and Hydrochlorothiazide Tablets (20/25)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Lisinopril	20.00
25.00	2	Hydrochlorothiazide	25.00
110.50	3	Dibasic calcium phosphate anhydrous, DC grade	110.50
30.00	4	Mannitol	30.00
10.00	5	Starch 1500	10.00
1.50	6	Yellow ferric oxide	1.50
1.00	7	Red ferric oxide	1.00
2.00	8	Magnesium stearate	2.00

Manufacturing Directions

1. Pass item 3 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 2, 5, 6, and 7 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 10% (=5.50 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity from step 4 into step 2.
6. Pass item 4 through 0.7-mm sieve and charge in step 2.
7. Transfer the remaining half quantity of step 4 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 8 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 200-mg tablets, using a suitable punch (6.5 mm × 7.5 mm, oval).

Lisinopril Tablets (10 mg), Zestril

Zestril is supplied as 2.5-, 5-, 10-, 20-, and 40-mg tablets for oral administration. The inactive ingredients are as follows: *2.5-mg tablets:* calcium phosphate, magnesium stearate, mannitol, and starch; *5-, 10-, and 20-mg tablets:* calcium phosphate, magnesium stearate, mannitol, red ferric oxide, and starch; *40-mg tablets:* calcium phosphate, magnesium stearate, mannitol, starch, and yellow ferric oxide.

Lisinopril Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Lisinopril	10.00
139.00	2	Ludipress	139.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve.
2. Mix intensively, and press with low-compaction force (10 kN).
3. Compress into 152-mg tablets, using 8-mm biplanar punches.

Lisinopril Tablets (2.5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000Tablets (g)
2.50	1	Lisinopril	2.50
66.50	2	Dibasic calcium phosphate Anhydrous, DC Grade	66.50
25.00	3	Mannitol	25.00
5.00	4	Starch 1500	5.00
1.00	5	Magnesium stearate	1.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass item 1 and item 4 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 15% (= 4.6 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity from step 4 into step 2.
6. Pass item 3 through 0.7-mm sieve and charge in step 2.
7. Transfer the remaining half quantity of step 4 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 5 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 100-mg tablets, using a suitable punch (5.0 mm × 5.5 mm, oval).

Lisinopril Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000Tablets (g)
5.00	1	Lisinopril	5.00
61.50	2	Dibasic calcium phosphate anhydrous, DC grade	61.50
27.00	3	Mannitol	27.00
5.00	4	Starch 1500	5.00
0.50	5	Red ferric oxide	0.50
1.00	6	Magnesium stearate	1.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 4, and 5 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 20% (= 6.2 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity from step 4 into step 2.
6. Pass item 3 through 0.7-mm sieve and charge in step 2.
7. Transfer the remaining half quantity of step 4 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 6 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 100-mg tablets, using a suitable punch (5.0 mm, round).

Lisinopril Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000Tablets (g)
10.00	1	Lisinopril	10.00
81.20	2	Dibasic calcium phosphate Anhydrous, DC Grade	81.20
30.00	3	Mannitol	30.00
6.50	4	Starch 1500	6.50
1.00	5	Red ferric oxide	1.00
1.30	6	Magnesium stearate	1.30

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass item 1, item 4 and item 5 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 15% (= 6.0 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity from step 4 into step 2.
6. Pass item 3 through 0.7-mm sieve and charge in step 2.
7. Transfer the remaining half quantity of step 4 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 6 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress to 130-mg tablets, using a suitable punch (5.0 mm × 6.0 mm, oval).

Lisinopril Tablets (15 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000Tablets (g)
15.00	1	Lisinopril	15.00
89.50	2	Dibasic calcium phosphate Anhydrous, DC Grade	89.50
35.00	3	Mannitol	35.00
7.50	4	Starch 1500	7.50
1.50	5	Red ferric oxide	1.50
1.50	6	Magnesium stearate	1.50

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 4, and 5 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 15% (= 6.7 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity from step 4 into step 2.
6. Pass item 3 through 0.7-mm sieve and charge in step 2.
7. Transfer the remaining half quantity of step 4 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 6 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 150-mg tablets, using a suitable punch (7 mm, round).

Lisinopril Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000Tablets (g)
20.00	1	Lisinopril	20.00
121.00	2	Dibasic calcium phosphate anhydrous, DC grade	121.00
45.00	3	Mannitol	45.00
10.00	4	Starch 1500	10.00
2.00	5	Red ferric oxide	2.00
2.00	6	Magnesium stearate	2.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 4, and 5 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 10% (= 6.0 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity from step 4 into step 2.
6. Pass item 3 through 0.7-mm sieve and charge in step 2.
7. Transfer the remaining half quantity of step 4 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 6 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 200-mg tablets, using a suitable punch (7.5 mm × 8.0 mm, oval).

Lisinopril Tablets (40 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000Tablets (g)
20.00	1	Lisinopril	20.00
121.00	2	Dibasic calcium phosphate Anhydrous, DC Grade	121.00
45.00	3	Mannitol	45.00
10.00	4	Starch 1500	10.00
2.00	5	Red ferric oxide	2.00
2.00	6	Magnesium stearate	2.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 4, and 5 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 10% (= 7.1 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity from step 4 into step 2.
6. Pass item 3 through 0.7-mm sieve and charge in step 2.
7. Transfer the remaining half quantity of step 4 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 6 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 250-mg tablets, using a suitable punch (8.0 mm, round).

Lithium Carbonate Tablets

Manufacturing Directions

1. Sodium chloride (8000 g) is milled through a Whistler Mill using a small slotted screen and 60,000 g of lithium carbonate are charged into a 5 ft^3 ribbon blender and the blending is carried out for 5 minutes.
2. The blender is discharged and the powder mixture is passed through a FitzMill at a high speed (hammers). The powder is then returned to the blender and wet granulated (16,000 g of water) with povidone.
3. The binder solution in water is added while the mixer is running. The resultant wet mass is passed through the FitzMill (1/2 in., perforated band, hammers forward) at high speed. The resultant mass is trayed and dried overnight (16 hours at 55°C).
4. The dried mixture is sized through the FitzMill (2A with knives at medium speed). The resultant blend is returned to the ribbon blender.
5. Sorbitol powder is passed through a 40-mesh screen along with Stearowet C (a combination of calcium stearate and sodium lauryl sulfate). 2000 g of the Stearowet C and 8000 g of the sorbitol powder are added to the blender along with 200 g of the sodium starch glycolate and the blend is mixed for 5 minutes.
6. The resultant mixture is compressed into 200,000 tablets using a 3/8-in. standard concave tooling, uppers plain, lowers plain.
7. Each tablet weighs 406 mg and has the following composition: lithium carbonate, 300 mg; sodium chloride, 49 mg; polyvinyl pyrrolidone, 15 mg; Stearowet C, 10 mg; sorbitol, 40 mg; and sodium starch glycolate, 1 mg. The compressed tablets have a hardness of 8 to 10 kPa, a friability of NMT 0.4%, and a thickness of 0.175 in.
8. The tablets are optionally coated using conventional procedures. The tablets are placed in Accela-Cota and 10,000 mL of a conventional clear film seal solution are sprayed thereon. Subsequently, 30,000 mL of a colored film seal (e.g., 1300 g of Opaspray K-1-1243 in 30,000 mL of a clear film seal solution) are sprayed. This is followed by spraying of 10,000 mL of half-strength film and color solution (e.g., 215 g of the same ingredient in 10,000 mL of half-strength film seal solution). The spraying is finished with 5000 mL of half-strength film seal solution. The coated tablets are dried in a pan for 1 hour using 800 to 1000 cfm of air at 30°C to 35°C. They are trayed and dried at 20°C to 23°C overnight. After submission of, e.g., 150 tablets to quality control for approval, the tablets are polished in a pan with 2 g of carnauba wax.

Lomefloxacin Hydrochloride Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Lomefloxacin, use lomefloxacin hydrochloride	442.00
123.00	2	Microcrystalline cellulose	123.00
13.50	3	Croscarmellose sodium Type A	13.50
1.80	4	Hydroxy propyl cellulose	1.80
3.50	5	Silicon dioxide, colloidal	3.50
2.70	6	Polyoxyl 40 stearate	2.70
81.00	7	Starch (maize)	81.00
7.50	8	Magnesium stearate	7.50
—	9	Water, purified, ca	65 mL
QS	10	Ethanol, ca	90 mL

Manufacturing Directions

1. If necessary, mill all items to remove any lumps.
2. Mix in a suitable mixer (double-cone or Y). Before this, sieve items 1 to 3 and item 7 through a 60-mesh screen (0.25 mm). Then mix at medium speed for 15 minutes.
3. In a suitable container, mix disperse items 4 and 6 and add items 9 and 10. Mix until dissolved. Allow to stand overnight.
4. Add the binder solution from step 3 to the mix obtained in step 2, and pass the wet mass through a 20-mesh sieve to obtain granules.
5. Dry the granules at 55°C for 15 hours to get a moisture content of not more than 2.5% (determined at 80°C for 4 hours).
6. Blend the granules with item 5 for over 5 minutes, then add item 8, and mix again for 3 minutes.
7. Compress tablets with a target weight of 675 mg.
8. Coat, using an HPMC coating. (See Appendix.)

Loperamide Hydrochloride Fast-Melt Tablets

Manufacturing Directions

1. Prepare granules by using loperamide hydrochloride, 5%; sodium bicarbonate, 27%; citric acid anhydrous, 27%; tartaric acid, 3%; microcrystalline cellulose, 15%; anhydrous lactose, 8%; xylitol, 12%; and Crodesta F160, 3%.
2. The above ingredients are dried at elevated temperature in the presence of a desiccant to significantly reduce the moisture content of each material.
3. The ingredients are then blended for 10 minutes and extruded in a hot melt extruder at 70°C to 100°C to soften and melt the thermal binders (sucrose stearate and xylitol) to form granules containing the effervescent ingredients.
4. Granules are passed through a screen and then blended with the following ingredients: LH-EFG (30–80 mesh) 50%, microcrystalline cellulose 31%, Mannitol 8%, AcDiSol 5%, L-HPC LH-11 2%, aspartame 3%, redberry flavor 0.4%, magnesium stearate 0.5%, and Cab-O-Sil M5P 0.1%, which are mixed for 5 minutes prior to compression.
5. Loperamide FICI tablets are then compressed to a hardness of approximately 1 to 3 kPa and tablets disintegrate in purified water in approximately 15 to 35 seconds.

Loperamide Hydrochloride Tablets (2 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.00	1	Loperamide hydrochloride	2.00
68.00	2	Starch (maize)	68.00
46.00	3	Lactose monohydrate	46.00
3.00	4	Starch (maize)	3.00
56.00	5	Dicalcium phosphate	56.00
2.00	6	Talc	2.00
2.00	7	Magnesium stearate	2.00
—	8	Water, purified, ca	60 mL

Manufacturing Directions

1. Sift items 2, 3, and 5 through a 250-μm sieve, and sift item 1 through #40 mesh. Charge them in a suitable mixing vessel by a geometric dilution process for item 1, and then mix for 30 minutes (this step is critical to content uniformity).
2. Charge item 3 in a suitable vessel, and add item 8. Heat it and mix to prepare a smooth slurry.
3. Add step 2 to step 1 slowly, and mix to obtain a lump-free mass.
4. Pass the wet mass through #6 mesh onto paper-lined trays.
5. Dry the granules in a fluid-bed dryer at 50°C for 1 hour to LOD of not more than 2.5%. Transfer to a blender.
6. Pass item 6 through a 500-μm sieve and item 7 through a 250-μm sieve, and add to step 6; blend for 2 minutes.
7. Compress into 170-mg tablets, using 8-mm punches.

Loratadine and Pseudoephedrine Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Loratidine	25.00
180.00	2	Pseudoephedrine sulfate	180.00
5.00	3	Polyvinylpyrrolidone	5.00
75.00	4	Low-substitutued hyydroxypropyl cellulose	75.00
75.00	5	Crospovidone	75.00
1.50	6	Colloidal silicon dioxide	1.50
250.00	7	Crystalline sugar seeds	250.00
120.00	8	Purified water	120.00

Manufacturing Directions

1. A binder solution is prepared by dissolving 5.0 g of polyvinylpyrrolidone in 120 g of water.
2. 25 g of loratadine, 180 g of pseudoephedrine sulfate, 25 g of microcrystalline cellulose, 75 g of low-substituted hydroxypropyl cellulose, 75 g of crospovidone, and 1.5 g of colloidal silicon dioxide are mixed and screened through a 20-mesh sieve to give a mixed powder.
3. The binder solution of step 1 is sprayed onto 250 g of crystalline sugar seeds in a centrifugal granulator, the mixed powder is dusted onto the crystalline sugar seeds in the centrifugal granulator to afford pellets using the rotation panel rate of 140 to 200 rpm, the spraying rate of the binder solution of 2 to 20 mL/min, air spraying pressure of 1 to 2 kg/cm^2, air spraying volume of 5 to 300 L/min, and powder (step 2) spraying rate of 5 to 30 g/min).

Loratidine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Loratidine	10.00
69.93	2	Pregelatinized starch	69.93
69.63	3	Microcrystalline cellulose	69.63
0.37	4	Colloidal silicon dioxide	0.37
0.25	5	Magnesium stearate	0.25

Manufacturing Directions

1. A multistep blending process is used in order to ensure proper distribution of the active. Initially, half of the Starch 1500® is combined with the drug and colloidal silicon dioxide.
2. This mixture is blended in a twin-shell V-blender for 5 minutes.
3. The mixture is then discharged and passed through a 40-mesh screen by hand.
4. This step not only breaks up the silicon dioxide but also helps to distribute the active.
5. The screened mixture is returned to the blender and the remainder of the Starch 1500® is added and blended for an additional 5 minutes.
6. Microcrystalline cellulose is then added and blended for 10 minutes.
7. Magnesium stearate is added last and blended for 5 minutes.
8. Magnesium stearate is passed through a 60-mesh screen prior to weighing.
9. Tablets are compressed at 100 mg or proportionally for different strengths.

Loratidine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Loratidine	10.00
67.30	2	Lactose monohydrate	67.30
22.00	3	Maize starch	22.00
10.00	4	Maize starch	10.00
5.00	5	Maize starch, dried	5.00
0.70	6	Magnesium stearate	0.70
QS	7	Purified water	QS

Manufacturing Directions

1. Sift items 1 to 3 through a 630-μm stainless steel sieve, load in mixer, and mix for 5 minutes.
2. In a separate container, prepare binder solution by mixing item 4 using purified water at 30°C to 40°C; heat translucent slurry to 90°C to 95°C, and cool to 45°C to 50°C.
3. Mix the binder solution with the first step, and granulate; dry on trays at 55°C for 8 hours; dry to LOD of 2% to 3% (2 hours after beginning drying, crush mixture for uniform drying).
4. Heat for additional 1 hour at 55°C if LOD is not within limits.
5. Add magnesium stearate, tumble mix, and compress using 7.00-mm round punches to 10 tablet weight of 1.15 (within 3%) to achieve thickness of 2.3 ± 0.3 mm and hardness of 4 to 7 kPa.

Loratidine and Chlorpheniramine Sustained-Release Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Loratidine	5.00
141.50	2	Lactose monohydrate	141.50
55.00	3	Microcrystalline cellulose	55.00
22.00	4	Starch	22.00
1.50	5	Magnesium stearate	1.50
18.00	6	Eudragit S100	18.00
9.00	7	Triethyl citrate	9.00
4.50	8	Talc	4.50
0.315	9	Ammonium hydroxide 1N solution	0.315
qs	10	Water	qs
14.00	11	Eudragit EPO	14.00
8.00	12	Citric acid	8.00
Qs	13	Water	Qs
4.00	14	Chlorpheniramine maleate	4.00
45.00	15	Lactose fine powder	45.00
15.00	16	Sucrose fine powder	15.00
2.00	17	Flavor optional	2.00
0.10	18	Polyvinylpyrrolidone	0.10
Qs	19	Ethanol 95%	Qs
qs	20	Water	qs

Manufacturing Directions

1. Prepare a granulation containing loratadine, lactose, microcrystalline cellulose, and starch.
2. Blend with magnesium stearate for 5 minutes.
3. Compress about 225 mg.
4. Compress the above granulation into CAT unit using tooling and tabletting apparatuses.
5. Prepare the coating solution by mixing water, Eudragit S100, ammonium hydroxide solution, triethyl citrate, and talc to form a uniform dispersion.
6. Coat loratadine from step 3 with Eudragit S coating solution using a coating pan or a fluid-bed coater until a desired coat weight is achieved (256.80).
7. Prepare a coating solution containing Eudragit E and citric acid in water.
8. Coat tablets from step 6 to 278.80 mg.
9. Prepare the solvent mixture containing polyvinylpyrrolidone, ethyl alcohol, and water.
10. Blend chloropheniramine maleate, lactose, sucrose, and flavoring agent. Screen to break lumps.
11. Mix until a moistened powder blend is achieved.
12. Double compress loratidine tablet with chlorpheniramine triturate.
13. The product contains 4 mg of chloropheniramine maleate in the molded triturate tablet for intraoral release and 5 mg of loratadine in the delayed release form as incorporated in the matrix. Enteric-coated loratadine starts to release 4 to 8 hours after administration of the dosage form.

Loratadine and Pseudoephedrine Sulfate Tablets (10 mg/240 mg) Claritin-D

Claritin-D® 12-hour extended-release tablets—These tablets contain 5 mg of loratadine in the tablet coating for immediate release and 120 mg of pseudoephedrine sulfate, which is equally distributed between the tablet coating for immediate release and the barrier-coated extended-release core. The inactive ingredients are acacia, butylparaben, calcium sulfate, carnauba wax, cornstarch, lactose, magnesium stearate, microcrystalline cellulose, neutral soap, oleic acid, povidone, rosin, sugar, talc, titanium dioxide, white wax, and zein.

Claritin-D 24-hour extended-release tablets—These tablets contain 10 mg of loratadine in the tablet film coating for immediate release and 240 mg pseudoephedrine sulfate in the tablet core, which is released slowly, allowing for once-daily administration. The inactive ingredients for oval, biconvex Claritin-D 24-hour extended-release tablets are calcium phosphate, carnauba wax, ethylcellulose, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol, povidone, silicon dioxide, sugar, titanium dioxide, and white wax.

Loratidine and Pseudoephedrine Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
240.00	1	Pseudoephedrine sulfate	240.00
15.00	2	Microcrystalline cellulose (Avicel PH 101)	15.00
200.00	3	Xanthan gum Keltrol TF	200.00
80.00	4	Sodium alginate keltone HVCR	80.00
53.00	5	Calcium carbonate	53.00
6.00	6	Magnesium stearate	6.00
6.00	7	Aerosil 200	6.00
10.00	8	Loratadine	10.00
95.00	9	Lactose monohydrate	95.00
66.50	10	Microcrystalline cellulose (Avicel PH 101)	66.50
1.00	11	FD&C Yellow No. 10	1.00
20.00	12	Starch (maize)	20.00
6.00	13	Starch (maize)	6.00
1.50	14	Magnesium stearate	1.50
–	15	Water, purified	60.00

Manufacturing Directions

1. Charge pseudoephedrine sulfate, microcrystalline cellulose, xanthan gum, sodium alginate, calcium carbonate, and one-half of the lubricants in a suitable mixer after sieving through a #44 sieve.
2. Pass the blend through a roll-compactor.
3. Sieve the compact through a #22 sieve to obtain granules.
4. Mix the granules with the remaining lubricants (items 6 and 7), and compress into tablets (600 mg) to form the first tablet layer.
5. Charge items 8 to 12 after passing through a #100 sieve in a suitable mixer. Blend these items for 10 minutes.
6. Charge item 13 in a separate vessel, and make a paste (10%) using item 14.
7. Add step 6 into step 5, and granulate.
8. Dry the granules and blend or sift item 14.
9. Compress into 200-mg tablets (the second layer).
10. Use appropriate tabletting equipment for bilayer tabletting or core tabletting.

Loratidine Fastab

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Loratadine (micronized)	10.00
180.60	2	Pharmaburst	180.60
2.70	3	Acesulfame K	2.70
2.00	4	Magnesium stearate	2.00
2.00	5	Talc (fine powder)	2.00
2.70	6	Dry anise flavor	2.70

Manufacturing Directions

1. Sift and mix items 1, 2, 3, and 6.
2. Lubricate with magnesium stearate and fine talc powder.
3. Compress into 200-mg tablets, using 6-mm punches.

Loratadine Tablets (10 mg), Claritin

Claritin® tablets contain 10 mg of micronized loratadine, an antihistamine, to be administered orally. They also contain the following inactive ingredients: cornstarch, lactose, and magnesium stearate.

Claritin Reditabs (rapidly disintegrating tablets) contain 10 mg of micronized loratadine, an antihistamine, to be administered orally. It disintegrates in the mouth within seconds after placement on the tongue, allowing its contents to be subsequently swallowed with or without water. Claritin Reditabs also contain the following inactive ingredients: citric acid, gelatin, mannitol, and mint flavor.

Loratidine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Loratadine	10.00
67.30	2	Lactose monohydrate	67.30
22.00	3	Starch (maize)	22.00
10.00	4	Starch (maize)	10.00
5.00	5	Starch (maize, dried)	5.00
0.70	6	Magnesium stearate	0.70
–	7	Purified water	40.00

Manufacturing Directions

Note: Avoid overmixing the lubricants, otherwise hardness is reduced.

1. Sieving and dry mixing: Sift items 1 to 3 through a stainless steel 630-μm sieve in a sifter. Load into mixer. Mix for 5 minutes at low speed.
2. Preparing the binder: Prepare a slurry of item 4 in 10 g of item 7 (30–40°C). Then make a translucent paste in a Guisti steam jacked vessel, using 30 g of item 7 (90–95°C). Cool to 45°C to 50°C. Check the unity of the paste. The theoretical weight is 50 g.
3. Kneading
   a. Knead the powder with starch paste, while mixing at low speed over a period of 2 minutes.
   b. Scrape sides and backs. Mix and chop at speed 1 for 2 minutes. Check the end point of granulation. If required, add additional purified water to get the end point. (The end point of the granulation is the point when the wet mass consists of little or no lumps of the granules.)
   c. Unload the wet granules into a stainless steel tray for drying.
4. Drying and LOD
   a. Dry the wet granules in an oven at 55°C for 8 hours. After 2 hours of drying, scrape the semidried granules to break any lumps (for uniform drying).
   b. Check the LOD, with a limit of 2% to 3%.
   c. If required, dry further at 55°C for 1 hour. Check the LOD.
   d. Transfer the dried granules into stainless steel drums.
5. Grinding and lubricating
   a. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect in stainless steel drums. Load the granules into a drum blender.
   b. Sift items 5 and 6 through a 500-μm sieve using a sifter, and add it into a drum blender. Mix for 2 minutes.
   c. Unload into stainless steel drums.
6. Compressing: Compress the granules using a rotary tabletting machine with a 7-mm flat, bevel-edge punches to 115 mg per tablet.

Lorazepam Tablets (0.50 mg/1 mg/2 mg), Ativan

Ach Ativan tablet, to be taken orally, contains 0.5, 1, or 2 mg of lorazepam. The inactive ingredients present are lactose and other ingredients.

Lorazepam Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.50	1	Lorazepam	0.50
50.00	2	Lactose	50.00
20.00	3	Starch (maize)	20.00
2.00	4	Methyl cellulose	2.00
25.00	5	Microcrystalline cellulose (Avicel PH 101)	25.00
1.00	6	Magnesium stearate	1.00

Manufacturing Directions

1. Mix lorazepam, lactose, starch, and one-half of the microcrystalline cellulose in a suitable mixer.
2. Granulate with a solution of methyl cellulose in water.
3. Dry the granules. Mix the remaining microcrystalline cellulose and magnesium stearate. Compress. Adjust the 1- and 2-mg strengths with lactose.

Losartan and Hydrochlorothiazide Tablets (50 mg/12.5 mg)

Hyzaar is available for oral administration, containing 50 mg of losartan potassium, 12.5 mg of hydrochlorothiazide, and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, and D&C Yellow No. 10 Aluminum Lake. Hyzaar contains 4.24 mg (0.108 mEq) of potassium.

Losartan Potassium Tablets (50 mg), Cozar

Cozaar is available for oral administration, containing either 25 or 50 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, titanium dioxide, D&C Yellow No. 10 Aluminum Lake, and FD&C Blue No. 2 Aluminum Lake. Cozaar 25- and 50-mg tablets contain potassium in the following amounts: 2.12 mg (0.054 mEq) and 4.24 mg (0.108 mEq), respectively.

Losartan Potassium Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Losartan potassium	50.00
46.00	2	Microcrystalline cellulose	46.00
75.50	3	Lactose, spray dried	75.50
7.50	4	Starch 1500	7.50
1.00	5	Magnesium stearate	1.00
3.00	6	Hypromellose	3.00
0.75	7	Talc, fine powder	0.75
0.75	8	Titanium dioxide	0.75
0.50	9	Polyethylene glycol	0.50
–	10	Ethanol	QS
–	11	Purified water	QS

Manufacturing Directions

1. Sift losartan potassium, lactose spray dried, and microcrystalline cellulose through a stainless steel 500-µm sieve.
2. Load sifted powder into a blender and blend well.
3. Sift magnesium stearate and Starch 1500 through a stainless steel 250-µm sieve.
4. Load step 3 into the blender (step 2), and blend well.
5. Compress into 185-mg tablets, using 12-mm punches.
6. Coat the tablet using Eudragit L-100 coating. (See Appendix.)

Lycopene Tablet Cores (6 mg)

Formulation: LycoVit 10% dry powder, 60 g; Ludipress, 330 g; Kollidon CL, 6 g; magnesium stearate, 4 g.

Manufacturing Directions

1. Mix LycoVit dry powder with the other components.
2. Sieve through a 0.8-mm screen and press with medium- to high-compression force at 400 mg.

Magaldrate Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Magaldrate, USP	500.00
400.00	2	Lactose monohydrate	400.00
50.00	3	Orange flavor (FDO)	50.00
20.00	4	Kollidon® 90F	20.00
6.00	5	Banana flavor (FDO)	6.00
6.00	6	Cocoa flavor (FDO)	6.00
1.00	7	Saccharin sodium	1.00
180.00	8	Water	180.00
5.00	9	Aerosil® 200	5.00
3.00	10	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with solution of items 4 to 8, pass through an 0.8-mm sieve, dry, mix with items 9 and 10, and press with low-compression force.
2. Compress into 1-g tablets, using 16-mm biplanar punches.

Magaldrate Chewable Tablets (500 mg)

Formulation: I—Magaldrate USP, 500 g; lactose monohydrate [8], 400 g; orange flavor (FDO), 50 g. II—Kollidon 90F [1], 20 g; banana flavor (FDO), 6 g; cocos flavor (FDO), 6 g; saccharin sodium, 1 g; water, 180 g. III—Aerosil 200, 5 g; magnesium stearate, 3 g.

Manufacturing Directions

Wet granulation: Granulate mixture I with solution II, pass through a 0.8-mm sieve, dry, mix with III, and press with low-compression force at 1000 mg.

Magaldrate Chewable Tablets (1000 mg)

Formulation: Magaldrate (Reheis), 1000 g; Ludipress LCE, 930 g; Lutrol E4000F [1], 60 g; aspartame, potassium (Searle), 10 g; peppermint flavor, q.s.

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with medium-compression force at 2 g.

Magaldrate-Dispersible Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
700.00	1	Magaldrate	700.00
435.00	2	Lactose monohydrate	435.00
10.00	3	Kollidon® 90F	10.00
50.00	4	Kollidon® CL	50.00
5.00	5	Magnesium stearate	5.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix, and press with low-compression force (4–6 kN).
2. Compress into 1.2-g tablets, using 16-mm biplanar punches.

Magaldrate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Magaldrate (powder, 100 mesh)	400.00
325.00	2	Sucrose	325.00
60.00	3	Cellulose (microcrystalline) (Avicel™ PH101)	60.00
30.00	4	Cornstarch	30.00
8.84	5	Guar gum	8.84
0.50	6	Saccharin sodium	0.50
–	7	Purified water	100.00 mL
–	8	Alcohol SD 3A (200 proof)	100.00 mL
QS	9	Flavor	0.60 mL
QS	10	Flavor	1.00 mL
0.06	11	Ethyl vanillin	0.06
8.00	12	Talc	8.00
16.00	13	Magnesium stearate	16.0

Manufacturing Directions

1. Pass granulated sugar (take about 10% excess) through 500-μm stainless steel screen on comminuting mill (impact forward, high speed).
2. Screen the milled sugar through 250-μm aperture on sieve shaker.
3. Weigh the required quantity and charge into a suitable mixer.
4. Discard remaining sugar.
5. Screen magaldrate powder (take about 5% excess) through 150-μm stainless steel screen on sieve shaker.
6. Weigh the required quantity and add to the blend above.
7. Mix well.
8. Screen, if necessary, microcrystalline cellulose, cornstarch, and guar gum through 500-μm aperture on sieve shaker.
9. Add to the first step and mix well.
10. Dissolve saccharin sodium in water.
11. To this add alcohol and mix well.
12. Add this hydroalcoholic solution to magaldrate blend and knead well.
13. Add more water, if necessary, and QS to mass.
14. Pass wet mass through 2.8-mm aperture on sieve shaker or oscillating granulator and spread uniformly on stainless steel trays.
15. Tray-dry granules at 70°C to 75°C.
16. After 3 to 4 hours of drying, screen semidried granules through 1.4-mm aperture on sieve shaker, and reload for further drying.
17. (This step helps in drying granules faster and more uniformly.) Dry to LOD of 1% to 1.5%.
18. Screen dried granules through 1.0-mm aperture on sieve shaker, and store in drums doubly lined with polyethylene bags.
19. Charge half of the granulation into a suitable blender.
20. From the balance of the granules, take out the fines (about 40 g of fines for a batch of 1000 tablets) through 250-μm aperture on sieve shaker.
21. Retain coarse particles for later use.
22. Mix together the flavors in a suitable vessel.
23. Add and dissolve the ethyl vanillin.
24. Check that the solution is clear before proceeding.
25. Charge a suitable mixer with the fines from above.
26. While mixing, disperse the flavor solution.
27. Add magnesium stearate and talc and mix thoroughly.
28. Pass the blend through a 250-μm aperture on sieve shaker.
29. Add the dispersed flavor blend to the granules.
30. Add remaining granules and blend for 8 to 10 minutes.
31. Discharge blended granules into suitable air-tight containers doubly lined with polyethylene bags.
32. Compress on a suitable machine fitted with 14.4-mm-diameter round punches with beveled edges.
33. Weight: 8.5 g/10 tablets; thickness: ~3.6 to 3.8 mm; hardness: 8 to 10 kPa.

Magaldrate with Simethicone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
525.00	1	Sucrose, NF	525.00
15.00	2	Lactose monohydrate, NF	15.00
60.00	3	Simethicone, USP	60.00
60.00	4	Cellulose microcrystalline (Avicel™ PH101), NF	60.00
12.00	5	Silione dioxide colloidal (International)	12.00
400.00	6	Magaldrate, USP	400.00
40.00	7	Acacia (special grade), NF	40.00
0.05	8	Dye	0.05
–	9	Distilled purified water, USP	100.00 mL
–	10	Alcohol SD 3A (200 proof)	100.00 mL
1.50	11	Flavor	1.50
0.15	12	Ethyl vanillin, NF	0.15
5.00	13	Silicon dioxide (colloidal)	5.00
30.00	14	Starch monohydrate	30.00
10.00	15	Lactose monohydrate	10.00
80.00	16	Talc powder, USP	80.00
5.30	17	Magnesium stearate	5.30

Manufacturing Directions

1. Pass the granulated sucrose (with about 10% excess) through a 500-μm-aperture stainless steel screen on comminuting mill (impact forward, high speed).
2. Screen the milled sugar through a 250-μm screen on sieve shaker.
3. Weigh the required quantity and charge into a suitable mixer (planetary mixer or dough mixer). Discard the remainder.
4. Screen lactose (item 2) through a 250-μm aperture screen on sieve shaker and add to powdered sugar from step above. Mix well.
5. While mixing vigorously, add and disperse simethicone (add slowly in a fine stream of flow to avoid lump formation). Mix well.
6. Rough blend colloidal silicon dioxide (item 5) and microcrystalline cellulose, and add to the simethicone dispersed mass from previous step.
7. Mix initially at low speed for 4 to 5 minutes and thereafter mix vigorously for 5 to 10 minutes.
8. Either screen simethicone dispersed mass through a 1.0-mm aperture on sieve shaker or pass through a comminuting mill using a 1.4-mm aperture screen (impact forward, medium speed).
9. Load into a mass mixer and continue mixing.
10. Screen magaldrate powder (with about 7% excess) through a 150-μm aperture screen on sieve shaker and weigh the required quantity.
11. To this quantity add acacia and rough blend.
12. Add this blend in the dough mixer, dispersing in small quantities, and mix well for 30 to 40 minutes until simethicone is well absorbed in the dry blend. Discard remaining magaldrate powder.
13. Dissolve dye in water, then add alcohol, and mix well.
14. Wet down mass with colored hydroalcoholic solution and knead well.
15. Add more hydroalcoholic solution, if necessary (1:1 water-to-alcohol ratio), to mass.
16. Screen wet mass through a 2.8-mm aperture screen on sieve shaker or oscillating granulator and spread uniformly on trays.
17. Tray-dry granules at 71°C to 74°C until LOD is within 1% to 1.5% (test at 105°C for 1 hour).
18. After about 3 to 4 hours of drying, screen semidried granules through a 1.4-mm aperture on sieve shaker and reload for further drying.
19. (*Note*: This step helps in drying granules faster and more uniformly and avoids color mottling on final product.) Screen dried granules through a 1.0-mm aperture screen on sieve shaker, and store in drums lined with double polyethylene bags. Alternative drying can be done in a fluid-bed dryer.
20. Pass dried granules through a 1.00-mm aperture screen on sieve shaker.
21. Pass coarse granules through a comminuting mill using a 1.4-mm aperture screen (knives forward, slow speed) and then through 1.0-mm aperture on sieve shaker.
22. Store granules in drums lined with double polyethylene bags.
23. Charge half of the base granulation into a suitable blender.
24. From the balance of the granules take out fines (about 50 g of fines for a batch of 1000 tablets) through a 250-μm aperture on sieve shaker, and hold in a suitable vessel.
25. Add and dissolve ethyl vanillin in liquid flavor.
26. Check for clarity and only then disperse over dried starch.

27. Rough blend colloidal silicon dioxide (item 13) with lactose monohydrate (item 15), talc, and magnesium stearate, and add to the flavored starch.
28. To this mixture, add fines from the second step above, and mix well by hand or in a suitable mixer.
29. Screen through a 250-µm aperture on sieve shaker.
30. Add this flavored, dispersed blend to the base granulation (first step) in a blender.
31. Add the remaining bulk granules from the second step to the base granulation and blend well for 8 to 10 minutes. (*Caution*: Do not mix for too long as the granules may crumble to a finer size, which may adversely affect hardness during compression.) Discharge blended granules into suitable airtight containers lined with double polyethylene bags until ready for compressing.
32. Compress on a suitable machine fitted with 14.4-mm-diameter round punches with beveled edges. Compress into 1244-mg tablets.

Magnesium Carbonate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
260.00	1	Magnesium carbonate, USP	262.00
238.00	2	Ludipress®	238.00
4.00	3	Magnesium stearate	4.00

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press with medium-compression force.
2. Compress into 500-mg tablets, using 12-mm biplanar punches.

Mebendazole Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Mebendazole	100.00
196.00	2	Ludipress	196.00
4.00	3	Magnesium stearate	4.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress into 294-mg tablets, using 12-mm biplanar punches.

Meclizine Hydrochloride Tablets (25 mg)

Meclizine hydrochloride tablets are multiple-layered tablets (MLT) available in 12.5-, 25-, and 50-mg strengths for oral administration. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, starch, stearic acid, and other ingredients. In addition, the 12.5-mg tablet contains FD&C Blue No. 1; the 25-mg tablet contains D&C Yellow No. 10 and FD&C Yellow No. 5; and the 50-mg tablet contains D&C Yellow No. 10, FD&C Blue No. 1, and FD&C Yellow No. 5.

Medroxyprogesterone Acetate Tablets (2.5 mg/5 mg/10 mg), Provera

Each Provera tablet for oral administration contains 2.5, 5, or 10 mg of medroxyprogesterone acetate. The inactive ingredients are calcium stearate, cornstarch, lactose, mineral oil, sorbic acid, sucrose, and talc. The 2.5-mg tablet contains FD&C Yellow No. 6.

Mefenamic Acid and Dicyclomine Hydrochloride Tablets (250 mg/10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Mefanamic acid	250.00
10.00	2	Dicyclomine hydrochloride	10.00
30.00	3	Lactose monohydrate	30.00
16.00	4	Starch (maize)	16.00
4.80	5	Gelatin	4.80
3.20	6	Polyvinylpyrrolidone potassium 30	3.20
6.00	7	Talc	6.00
6.00	8	Magnesium stearate	6.00
6.00	9	Sodium starch glycolate	6.00
4.00	10	Aerosil 200	4.00
0.80	11	Methyl paraben	0.80
0.08	12	Propyl paraben	0.08
–	13	Water, purified, ca	75 mL

Manufacturing Directions

1. Charge items 1 to 3 in a suitable mixer after passing them through a 250-μm sieve. Mix the items for 10 minutes.
2. In a separate vessel, bring to boil item 13 and add items 11 and 12 at 90°C to dissolve. Add items 4 to 6 to the hot solution, and stir to disperse into a smooth slurry. Cool to 50°C.
3. Add step 2 into step 1, and mix thoroughly to obtain a lump-free wet mass. Pass the wet mass through a 2.38-mm sieve onto paper-lined trays. Dry the granules at 50°C overnight until an LOD of not more than 2% is reached.
4. Pass the dried granules through a 1.19-mm mesh screen into a suitable tumbler.
5. Sift items 9 and 10 through a 500-μm sieve and item 8 through a 250-μm sieve into step 4, and blend for 3 minutes.
6. Compress into 335-mg tablets, using 9.5-mm punches.

Mefenamic Acid Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Mefenamic acid	250.00
40.00	2	Starch (maize)	40.00
5.00	3	Kollidon 90F	50.00
–	4	Isopropyl alcohol	QS
12.00	5	Kollidon CL	12.00
85.00	6	Microcrystalline cellulose (Avicel PH 101)	85.00
5.00	7	Magnesium stearate	5.00

Manufacturing Directions

1. Granulate a mixture of items 1 and 2 with the solution of items 3 and 4, sieve, dry, and add a mixture of items 5 to 7.
2. Compress with medium-compression force. Compress into 404-mg tablets, using 12-mm punches.

Mefloquine Hydrochloride Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00 275.00	1	Mefloquine, use mefloquine hydrochloride	250.00 275.00
50.00	2	Lactose monohydrate	50.00
65.00	3	Maize (starch)	65.00
3.00	4	Polyoxyl 40 stearate	3.00
10.00	5	Polyvinyl pyrrolidone (PVP K-30)	10.00
65.00	6	Microcrystalline cellulose (Avicel PH 102)	65.00
25.00	7	Crospovidone (Kollidone CL)	25.00
2.00	8	Magnesium stearate	2.00
5.00	9	Talc, fine powder	5.00
QS	10	Purified water	QS

Manufacturing Directions

1. Sift mefloquine hydrochloride, lactose monohydrate, and maize starch through a 0.500-mm stainless steel sieve.
2. Dissolve polyoxyl 40 stearate and PVP K-30 in purified water (70–80°C) by slow stirring, until it becomes clear. Cool the solution to 25°C to 30°C. This is the granulating solution.
3. Knead the powder mix with granulating solution to get the desired wet mass.
4. Pass the wet mass through #8 mesh onto drying trays.
5. Dry the granules to a targeted LOD of 2%.
6. Pass the dried granules through #16 mesh.
7. Sift Avicel PH 102 and Kollidone CL through a 0.500-mm stainless steel sieve.
8. Load the ground granules from step 5 and the powder mix from step 6 into a suitable blender. Blend for 2 minutes to get a homogeneous mixture.
9. Sift magnesium stearate and talc fine powder through a stainless steel 500-μm sieve. Add the powder mix in step 7. Blend these items for 1 minute.
10. Compress into 500-mg tablets, using 15-mm suitable punches.
11. Coat using a hypermellose coating. (See Appendix.)

Meprobamate and Phenobarbital Tablets (400 mg/30 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Meprobamate	400.00
30.00	2	Phenobarbital	30.00
76.00	3	Microcrystalline cellulose (Avicel PH 101)	76.00
13.00	4	Kollidon VA 64	13.00
21.00	5	Kollidon CL	21.00
8.00	6	Talc	8.00
1.00	7	Aerosil 200	1.00
1.00	8	Calcium arachinate	1.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with low-compression force.
2. Compress into 551-mg tablets, using 12-mm biplanar punches.

Meprobamate and Phenobarbital Tablets (400 mg/30 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Meprobamate	400.00
30.00	2	Phenobarbital	30.00
13.00	3	Kollidon VA 64	13.00
—	4	Isopropyl alcohol	QS
21.00	5	Kollidon CL	21.00
50.00	6	Starch (maize)	50.00
8.00	7	Talc	8.00
1.00	8	Aerosil 200	1.00
1.00	9	Calcium arachinate	1.00

Manufacturing Directions

1. Granulate a mixture of items 1 and 2 with a solution of items 3 and 4. Dry, pass through a 0.8-mm sieve, mix with items 5 to 9, and press with low-compression force.
2. Compress into 559-mg tablets, using 12-mm biplanar punches.

Meprobamate Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Meprobamate	400.00
80.00	2	Microcrystalline cellulose (Avicel PH 101)	80.00
30.00	3	Starch (maize)	30.00
20.00	4	Kollidon VA 64	20.00
20.00	5	Kollidon CL	20.00
7.00	6	Talc	7.00
3.00	7	Magnesium stearate	3.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with high-compression force (20 kN).
2. Compress into 560-mg tablets, using 12-mm biplanar punches.

Meprobamate Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Meprobamate	400.00
100.00	2	Starch (maize)	100.00
15.00	3	Kollidon 25 or Kollidon VA 64	15.00
4.50	4	Lutrol E 400[a]	4.50
–	5	Isopropyl alcohol	QS
2.00	6	Talc	2.00
0.20	7	Aerosil 200	0.20
0.30	8	Calcium arachinate	0.30

[a]Use only if selecting Kollidon 25 as item 3.

Manufacturing Directions

1. Granulate the mixture of items 1 and 2 with a solution of items 3 to 5. Pass through a 0.8-mm sieve, add items 6 to 8, and press.
2. Compress into 520-mg tablets (515 mg if deleting item 4), using 12-mm biplanar punches.

Metamizol Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Metamizol sodium (dipyrone)	500.00
100.00	2	Ludipress	100.00
10.00	3	Kollidon CL	10.00
10.00	4	Magnesium stearate	10.00

Manufacturing Directions

1. Mix all components, pass through a 0.5-mm sieve, and press with low-compression force.
2. Compress into 625-mg tablets, using 12-mm biplanar punches.

Metamizol Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Metamizol sodium (dipyrone)	500.00
100.00	2	Microcrystalline cellulose (Avicel PH 101)	100.00
15.00	3	Kollidon 30	15.00
25.00	4	Kollidon CL	25.00
1.00	5	Aerosil 200	1.00
8.00	6	Talc	8.00
1.00	7	Calcium arachinate	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.5-mm sieve, and press with low-compression force.
2. Compress into 654-mg tablets, using 12-mm biplanar punches.

Metformin Hydrochloride Biphasic Tablet

Manufacturing Directions

1. 25 g of ethylcellulose N10 NF is dissolved/dispersed in 100 mL of 95% ethanol.
2. This dispersion is gradually added to 500 g of metformin hydrochloride in a planetary mixer to produce a uniform damp granulation.
3. The granulation is dried at 55°C for 1 hour and passed through a 0.8 mm aperture screen to break down agglomerates.
4. The metformin–ethylcellulose granules (541 g) are blended with 351.5 g of hydroxypropyl methylcellulose 2208 USP (100,000 cps grade), 10 g of hydroxypropyl methylcellulose 2910 USP (5 cps grade), and 100.5 g of microcrystalline cellulose in a planetary mixer for 10 minutes.
5. Finally this mix is lubricated with 1% w/w magnesium stearate and compressed into capsule shaped tablets, each containing 500 mg of metformin hydrochloride.

Metformin Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Metformin hydrochloride	500.00
100.00	2	Dicalcium phosphate	100.00
15.00	3	Kollidon 90F	15.00
8.00	4	Kollidon 90F	8.00
—	5	Isopropyl alcohol	90.00
5.00	6	Kollidon CL	5.00
15.00	7	Polyethylene glycol 6000 powder	15.00

Manufacturing Directions

1. Granulate the mixture of items 1 to 3 with the solution of items 4 and 5. Mix these granules with items 6 and 7, pass through a 0.8-mm sieve, and press with medium-compression force.
2. Compress into 650-mg tablets, using 12-mm biplanar punches. If hardness is the problem, reduce the amount of Kollidon 90F.

Metformin Hydrochloride Tablets, Extended Release (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Metformin hydrochloride	500.00
240.00	2	Lactose anhydrous	240.00
250.00	3	Hydroxypropyl cellulose	250.00
5.00	4	Colloidal silicon dioxide	5.00
5.00	5	Magnesium stearate	5.00

Manufacturing Directions

1. Pass items 1 to 4 through a 250-μm mesh, and charge in a suitable blender. Mix these materials for 15 minutes.
2. Add item 5, and mix for 3 to 7 minutes.
3. Compress 1000 mg to a hardness of 16 to 20 kPa in a suitable 15-mm punch. Adjust the weight and punch size for lower or higher strength.

Metformin Tablets (500 mg)

Metformin HCl tablets contain 500 and 850 mg of metformin HCl. In addition, each tablet contains the following inactive ingredients: povidone, magnesium stearate, and hydroxypropyl methylcellulose (hypromellose) coating.

Metformin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Metformin hydrochloride	500.00
190.00	2	Lactose anhydrous	190.00
300.00	3	Polyethylene oxide	300.00
5.00	4	Colloidal silicon dioxide	5.00
5.00	5	Magnesium stearate	5.00

Manufacturing Directions

Compress 1000 mg; adjust the weight for higher or lower strength.

Metformin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Metformin hydrochloride	500.00
160.00	2	Lactose anhydrous	160.00
330.00	3	Hydroxypropyl cellulose	330.00
5.00	4	Colloidal silicon dioxide	5.00
5.00	5	Magnesium stearate	5.00

Manufacturing Directions

Compress 1000 mg; adjust the weight for lower or higher strength.

Metformin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Metformin hydrochloride	500.00
45.90	2	Dibasic calcium phosphate	45.90
329.60	3	Hydroxypropyl cellulose	329.60
92.70	4	Ethyl cellulose	92.70
51.50	5	Povidone	51.50
5.15	6	Colloidal silicon dioxide	5.15
5.15	7	Magnesium stearate	5.15

Compress 1030 mg; adjust the weight for higher or lower strength.

Metformin Tablets, Extended Release (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Metformin	500.00
240.00	2	Lactose monohydrate	240.00
250.00	3	Hydroxypropyl cellulose	250.00
5.00	4	Silicon dioxide colloidal	5.00
5.00	5	Magnesium stearate	5.00

Manufacturing Directions

1. Charge items 1 to 3 in a suitable blending vessel, after passing through a 250-μm sieve.
2. Sift items 4 and 5 through a 250-μm sieve, and add to step 1.
3. Blend for 3 to 5 minutes.
4. Compress into 1000-mg tablets at 18 to 20 kp.

Methenamine Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Methenamine powder	500.00
0.50	2	Gelatin powder	0.50
4.50	3	Magnesium stearate	4.50

Manufacturing Directions

1. Accurately weigh methenamine, gelatin, and magnesium stearate.
2. Mix methenamine and gelatin in a suitable blender for 15 minutes. Add magnesium stearate, and mix for additional 5 minutes.
3. Compress into 505-mg tablets, using 3/8-in. round punch at 5 kg of pressure.

Methyclothiazide and Deserpidine Tablets (5 mg/0.25 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Methyclothiazide	5.00
0.25	2	Deserpidine	0.25
7.80	3	Starch (corn)	7.80
166.80	4	Lactose monohydrate	166.80
6.80	5	Starch (corn)	6.80
QS	6	Water, purified, ca	30 mL
6.80	7	Talc	6.80
1.50	8	Magnesium stearate	1.50

Manufacturing Directions

Caution: This is an expensive preparation—keep losses to a minimum. Deserpidine is poisonous—handle carefully. Maintain a low relative humidity during processing and storing.

1. Granulation
   a. Load methyclothiazide, deserpidine, and starch (item 3) together with an equal quantity of lactose into a mixer, and blend for 30 minutes. Cover the mixing bowl during this operation.
   b. Pass blended materials from step 1 through a 250-μm sieve aperture screen at high speed (hammers forward using an Apex mill or similar mill).
   c. Load the milled ingredients from step 2 into the mixer, add the balance of the lactose, and dry blend for 30 minutes.
   d. Mix starch (item 5) with 30 mL of cold purified water, and heat to make a paste.
   e. Add the hot starch paste to the blended powders in the mixer, and mass for 1 to 3 minutes. *Note:* Overmixing and overwetting will prolong tablet disintegration time.
   f. Pass the wet mass through a 4.76-mm aperture screen, and spread onto trays.
   g. Load trays of wet granulation into the oven, and dry for 4 hours at 49°C. *Note:* It is essential to use a full oven load of trays.
   h. Remove the dried granulation from the oven, and pass through an 840-μm aperture screen, or pass mill-dried granulation through a 600-μm aperture screen using a FitzMill, impact forward, high speed into polyethylene-lined drums. Tie liners tightly. *Note:* The FitzMill method may improve dissolution.
2. Lubrication
   a. Load approximately 20% of granulation into blender.
   b. Mix talc and magnesium stearate, while milling through a 600-μm aperture screen, impact forward, high speed on a FitzMill or similar mill, and load into the blender.
   c. Charge the remaining granulation into blender, and *blend only for 14 minutes. Note:* If lumps are present after several minutes of blending, it may be necessary to put the entire granulation through a 1.19-mm aperture, and then continue blending to the required time. Also note that overblending results in increased tablet disintegration time.
   d. Discharge into polyethylene-lined drums. Seal containers well.
3. Compression: Compress using standard 7-mm concave square punches.

Methyclothiazide Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	item	Material Name	Quantity/1000 Tablets (g)
5.20	1	Starch (corn)	5.20
QS	2	Dyes	QS
5.00	3	Methyclothiazide	5.00
9.40	4	Starch (corn)	9.40
166.40	6	Lactose monohydrate	166.40
QS	7	Water, purified, ca	25 mL
6.80	8	Talc	6.80
2.00	9	Magnesium stearate	2.00

Manufacturing Directions

1. Granulation and lubrication
   a. Make starch paste, using cornstarch (item 1) and purified water.
   b. Mix dyes with item 3, cornstarch (item 4), and an equal amount of lactose, and mill through a comminuting mill using a 177-μm aperture screen, impact forward, high speed. Charge into the mixer. Add the balance of lactose to the mixer (mill through a 420-μm aperture screen, impact forward, high speed, if lumpy), and dry mix for 10 minutes.
   c. Add hot starch paste from step 1 to the mixer. Mix until granular but not longer than 5 minutes. If necessary, 1.8 mL of purified water may be added to wet the mass during mixing. *Note:* Over mixing and over wetting will prolong the tablet disintegration time.
   d. Granulate the wet mass through a comminuting mill, using a 15.88-mm aperture band, and spread on trays.
   e. Dry at 60°C until the LOD is 1%, or less, when tested for 60 minutes in a Brabender (or equivalent) set at 105°C.
   f. Sift the dried granulation through a 1.19-mm aperture screen, and mill the coarse material through a comminuting mill fitted with a 1.59-mm aperture band, knives forward, at medium speed.
   g. Charge one-half of the granulation into the blender. Mix talc and magnesium stearate, while milling through a 600-μm aperture screen, impact forward, high speed, and charge into the blender. Charge the remaining half of the granulation into the blender, and *blend only for 4 minutes*.
   h. Discharge a portion of the granulation from the blender, and check for white lumps. If present, discharge the entire granulation from the blender through a 1.19-mm aperture screen to break lumps, and then return to the blender. Charge the remaining granulation into the blender, and *blend only for 10 minutes*. *Note:* Over blending results in increased tablet disintegration time.
   i. Discharge the blender into tared, polyethylene-lined drums. Seal, weigh, and deliver the drums to the storage area.
2. Compress using concave 7.1-mm punches; weight is 195 mg (to be determined based on amount of dyes used).

Methyl Cysteine Tablets (100 mg)

Formulation: Methyl cysteine hydrochloride, 100 g; Ludipress, 200 g; magnesium stearate, 3 mg; menthol, 4 mg

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press with low-compression force at 307 mg.

Methylphenidate Hydrochloride Tablets Extended Release (18 mg/36 mg), Concerta

Concerta also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hydroxypropyl methylcellulose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin. Concerta uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients and a push layer containing osmotically active components. There is a precision-laser-drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within 1 hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, that, in turn, controls drug delivery. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell, along with insoluble core components.

Methylergotamine Malate Tablets (0.5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.50	1	Methylergotamine malate, 10% excess	0.55
0.15	2	Maleic acid	0.15
5.25	3	Starch (maize)	5.25
47.08	4	Lactose monohydrate	47.08
1.00	5	Starch (maize)	1.00
0.50	6	Stearic acid	0.50
2.30	7	Talc	2.30
2.30	8	Magnesium stearate	2.30
	9	Water, purified, ca	60 mL

Manufacturing Directions

1. Sift items 2, 4, and 5 through a 250-μm sieve in a suitable mixing vessel. Mix the items for 5 minutes.
2. In a separate vessel, charge item 5 and add a sufficient amount of hot item 9 to make a paste.
3. Add step 2 into step 1, and make a suitable wet mass. Pass the wet mass through a 2.38-mm sieve onto drying trays.
4. Dry the granules at 50°C overnight to an LOD of not more than 3%.
5. Pass the granules through a #20-mesh sieve into a blending vessel.
6. Pass item 1 through a 250-μm sieve, and, using a geometric dilution with granules in step 5, add and mix item 1 into step 5.
7. Pass items 6 and 7 through a 500-μm sieve and item 8 through a 250-μm sieve, and add all three items to step 6. Blend for 2 minutes. (Do not over blend.)
8. Compress into 58-mg tablets, using 3-mm punches.
9. Provide a sugar coating to a final weight of 100 mg per tablet and a diameter of 5 mm. (See Appendix for sugar coating formulations.)

Methylprednisolone Tablets (2 mg/4 mg/8 mg/16 mg/24 mg/32 mg), Medrol

Each Medrol tablet for oral administration contains 2, 4, 8, 16, 24, or 32 mg of methylprednisolone. The inactive ingredients found in Medrol are as follows. *2 mg:* calcium stearate, cornstarch, erythrosine sodium, lactose, mineral oil, sorbic acid, and sucrose; *4 and 16 mg:* calcium stearate, cornstarch, lactose, mineral oil, sorbic acid, and sucrose; *8 and 32 mg:* calcium stearate, cornstarch, FD&C Yellow No. 6, lactose, mineral oil, sorbic acid, and sucrose; *24 mg:* calcium stearate, cornstarch, FD&C Yellow No. 5, lactose, mineral oil, sorbic acid, and sucrose.

Metoclopramide Tablets (10 mg), Reglan

Reglan tablets (metoclopramide tablets, USP), 10 mg, are white, scored, capsule-shaped tablets engraved with "Reglan" on one side and "AHR 10" on the opposite side. Each tablet contains 10 mg of metoclopramide base (as the monohydrochloride monohydrate). The inactive ingredients are magnesium stearate, mannitol, microcrystalline cellulose, and stearic acid.

Reglan tablets, 5 mg, are green, elliptical-shaped tablets engraved with "Reglan 5" on one side and "AHR" on the opposite side. Each tablet contains 5 mg of metoclopramide base (as the monohydrochloride monohydrate). The inactive ingredients are cornstarch, D&C Yellow No. 10 Lake, FD&C Blue No. 1 Aluminum Lake, lactose, mic rocrystalline cellulose, silicon dioxide, and stearic acid.

Metoclopramide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Anhydrous metoclopramide hydrochloride; use metoclopramide hydrochloride	10.54
7.00	2	Maize starch (dried)	7.00
1.00	3	Silicon dioxide (colloidal)	1.00
0.76	4	Magnesium stearate	0.76
5.00	5	Starch (pregelatinized)	5.00
101.24	6	Lactose	101.24
QS	7	Purified water	~15.00 mL

Manufacturing Directions

1. Dried maize starch must be used for lubrication.
2. Dry the starch at 80°C for 36 hours prior to its use in manufacturing.
3. Check LOD of starch; the LOD must be less than 2.0%.
4. Pass the lactose, pregelatinized starch, and metoclopramide hydrochloride through a 1.25-mm aperture screen, and transfer it to a suitable mass mixer; mix for 5 minutes.
5. Add the water slowly to the mixer, and mix for 30 minutes or until a suitable consistency is obtained. Add extra water, if required.
6. Pass the mass through a 4.80-mm aperture screen or an oscillating granulator (or by hand), and dry in a tray dryer or fluid-bed dryer at 50°C until the moisture content is below 5.5%.
7. Pass the granules through a 875-μm aperture screen on an oscillating granulator (or comminuting mill at medium speed, knives forward) into tared, polyethylene-lined drums; seal and weigh.
8. Carry out remaining steps at a relative humidity below 50% and temperature below 26°C.
9. Transfer the dried granulation to a suitable blender.
10. Screen the starch (item 2), magnesium stearate, and silicon dioxide through a 250-μm aperture screen on a sieve shaker, and add to the blender.
11. Blend for 10 minutes.
12. Discharge the granules into polyethylene-lined drums; seal and weigh for yield.
13. Compress into 1.255-g per 10 tablets, using 6.35- or 7.14-mm standard concave punches.

Metoclopramide Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Metoclopramide hydrochloride	10.00
89.50	2	Ludipress	89.50
0.50	3	Magnesium stearate	0.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium-compression force.
2. Compress into 100-mg tablets, using 6-mm biplanar punches.

Metoclopramide Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Metoclopramide hydrochloride anhydrous, use metoclopramide hydrochloride	10.54
7.00	2	Starch (maize), dried	7.00
1.00	3	Silicon dioxide colloidal	1.00
0.76	4	Magnesium stearate	0.76
5.00	5	Starch pregelatinized	5.00
101.24	6	Lactose	101.24
–	7	Water purified (deionized)	15.00 mL

Manufacturing Directions

1. Granulation
   Note: Dried cornstarch must be used for lubrication. Dry the starch at 80°C for 36 hours before its use in manufacturing. Check the LOD of the starch. The LOD must be less than 2% (1 hour on Brabender at 105°C or equivalent).
   a. Pass the lactose, starch pregelatinized, and metoclopramide hydrochloride through a 1.25-mm aperture screen, transfer to a suitable mass mixer, and mix for 5 minutes.
   b. Add the water slowly to the mixer, and mix for 30 minutes or until a suitable consistency is obtained. Add extra water if required.
   c. Pass the mass through a 4.8-mm aperture screen or an oscillating granulator (or by hand), and dry in a tray dryer or fluid-bed dryer at 50°C until the moisture content is below 5.5%.
   d. Arrange for samples.
   e. Pass the granule through an 875-μm aperture screen on an oscillating granulator (or comminuting mill at medium speed, knives forward) into tared polyethylene-lined drums. Then seal the drums and weigh.
2. Lubrication
   Note: Carry out at a relative humidity below 50% and temperature below 26°C.
   a. Transfer the dried granulation to a suitable blender.
   b. Screen the starch (item 2), magnesium stearate, and silicon dioxide through a 250-μm sieve aperture screen on a sieve shaker, and add to the blender. Blend for 10 minutes.
   c. Discharge the granules into polyethylenelined drums, seal, and weigh for yield.
3. Compressing
   Note: Carry out at a relative humidity below 50% and at temperature below 26°C.
   a. Compress using 7.14-mm round, standard concave punches or 6.35-mm round, standard concave punches.
   b. Compress to the following specifications: weight of 10 tablets = 1.255 g ± 3%.

Metoprolol Succinate Tablets (95 mg) Toprol

Toprol-XL is formulated to provide a controlled and predictable release of metoprolol for once-daily administration. The tablets comprise a multiple unit system containing metoprolol succinate in a multitude of controlled-release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 47.5, 95, and 190 mg of metoprolol succinate equivalent to 50, 100, and 200 mg of metoprolol tartrate, USP, respectively. The inactive ingredients are silicon dioxide, cellulose compounds, sodium stearyl fumarate, polyethylene glycol, titanium dioxide, and paraffin.

Metoprolol Succinate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
95.00	1	Metoprolol succinate	95.00
25.00	2	Polyoxol 40 hydrogenated	25.00
230.00	3	Hydroxypropyl methyl cellulose	230.00
94.00	4	Aluminum silicate	94.00
–	5	Alcohol	QS

Manufacturing Directions

1. Mix metroprolol with polyoxyl 40 hydrogenated castor oil, and then carefully mix it with the carrier materials (HPMC and aluminium silicate).
2. Granulate the mixture with ethanol, and dry the granules.
3. Add lubricant, and compress.

Metoprolol Tartrate Tablets

Metoprolol tartrate is a selective β_1-adrenoreceptor blocking agent, available as 50- and 100-mg tablets for oral administration and in 5-mL ampules for intravenous administration. Each ampule contains a sterile solution of metoprolol tartrate (5 mg) and sodium chloride (45 mg). Metoprolol tartrate is (±)-1-(isopropylamino)-3-(*p*-(2-(methoxyethyl)phenoxy)-2-propanol (2:1) *dextro*-tartrate salt.

Metoprolol tartrate is a white, practically odorless, crystalline powder with a molecular weight of 684.82. It is very soluble in water; freely soluble in methylene chloride, in chloroform, and in alcohol; slightly soluble in acetone; and insoluble in ether.

The Lopressor tablets contain the following inactive ingredients: cellulose compounds, colloidal silicon dioxide, D&C Red No. 30 Aluminum Lake (50-mg tablets), FD&C Blue No. 2 Aluminum Lake (100-mg tablets), lactose, magnesium stearate, polyethylene glycol, propylene glycol, povidone, sodium starch glycolate, talc, and titanium dioxide.

Metronidazole Tablet Cores (400 mg)

Formulation: Metronidazole, 400 g; Avicel PH 102, 150 g; Kollidon VA 64, 25 g; Kollidon CL, 15 g; Aerosil 200, 5 g; polyethylene glycol 6000, powder, 50 g;

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press with high-compression force (25–30 kN) at 645 mg.

Metronidazole Tablets (200 mg)

Formulation: Metronidazole, 200 g; Avicel PH 101, 200 g; Kollidon, 6 g; Kollidon CL, 10 g; Aerosil 200, 5 g; magnesium stearate, 5 g;

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press with high-compression force (25–30 kN) at 426 mg.

Metronidazole Effervescent Vaginal Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Materials Name	Quantity/1000 Tablets (g)
500.00	1	Metronidazole	500.00
600.00	2	Sodium bicarbonate	600.00
30.00	3	Kollidon 30	30.00
10.00	4	Kollidon 30	10.00
–	5	Isopropyl alcohol	150 mL
500.00	6	Tartaric acid	500.00
50.00	7	Polyethylene glycol 6000 powder	50.00

Manufacturing Directions

1. Granulate items 1 and 2 with the solution of items 3 and 4. Pass through a 0.8-mm sieve, mix with items 6 and 7, and press.
2. Compress into 1700-mg tablets, using 16-mm biplanar punches.

Metronidazole, Furazolidone, and Loperamide Tablets (200 mg/25 mg/2 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Metronidazole	200.00
25.00	2	Furazolidone	25.00
2.00	3	Loperamide	2.00
200.00	4	Starch (maize)	200.00
175.00	5	Dicalcium phosphate	175.00
5.00	6	Gelatin	5.00
110.00	7	Starch (maize)	110.00
1.16	8	Yellow dye	1.16
4.00	9	Magnesium stearate	4.00
2.00	10	Talc	2.00
–	11	Water, purified, ca	500 mL

Manufacturing Directions

1. Sift items 1, 2, 4, and 5 through a #40-mesh sieve into a mixing vessel.
2. Mix for 10 minutes, and use this mix to dilute item 1 into the same vessel.
3. In a separate vessel, heat item 11°C to 90°C, and add items 6 to 8. Stir to make a smooth slurry containing 30% starch.
4. Add the slurry in step 3 into step 2, and mix until a suitable mass for granulation is obtained.
5. Pass the wet mass through a 2.38-mm sieve onto paper-lined trays.
6. Dry the granules at 50°C overnight to meet an LOD of not more than 2.5%.
7. Pass the dried granules through a 1.19-mm mesh into a blending vessel.
8. Pass item 9 though a 250-µm sieve and item 10 through a 500-µm sieve into step 6. Blend for 2 minutes.
9. Compress into 680-mg tablets, using 13-mm punches.

Metronidazole Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Metronidazole	200.00
200.00	2	Avicel PH 101	200.00
6.00	3	Kollidon 30	6.00
10.00	4	Kollidon CL	10.00
5.00	5	Aerosil 200	5.00
5.00	6	Magnesium stearate	5.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with high-compression force (25–30 kN).
2. Compress into 426-mg tablets, using 12-mm biplanar punches.

Metronidazole Tablets (200 mg/400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Metronidazole	400.00
150.00	2	Lactose monohydrate	150.00
37.50	3	Starch (corn)	37.50
30.00	4	Povidone K 29–32	30.00
37.50	5	Starch (corn)	37.50
QS	6	Water, purified	121.00 mL
13.00	7	Starch (corn)	13.00
1.25	8	Magnesium stearate	1.25

Note: For 200-mg strength, scale down the BOM proportionally, as given above, and compress using a 9.5-mm round, standard concave punch. The thickness should be 4.3 to 4.9 mm (range: *not more than* ± 5%); hardness: NTL 7 to 17 kPa; disintegration time: *not more than* 15 minutes in water.

Manufacturing Directions

1. Granulation
   a. Make a starch paste using starch (corn) (item 3) and purified water (distilled) (item 6) in a stainless steel container.
   b. Pass the following items through a 595-μm aperture screen, and transfer to a suitable mixer: metronidazole, lactose, and starch (corn) (item 5).
   c. Add the povidone to the mixer, and mix for 5 minutes.
   d. Add the starch paste from step 1 to the mixer, and mix until a suitable consistency mass is obtained. Add extra water if required.
   e. Pass the wet mass through a 2.36-mm screen on a suitable granulator.
   f. Spread the granules on paper-lined trays, and dry in an oven at 50°C until the moisture content is not more than 5.5%.
   g. Request samples for moisture content.
   h. Pass the dried granules through a 1.59-mm aperture screen on a suitable comminuting mill, at medium speed, with knives forward, into tared, polyethylene-lined drums. Then seal the drums and weigh.
2. Lubrication
   a. Transfer the dried granulation to a suitable blender.
   b. Screen the following items through a 595- μm aperture screen, and add the following to the blender: starch (corn) (item 7) and magnesium stearate. Blend for 5 minutes.
   c. Discharge the granule into polyethylenelined drums, seal, and weigh for yield.
3. Compression: Compress using 12.7-mm round, standard concave punches.
4. Coating: Coat using a methocel coating. (See Appendix.)

Metronidazole Tablets (400 mg)

Metronidazole is an oral synthetic antiprotozoal and antibacterial agent, 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole. Metronidazole tablets contain 250 mg or 500 mg of metronidazole. Inactive ingredients include cellulose, FD&C Blue No. 2 Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyethylene glycol, stearic acid, and titanium dioxide.

Bill of Materials			
Scale (mg/tablet)	Item	Materials Name	Quantity/1000 Tablets (g)
400.00	1	Metronidazole	400.00
150.00	2	Avicel PH 102	150.00
25.00	3	Kollidon VA 64	25.00
15.00	4	Kollidon CL	15.00
5.00	5	Aerosil 200	5.00
50.00	6	Polyethylene glycol 6000, powder	50.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with high-compression force (25–30 kN).
2. Compress into 645-mg tablets, using 12-mm biconvex punches.

Metronidazole Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Metronidazole	500.00
220.00	2	Sorbitol, crystalline	220.00
10.00	3	Kollidon 90F	10.00
–	4	Ethanol 96%, ca	75.00
20.00	5	Kollidon CL	20.00
4.00	6	Talc	4.00
0.50	7	Aerosil 200	0.50
0.50	8	Calcium arachinate	0.50

Manufacturing Directions

1. Granulate the mixture of items 1 and 2 with the solution of items 3 and 4. Pass the mixture through a 0.8-mm sieve, dry it, mix it with items 5 to 7, and press it with medium-compression force.
2. Compress into 755-mg tablets, using 16-mm biplanar punches.

Midodrine Hydrochloride Controlled-Release Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Midodrine hydrochloride	15.00
18.80	2	Microcrystalline cellulose PH101	18.80
65.20	3	Lactose monohydrate	65.20
1.00	4	Sodium carboxymethyl cellulose	1.00
28.00	5	Water	28.00

Manufacturing Directions

1. The following preparation provides a zero-order release profile.
2. Items 1 to 4 are mixed in mixer intensely.
3. Apply item 5 to step 2 and continue mixing until wet properly.
4. Extrude the mass in step 3 through a screen with apertures between 0.4 and 1.0 mm to give spheronized pellets with smooth surface.
5. Apply inner coat using a fluid-bed to increase the weight of pellets by 8.5% w/w using hydroxypropylmethylcellulose (13.5 g), magnesium stearate (2.9 g), talc (25.2 g), Eudragit NE 30 D (895.1 g), and purified water (1135.4 g).
6. Apply outer coat in a fluid-bed to increase the weight by another 1% w/w using hydroxypropylmethylcellulose (20.0 g), talc (20.0 g), and purified water (460.0) g.
7. The release profile can be changed by mixing fractions of pellets with different amounts of inner coating applied or the release profile can be changed by coating with other acrylic resins such as Eudragit RL 30 D, Eudragit RS 30 D or combinations thereof, or using other types of film forming agents such as ethylcellulose or silicone polymers. Furthermore, the release profile can be changed by applying a fraction of non-coated pellets or by applying an enteric coating to a fraction of pellets.

Midodrine Hydrochloride Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Midodrine hydrochloride	50.00
2.00	2	Klucel MF	2.00
93.00	3	Methocel E50	93.00
1.50	4	Midodrine hydrochloride	1.50
6.6	5	Klucel MF	6.6
156.90	6	Methocel E50	156.90
2.80	7	Midodrine hydrochloride	2.80
247.20	8	Methocel E50	247.20
1.20	9	Midodrine hydrochloride	1.20
9.70	10	Methocel E50	9.70
8.50	11	Talc	8.50

Manufacturing Directions

1. Ingredients 1 to 3, 4 to 6, and 7 to 8 are compressed as the core, the first, and the second layer, respectively. Using the core composition, a core weighing 100 mg is compressed using a punch 6 mm in diameter. The core is compression coated using 165 mg of the 1st compression layer composition and a punch of 9 mm in diameter. The thus compression-coated core is compression coated again using 250 mg of the 2nd compression layer composition and a punch of 11 mm in diameter.
2. Ingredient 9 to 11 are applied as spray coating.

Midodrine Hydrochloride Triple Layer Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Midodrine hydrochloride	5.00
2.00	2	Klucel MF	2.00
93.00	3	Methocel E50	93.00
1.50	4	Midodrine hydrochloride	1.50
6.60	5	Klucel MF	6.60
156.90	6	Methocel E50	156.90
2.80	7	Midodrine hydrochloride	2.80
247.20	8	Methocel E50	247.20
1.20	9	Midodrine hydrochloride	1.20
9.70	10	Methocel E5	9.70
8.50	11	Talc	8.50

Manufacturing Directions

1. Items 1 to 3 are compressed to form a core using 6-mm diameter punch.
2. Coat the core using items 4 to 6 using 9-mm diameter punch.
3. Coat the tablet above (step 2) with items 7 to 8 using 11-mm diameter punch.
4. Spray coat step 3 with items 9 to 11.

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.66	1	Midodrine hydrochloride	1.66
48.34	2	Hydroxypropylmethyl cellulose E50	48.34
10.00	3	Croscarmellose sodium	10.00
0.62	4	Midodrine hydrochloride	0.62
126.38	5	Hydroxypropylmethyl cellulose E15	126.38
135.00	6	Hydroxypropylmethyl cellulose K100 LV8	135.00
1.99	7	Midodrine hydrochloride	1.99
143.01	8	Hydroxypropyl methyl cellulose E50	143.01
1.79	9	Hydroxypropylmethyl cellulose E5	1.79
1.25	10	Talc	1.25
0.36	11	Propylene glycol	0.36
0.73	12	Midodrine hydrochloride	0.73
3.58	13	Hydroxypropylmethyl cellulose E5	3.58
2.51	14	Talc	2.51
0.71	15	Propylene glycol	0.71

Manufacturing Directions

1. Compress core using 6-mm punch using items 1 to 3.
2. Compress core in step 1 with items 4 to 6 in 9-mm diameter punch.
3. Compress tablet in step 2 using items 7 and 8 using 11-mm diameter punch.
4. Apply coating by spray method using items 9 to 12.
5. Apply coating by spray method using items 12 to 15.

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Midodrine hydrochloride	10.00
340.00	2	Klucel LF	340.00
0.20	3	Methocel E5	0.20
0.10	4	Magnesium stearate	0.10
0.40	5	Talc Ponderax	0.40
0.0048	6	Antifoam agent	0.0048
4.50	7	Eudragit NE 30D	4.50
1.80	8	Methocel E5	1.80
1.80	9	Talc Ponderax	1.80

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Midodrine hydrochloride	10.00
340.00	2	Klucel MF	340.00
0.20	3	Methocel E5	0.20
0.10	4	Magnesium stearate	0.10
0.40	5	Talc Ponderax	0.40
0.0048	6	Antifoam	0.0048
4.50	7	Eudragit NE30D	4.50
1.80	8	Methocel E5	1.80
1.80	9	Talc Ponderax	1.80

Manufacturing Directions

1. Core: items 1 and 2.
2. Insoluble inner coat: items 3 to 7.
3. Soluble outer coat: items 8 and 9.

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Core (non pareil)	200.00
4.00	2	Midodrine hydrochloride	4.00
0.30	3	Methocel E5M	0.30
0.06	4	Magnesium stearate	0.06
0.50	5	Talc Ponderax	0.50
0.004	6	Antifoam agent	0.004
5.20	7	Eudragit NE 30D	5.20
3.00	8	Midodrine hydrochloride	3.00
0.30	9	Methocel E5M	0.30
0.06	10	Magnesium stearate	0.06
0.50	11	Talc ponderax	0.50
0.004	12	Antifoam	0.004
6.10	13	Eudragit NE 30D	6.10
2.00	14	Midodrine hydrochloride	2.00
0.30	15	Methocel E5 M	0.30
0.08	16	Magnesium stearate	0.08
0.70	17	Talc ponderax	0.70
0.006	18	Antifoam	0.006
1.00	19	Midodrine hydrochloride	1.00
0.40	20	Methocel E5M	0.40
0.08	21	Magnesium stearate	0.08
1.00	22	Talc ponderax	1.00
0.006	23	Antifoam	0.006
78.00	24	Eudragit NE 30D	78.00
1.00	25	Methocel E5	1.00
1.00	26	Talc ponderax	1.00

Manufacturing Directions

1. Coat item with items 2 to 7.
2. Coat step 1 with items 8 to 13.
3. Coat step 2 with items 14 to 18.
4. Coat step 3 with items 19 to 24.
5. Coat step with final outer coat with items 25 and 26
6. Cure tablets at 70°C

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Non-pareil seeds	200.00
4.00	2	Midodrine hydrochloride	4.00
0.30	3	Paraffin solid	0.30
0.10	4	Acetyltributyl citrate	0.10
1.90	5	Ethylcellulose	1.90
0.028	6	Aerosil 200	0.028
3.00	7	Midodrine hydrochloride	3.00
0.30	8	Paraffin solid	0.30
0.10	9	Acetyltributylcitrate	0.10
2.20	10	Ethylcellulose	2.20
0.032	11	Aerosil 200	0.032
2.00	12	Midodrine hydrochloride	2.00
0.40	13	Paraffin solid	0.40
0.20	14	Acetyltributyl citrate	0.20
2.80	15	Ethyl cellulose	2.80
0.04	16	Aerosil 200	0.04
0.50	17	Paraffin solid	0.50
0.20	18	Acetyltributyl citrate	0.20
3.30	19	Ethylcellulose	3.30
0.05	20	Aerosil 200	0.05

Manufacturing Directions

1. Coat item 1 with items 2 to 6.
2. Coat step 1 with items 7 to 11.
3. Coat step 2 with items 12 to 16.
4. Final outer coat use items 17 to 20.

Montelukast Sodium Tablets Mirtazapaine, Rameron, Singulair

Each 10-mg film-coated Singulair tablet contains 10.4 mg of montelukast sodium. Remeron is supplied for oral administration as scored film-coated tablets containing 15 or 30 mg of mirtazapine and unscored film-coated tablets containing 45 mg of mirtazapine. Each tablet also contains cornstarch, hydroxypropyl cellulose, magnesium stearate, colloidal silicon dioxide, lactose, and other inactive ingredients. Singular tablet is equivalent to 10 mg of free acid, and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The film coating consists of hydroxypropyl methylcellulose, hydroxypropyl cellulose, titanium dioxide, red iron oxide, yellow iron oxide, and carnauba wax.

Each 5-mg chewable Singulair tablet contains 5.2 mg of montelukast sodium, which is the molar equivalent to 5 mg of free acid, and the following inactive ingredients: mannitol, microcrystalline cellulose, hydroxypropyl cellulose, red ferric oxide, croscarmellose sodium, cherry flavor, aspartame, and magnesium stearate.

Morphine Sulfate and Granisetron Hydrochloride Sustained-Release Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
30.00	1	Morphine sulfate	30.00
130.00	2	Hydroxypropyl methyl cellulose	130.00
70.00	3	Lactose monohydrate	70.00
10.00	4	Polyvinylpyrrolidone	10.00
2.00	5	Silicon dioxide	2.00
1.12	6	Granisetron hydrochloride	1.12
60.00	7	Lactose fine powder	60.00
5.00	8	Sucrose fine powder	5.00
1.00	9	Flavor	1.00
0.06	10	Polyvinylpyrrolidone	0.06
qs	12	Ethyl alcohol 95%	qs
qs	13	Water	qs

Manufacturing Directions

1. Prepare a granulation blend containing morphine sulfate, hyproxypropyl methylcellulose, lactose, and polyvinylpyrrolidone. Add silicon dioxide and stearic acid to the granulation and blend for additional 5 to 10 minutes.
2. Compress the above morphine sulfate sustained-release granulation using appropriate tooling and tabletting machine to fill weight of 244 mg.
3. Prepare the solvent mixture containing polyvinylpyrrolidone in water or a mixture of water and ethanol.
4. Blend Granisetron hydrochloride, lactose, sucrose, and the flavoring agent. Screen to break lumps.
5. Add the mixture of step 3 to that of step 4, while mixing until a moistened powder blend is achieved.
6. Compress about 67.80 mg of moistened blend with morphine sulfate tablet.

Morphine Sulfate Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
24.00	1	Morphine sulfate	24.00
27.00	2	Sodium bicarbonate	27.00
27.00	3	Citric acid anhydrous	27.00
10.00	4	Microcrystalline cellulose	10.00
10.00	5	Xylitol	10.00
2.00	6	Sucrose stearate	2.00

Manufacturing Directions

1. Morphine sulfate is dried at 100°C for 2 to 4 hours to reduce the moisture content of the material. Other ingredients are dried at 40°C to 60°C to significantly reduce the moisture content of the material.
2. Items 1 to 6 are blended for 10 minutes and extruded in a hot melt extruder at 70°C to 100°C to soften and melt the thermal binders (sucrose stearate and xylitol) and to form granules containing the effervescent couple.
3. Granules are then screened and blended with the ingredients: MS-EGF (30–60 mesh), 50%; microcrystalline cellulose, 31%; Mannitol, 10%; AcDiSol, 5%; aspartame, 3%; redberry flavor, 0.4%; magnesium stearate, 0.5%; Cab-O-Sil M5P, 0.1%, for 5 minutes prior to compression.
4. Morphine sulfate tablets are then compressed to a hardness of approximately 1 to 5 kPa and tablets disintegrate in water in approximately 15 to 35 seconds.

Multivitamin and Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
7.00	2	Beta-carotene; use beta-carotene dry powder (10%, Pharma)	70.00
2.20	3	Thiamine mononitrate	2.20
2.20	4	Riboflavin	2.20
6.50	5	Nicotinamide	6.50
11.50	6	Calcium D-pantothenate	11.50
2.20	7	Pyridoxine hydrochloride	2.20
0.06	8	Cyanocobalmine; use cyanocobalamin dry powder (0.1%)	6.00
85.00	9	Ascorbic acid (powder)	85.00
32.00	10	Vitamin E acetate (dry powder; SD 50)	32.00
210.00	11	Ludipress®	210.00
7.00	12	Kollidon® VA 6 4	7.00
3.00	13	Magnesium stearate	3.00
7.00	14	Orange flavor	7.00
2.50	15	Saccharin sodium	2.50

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, mix, and press with medium-compression force.
2. Compress into 448-mg tablets, using 12-mm planar punches.

Multivitamin and Carbonyl Iron Tablets

Bill of Materials			
Scale (per tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5000 IU	1	Vitamin A acetate (dry powder; 500000 IU/g)	10.00
2.20 mg	2	Thiamine mononitrate, BASF	2.20
2.20 mg	3	Riboflavin	2.20
16.50 mg	4	Nicotinamide	16.50
11.50 mg	5	Calcium D-pantothenate	11.50
2.20 mg	6	Pyridoxine hydrochloride	2.20
6.00 mg	7	Cyanocobalamin (dry powder; 0.1%)	6.00
85.00 mg	8	Ascorbic acid (powder)	85.00
31.00 mg	9	Vitamin E acetate (dry powder; SD 50)	31.00
311.00 mg	10	Ludipress®	311.00
10.00 mg	11	Carbonyl iron (powder OF)	10.00
3.00 mg	12	Magnesium stearate	3.00
7.20 mg	13	Orange flavor	7.20
2.50 mg	14	Saccharin sodium	2.50

Manufacturing Directions

1. Mix all ingredients, pass through an 0.8-mm sieve, mix, and press with high-compression force (20 kN).
2. Compress into 500-mg tablets, using 12-mm biplanar punches.

Multivitamin and Fluoride Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.20	1	Riboflavin; use coated riboflavin (25% excess)	5.28
0.30	2	Folic acid (powder)	0.31
1.00	3	Fluoride; use sodium fluoride (powder)	2.21
19.50	4	Starch (Bright Yellow 2 LA)	19.50
1.05	5	Pyridoxine; use pyridoxine hydrochloride (6% excess)	4.02
1.05	6	Thiamine HCl; use coated thiamine mononitrate (5% excess)	3.21
13.50	7	Niacin; use nicotinamide	40.20
4.50 μg	8	Vitamine B12; use cyanocobalamin oral powder in starch (10% excess)	5.17
20.00	9	Ascorbic acid; use surface-coated ascorbic acid and sodium	21.00
40.00	10	Sodium ascorbate; use surface-coated sodium ascorbate (5% excess)	47.25
7.49	11	Anhydrous citric acid	7.49
15 IU	12	Vitamin E; use vitamin E (*d,l*-α-tocopheryl) (5% excess)	31.50
400 IU (10 μg)	13	Vitamin D; use vitamin D3 beadlets (25% excess)	0.65
9.36	14	Flavor	9.36
2500 IU or 0.75 mg	15	Vitamin A; use vitamin A palmitate beadlets (500 mU/g), USP (60% excess)	8.25
500.60	16	Sugar (compressible)	500.60

Manufacturing Directions

Manufacture this product at less than 40% relative humidity and a temperature below 26.7°C.

1. If lumpy, hand screen riboflavin through an 8-mesh screen, and then mix with folic acid, sodium fluoride powder, and approximately 3.5 g of Bright Yellow starch in a suitable blender until the yellow color of premix is uniform.
2. Cross-feed the premixed items, pyridoxine hydrochloride, thiamine mononitrate, nicotinamide, cyanocobalamin oral powder in starch, ascorbic acid, citric acid, and vitamin E through an 846-μm screen on a comminuting mill (knives forward, medium speed).
3. Transfer the powders to a suitable blender.
4. Clear mill with a part of the compressible sugar, and transfer to the blender.
5. Charge vitamin D3 beadlets, sodium ascorbate, flavor, and vitamin A palmitate into the blender.
6. Blend for 10 minutes.
7. Discharge the contents of the blender into polyethylene-lined drums.
8. Pass the remaining compressible sugar through an 846-μm screen on a comminuting mill (knives forward, medium speed).
9. Transfer to the blender.
10. Screen the material from previous step, magnesium stearate, and the remaining Bright Yellow starch through an 846-μm screen, and transfer to the blender. (*Note*: Mill material not passing through the screen through an 846-μm screen on a comminuting mill at medium speed with knives forward.) Blend for 20 minutes.
11. Discharge blender into polyethylene-lined drums, and weigh for yield.
12. Use precompression, if available, to obtain a tablet with adequate friability.
13. Coat as needed. (See Appendix.)

Multivitamin and Mineral Tablets

Bill of Materials			
Scale (per tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4000 IU/400 IU	1	Vitamin A/vitamin D crystalets (500000 A/50000 D per g) (25% excess)	10.00
40.00 mg	2	Vitamin A acetate (powder; 500 MA) (20% excess)	50.00
10.00 mg	3	Thiamine hydrochloride (10% excess)	11.00
5.00 mg	4	Riboflavin	5.00
100.00 mg	5	Nicotinamide niacinamide (white powder)	100.00
200.00 mg	6	Ascorbic acid (white powder) (10% excess)	220.00
20.00 mg	7	Calcium pantothenate (dextro) (30% excess)	26.00
5.00 mg	8	Pyridoxine hydrochloride	5.00
7.33 mg	9	Povidone (K-29–32)[a]	7.33
29.16 mg	10	Anydrous refined alcohol isopropyl	29.16
24.20 mg	11	Talc powder	24.20
6.07 mg	12	Magnesium stearate (impalpable powder)	6.07
4.75 mg	13	Stearic acid (fine powder)	4.75
10.0 mg	14	Iron, use; iron sulfate (dried)	31.26
1.00 mg	15	Copper[a]	1.00
0.15 mg	16	Iodine[a]	0.15
1.00 mg	17	Manganese[a]	1.00
5.00 mg	18	Magnesium[a]	5.00
1.50 mg	19	Zinc[a]	1.50
0.10 mg	20	Cobalt; use cobalt sulfate	0.47
5.00 mg	21	Potassium; use potassium sulfate	11.14
0.20 mg	22	Molybdenum; use sodium molybdate (dihydrate)	0.50
6.00 μg	23	Vitamin B12; use cyanocobalamin (1000 μg/g oral powder in gelatin; 5% excess)	6.30

[a]Provided as mineral mix (includes 3% excess).

Bill of Materials: Mineral Mix			
Scale (mg/Tablet)	Item	Material Name	Quantity/1000 Tablets (g)
13.85	1	Copper sulfate	14.28
0.01175	2	Calcium iodate monohydrate	0.01212
0.1228	3	Manganese sulfate monohydrate	0.1267
0.1480	4	Zinc sulfate (pure dry powder)	0.1526

Manufacturing Directions

1. Mineral mix processing: Grind copper sulfate, calcium iodate, manganese sulfate, and zinc sulfate through FitzMill screen 0 band (high speed, impact forward).
   Note: Vitamin A is susceptible to destruction by oxidation and also excessive exposure to actinic light and moisture. Compression of this tablet should be done with relative humidity less than 40%. Protect granulation with CO_2 if material is not to be compressed soon after granulation.
2. Hand screen vitamin A and D crystallets and vitamin A acetate through 1.2-mm aperture screen.
3. Load into mass mixer (screen using 1.2-mm aperture screen, if necessary) thiamine HCl, riboflavin, nicotinamide, ascorbic acid, calcium pantothenate, pyridoxine HCl, and the vitamin A and D mix from above.
4. Blend for 10 minutes.
5. Dissolve Povidone in alcohol (~26 mL).
6. Add Povidone solution to blended materials, and mix for 5 minutes.
7. Scrape mixer, and then add alcohol to mass (~11 mL).
8. Pass wet mass through a 15.88-mm aperture (or similar), band-fitted to rotary granulator. (*Note*: Wet mass can set hard; therefore, granules should be spread quickly onto trays.) Dry the granulation at 49°C until LOD is less than 1.0%.

9. Pass the dried granulation through a 1.2-mm aperture screen fitted to an oscillating granulator.
10. Mill the talc (item 11), magnesium stearate, stearic acid, iron sulfate, mineral mix, cobalt sulfate, potassium sulfate, and sodium molybdate through a 595-μm-aperture screen at high speed, impact forward.
11. Load half of the granulation into a suitable blender; add mineral mix and cyanocobalamin oral powder.
12. Add balance of granulation and blend for 30 minutes.
13. Compress and coat using a sealing subcoating of polyvinylpyrrolidone (PVP) (see Appendix), followed by HPMC coating solution and clear methocel gloss.

Multivitamin and Mineral Tablets with Beta Carotene

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Beta carotene (dry powder; 10%)	150.00
2.50	2	Thiamine mononitrate	2.50
2.90	3	Riboflavin	2.90
2.00	4	Pyridoxine hydrochloride	2.00
22.00	5	Nicotinamide	22.00
12.00	6	Calcium D-pantothenate	12.00
110.00	7	Ascorbic acid for direct compression	110.00
550.00	8	Calcium phosphate (dibasic)	550.00
82.00	9	Ferrous fumarate	82.00
166.00	10	Magnesium oxide	166.00
2.50	11	Cupric sulfate	2.50
13.80	12	Manganese sulfate	13.80
57.20	13	Potassium chloride	57.20
37.00	14	Zinc sulfate	37.00
57.00	15	Avicel™ PH102	57.00
50.00	16	Kollidon® CL	50.00
5.70	17	Stearic acid	5.70
5.00	18	Magnesium stearate	5.00

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press with high-compression force.
2. Compress into 1300-mg tablets, using 16-mm biplanar punches.

Multivitamin + Calcium + Iron Tablets (1 RDA of Vitamins)

Formulation: Vitamin A acetate dry powder, 5.0 g, 500,000 IU/g (BASF); Vitamin D dry powder,2.0 g, 100000 IU/g; thiamine mononitrate, 1.2 g; riboflavin,1.8 g; nicotinamide, 12.0 g; vitamin E acetate dry powder SD, 50.4.0 g; ascorbic acid, powder, 50.0 g; ferrous fumarate, 60.0 g; dibasic calcium phosphate [9], 200.0 g; granulated with 5% Kollidon 30; calcium carbonate,125.0 g; Avicel PH 101, 45.0 g; Aerosil 200, 1.5 g.

Manufacturing Directions

Mix all components, pass through a sieve, and press to tablets at 500 mg.

Multivitamin, Calcium, and Iron Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Vitamin A acetate (dry powder)	5.00
2.00	2	Vitamin D (dry powder; 500000 IU/g)	2.00
1.20	3	Thiamine mononitrate (100000 IU/g)	1.20
1.80	4	Riboflavin, BASF	1.80
12.00	5	Nicotinamide	12.00
4.00	6	Vitamin E acetate (dry powder; SD 50)	4.00
50.00	7	Ascorbic acid (powder), BASF	50.00
60.00	8	Ferrous fumarate	60.00
200.00	9	Dibasic calcium phosphate granulated with 5% Kollidon® 30	200.00
125.00	10	Calcium carbonate	125.00
45.00	11	Avicel™ PH101	45.00
1.50	12	Aerosil® 200	1.50

Manufacturing Directions

1. Mix all components, pass through a sieve, and press to tablets.
2. Compress into 500-mg tablets, using 11-mm biplanar punches.

Multivitamin + Carbonyl Iron Tablets (1–2 RDA of Vitamins)

Formulation: Vitamin A acetate dry powder 500,000 IU/g, 10.0 g; thiamine mononitrate, 2.2 g; riboflavin, 2.2 g; nicotinamide, 16.5 g; calcium D-pantothenate, 11.5 g; pyridoxine hydrochloride, 2.2 g; cyanocobalamin, dry powder 0.1%, 6.0 g; ascorbic acid, powder, 85.0 g; vitamin E acetate dry powder SD 50, 31.0 g; Ludipress, 311.0 g; carbonyl iron powder, 10.0 g; magnesium stearate, 3.0 g; orange flavor, 7.2 g; saccharin sodium, 2.5 g.

Manufacturing Directions

Mix all ingredients, pass through a 0.8-mm sieve, mix, and press with high-compression force (20 kN) at 500 mg.

Multivitamin Chewable Tablets for Children

Formulation: Vitamin A acetate dry powder, 7.0 g, 500000 IU/g; thiamine mononitrate, 1.2 g; riboflavin, 1.2 g; nicotinamide, 20.0 g; pyridoxine hydrochloride, 1.8 g; cyanocobalamin 0.1%, dry powder, 6.5 g; ascorbic acid, powder, 60.0 g; vitamin D3 acetate dry powder, 100,000 IU/g, 5.0 g; vitamin E acetate, 31.0 g; dry powder SD 50; sorbitol, crystalline [10], 200.0 g; sucrose, crystalline, 200.0 g; Kollidon VA 64, 20.0 g; Aerosil 200, 1.0 g; orange flavor, dry powder, 30.0 g; raspberry flavor, dry powder, 6.0 g; passion fruit flavor, dry powder, 3.0 g; cyclamate sodium, 2.0 g.

Manufacturing Directions

Mix all ingredients, pass through a 0.8-mm sieve, and press with medium- to high-compression force (20 kN) at 575 mg.

Multivitamin Chewable Tablets for Children

Bill of Materials			
Scale (per tablet)	Item	Material Name	Quantity/1000 Tablets (g)
3500 IU	1	Vitamin A acetate (dry powder; 500,000 IU/g)	7.00
1.20 mg	2	Thiamine mononitrate	1.20
1.20 mg	3	Riboflavin	1.20
20.00 mg	4	Nicotinamide	20.00
1.80 mg	5	Pyridoxine hydrochloride	1.80
6.50 mg	6	Cyanocobalamin (dry powder; 0.1%), BASF	6.50
60.00 mg	7	Ascorbic acid (powder)	60.00
5.00 mg	8	Vitamin D3 acetate (dry powder; 100000 IU/g)	5.00
31.00 mg	9	Vitamin E acetate (dry powder, SD 50)	31.00
200.00 mg	10	Sorbitol (crystalline)	200.00
200.00 mg	11	Sucrose (crystalline)	200.00
20.00 mg	12	Kollidon® VA 64	20.00
1.00 mg	13	Aerosil® 200	1.00
30.00 mg	14	Orange flavor (dry powder)	30.00
6.00 g	15	Raspberry flavor (dry powder)	6.00
3.00 mg	16	Passion fruit flavor (dry powder)	3.00
2.00 mg	17	Cyclamate sodium	2.00

Manufacturing Directions

1. Mix all ingredients, pass through an 0.8-mm sieve, and press with medium- to high-compression force (20 kN).
2. Compress into 575-mg tablets, using 12-mm biplanar punches.

Multivitamin Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
13.00	1	Thiamine mononitrate	13.00
4.00	2	Riboflavin	4.00
11.00	3	Pyridoxine hydrochloride	11.00
66.00	4	Nicotinamide	66.00
17.00	5	Calcium D–pantothenate	17.00
360.00	6	Tartaric acid (powder)	360.00
550.00	7	Sodium bicarbonate	550.00
300.00	8	Sucrose (crystalline)	300.00
300.00	9	Sucrose (powder)	300.00
35.00	10	Kollidon® 30	35.00
5.00	11	Kollidon® 30	5.00
QS	12	Isopropanol	~80.00
6.00	13	Riboflavin	6.00
550.00	14	Ascorbic acid (powder)	550.00
20.00	15	Cyanocobalamin (dry powder, 0.1%)	20.00
12.00	16	Vitamin A palmitate (250000 IU/g dry powder CWD)	12.00
60.00	17	Vitamin E acetate (dry powder; 50%)	60.00
80.00	18	PEG-6000 (powder)	80.00
100.00	19	Kollidon® CL	100.00

Manufacturing Directions

1. Granulate the mixture of items 1 to 10 with solution of items 11 and 12; dry at 60°C with vacuum.
2. Mix with items 13 to 19, and press with high-compression force at maximum 30% of relative atmospheric humidity.
3. Compress into 2.5-g tablets, using 20-mm biplanar punches.

Multivitamin Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.50	1	Thiamine mononitrate	5.50
5.50	2	Riboflavin	5.50
6.50	3	Pyridoxine hydrochloride	6.50
60.00	4	Nicotinamide	60.00
30.00	5	Calcium D–pantothenate	30.00
200.00	6	Ascorbic acid (powder)	200.00
0.20	7	Cyanocobalamin (dry powder, 0.1%)	20.00
30.00	8	Vitamin A acetate (dry powder; 325000 IU/g CWD)	30.00
55.00	9	Vitamin E acetate (dry powder; 50%)	110.00
500.00	10	Citric acid (powder)	500.00
400.00	11	Tartaric acid (powder)	400.00
500.00	12	Sodium bicarbonate	500.00
600.00	13	Ludipress®	600.00
70.00	14	PEG-6000 (powder)	70.00
0.50	15	Saccharin sodium	0.50
40.00	16	Cyclamate sodium	40.00
200.00	17	Sucrose, crystalline	200.00
200.00	18	Fructose	200.00
100.00	19	Flavors (Firmenich)	100.00

Manufacturing Directions

1. Mix all components, and sieve through an 0.8-mm screen.
2. Press with high-compression force at maximum 30% relative atmospheric humidity.
3. Compress into 3-g tablets, using 20-mm biplanar punches.

Multivitamin Effervescent Tablets I, DC (1–2 RDA of Vitamins)

Formulation: Lucarotene dry powder 10%, 23.0 g, CWD G/Y; dry vitamin E acetate 50% DC, 40.0 g; thiamine mononitrate, 2.0 g; riboflavin C, 2.0 g; nicotinamide, 22.0 g; calcium D-pantothenate, 11.0 g; pyridoxine hydrochloride, 2.0 g; cyanocobalamin 0.1% dry powder, 6.0 g; ascorbic acid, powder, 85.0 g; Ludipress LCE, 477.0 g; sodium bicarbonate, 600.0 g; tartaric acid, 400.0 g; polyethylene glycol 6000, powder, 90.0 g; orange flavor (Dragoco), 60.0 g; apartame (Searle), 30.0 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, mix and press with high-compression force at a maximum of 30% of relative atmospheric humidity at 1850 mg.

Multivitamin Effervescent Tablets with Beta Carotene

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.00	1	Thiamine mononitrate	2.00
2.00	2	Riboflavin	2.00
2.00	3	Pyridoxine hydrochloride	2.00
22.00	4	Nicotinamide	22.00
11.00	5	Calcium D-pantothenate	11.00
400.00	6	Tartaric acid (powder)	400.00
300.00	7	Lactose monohydrate	300.00
100.00	8	Cornstarch	100.00
3.00	9	Cornstarch	3.00
50.00	10	Water	50.00
23.00	11	Beta carotene (dry powder; 10% CWD; food grade)	23.00
6.00	12	Cyanocobalamin (powder; 0.1%)	6.00
85.00	13	Ascorbic acid (powder)	85.00
40.00	14	Vitamin E acetate (dry powder; 50%)	40.00
600.00	15	Sodium bicarbonate	600.00
80.00	16	Flavors	80.00
QS	17	Saccharin sodium	QS

Manufacturing Directions

1. Granulate mixture of items 1 to 6 with solution of items 9 and 10 prepared at 70°C.
2. Dry and sieve; add items 11 to 17, pass through a 0.4-mm sieve, and press with high-compression force at maximum 30% of relative atomspheric humidity.
3. Compress into 1.63-g tablets, using 16-mm biplanar punches.

Multivitamin Effervescent Tablets, DC (3–4 RDA of Vitamins)

Formulations: Thiamine mononitrate, 5.5 g; riboflavin, 5.5 g; pyridoxine hydrochloride, 6.5 g; nicotinamide, 60.0 g; calcium D-pantothenate, 30.0 g; ascorbic acid, powder, 200.0 g; cyanocobalamin 0.1% dry powder, 20.0 g; vitamin A palmitate dry powder 325000 IU/g CWD, 30.0 g; vitamin E acetate dry powder 50%, 110.0 g; tartaric acid, powder, 400.0 g; sodium bicarbonate, 500.0 g; Ludipress, 600.0 g; polyethylene glycol 6000, powder, 70.0 g; saccharin sodium, 0.5 g; cyclamate sodium, 40.0 g; sucrose, crystalline, 200.0 g; fructose, 200.0 g; flavors (Firmenich), 100.0 g;

Manufacturing Directions

Mix all components, sieve through a 0.8-mm screen, and press with high-compression force at maximum 30% relative atmospheric humidity.

Multivitamin + Minerals Tablets with Beta Carotene (1 RDA of Vitamins)

Formulation: Beta carotene dry powder, Betavit 20%, 16.5 g; thiamine mononitrate, 1.7 g; riboflavin, 1.9 g; nicotinamide (Degussa), 22.0 g; calcium D-pantothenate, 12.0 g; pyridoxine hydrochloride, 2.2 g; ascorbic acid, cryst., 72.0 g; vitamin E acetate dry powder 50%, 66.0 g; ferrous fumarate, 54.7 g; magnesium oxide, high density type, 165.8 g; copper II oxide, powder, 2.5 g; manganese sulfate, 6.9 g; zink oxide, 18.7 g; potassium chloride (Baker), 76.3 g; dicalcium phosphate, DI-TAB [9], 550.0 g; Avicel PH 102, 60.0 g; croscarmellose, 32.0 g; Syloid® 244 FP (Grace), 6.0 g; stearic acid, 6.0 g; magnesium stearate, 6.0 g.

Manufacturing Directions

All ingredients are passed through a 0.8-mm sieve, blended in a mixer, and then compressed with medium- to high-compression force at 1193 mg.

Multivitamin Tablet Cores with Beta-Carotene (1–2 RDA of Vitamins)

Formulation: Vitamin A acetate dry powder, 1.27%, 500,000 IU/g; beta carotene dry powder BetaVit 10%, 11.50%; thiamine mononitrate, 1.24%; Riboflavin, 0.96%; nicotinamide, 11.50%; calcium D-pantothenate, 1.91%; pyridoxine hydrochloride, 1.15%; cyanocobalamin gelatin coated 1%, 2.86%; D-biotin, 1% trituration, 1.91%; folic acid, 0.09%; ascorbic acid 38, 20%; vitamin D3 dry powder 100,000 IU/g, 0.76%; vitamin E acetate dry powder 50 DC, 28.40%; phytomenadione dry powder 5% (GFP 0.19%), 270.2 g; Ludipress, 69.1 g; magnesium stearate, 3.3 g;

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with high-compression force at 459 mg.

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Thiamine mononitrate (powder), USP (5% excess; 5–10%)	10.50
5.00	2	Riboflavin, USP	5.00
100.00	3	Nicotinamide niacinamide (white powder), USP	100.00
200.00	4	Ascorbic acid, use sodium ascorbat (microcrystalline) (2% excess)	229.47
20.00	5	Calcium pantothenate; use calcium pantothenate racemic (20% excess)	48.00
5.00	6	Pyridoxine hydrochloride, USP	5.00
6.10	7	Povidone (PVP K-25), USP	6.10
—	8	Alcohol dehydrated (200 proof), USP	25.00 mL
21.90	9	PEG-8000, NF	21.90
25000 IU	10	Vitamin A (275000 IU[a]) (20% excess)	7.50 mg
400 IU	11	Vitamin D as D2 powder (850 mD[a])	1.77
6.00	12	Vitamin B12 oral powder in gelatin (5% excess)	6.30
16.00	13	PEG-8000 (milled), NF	16.00
5.30	14	Magnesium stearate	5.30
23.20	15	Talc	23.20

[a]Adjust quantities according to regulatory allowance for OTC label.

Manufacturing Directions

Vitamin A is susceptible to destruction by oxidation and also excessive exposure to actinic light and moisture. Oxidation and destruction are catalyzed by traces of copper and other heavy metals. Dry granulation and compression of this tablet should be done where relative humidity is less than 40%. Protect with CO_2 at blending and storage stages.

1. Charge the following into a suitable mixer (screen if necessary): thiamine mononitrate, riboflavin, nicotinamide, sodium ascorbate, calcium pantothenate, and pyridoxine HCl.
2. Dissolve PVP (item 7) in approximately 16 mL alcohol.
3. Add PVP solution to the powders from first step, and QS with alcohol to mass.
4. Granulate the mass through a 4-mesh (4.76-mm aperture, or similar) screen.
5. Dry at 50°C until the LOD is below 1.0%.
6. Grind to 16 mesh (1.2 mm, or similar).
7. Melt the PEG-8000 (item 10), and incorporate vitamins A and D with thorough agitation.
8. Mix until mass cools and becomes granular.
9. Screen through a 16-mesh (1.2-mm aperture, or similar) screen, and grind coarse material through a FitzMill, or similar, No. 2 band (1.59-mm aperture, or similar) at slow speed or a 16-mesh (1.2-mm aperture, or similar).
10. Reserve for lubrication.
11. Mix milled PEG-8000 (item 13) with talc and magnesium stearate, and pass through a FitzMill, using a 60-mesh (250-μm aperture, or similar) screen (impact forward, high speed).
12. If a FitzMill is unavailable, pass the mixture through a 30-mesh (595-μm aperture, or similar) screen.
13. Load base granulation into a mixer along with vitamin B12, the mixture from above, and the PEG-coated vitamin A and D mixture from the first step. Blend thoroughly.
14. Store dry mixed granulation with CO_2 protection.
15. Compress.
16. Apply a PVP subcoat, a CAP-carbowax or other aqueous coating and finish with a polish coat. (See Appendix.)

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Riboflavin	10.00
100.00	2	Niacinamide (white powder)	100.00
5.00	3	Pyridoxine hydrochloride (15% excess)	5.75
15.00	4	Thiamine mononitrate (powder) (5% excess)	15.75
500.00	5	Ascorbic acid, EP	500.00
100.00	6	Lactose	100.00
40.00	7	Povidone (K-29–32)	40.00
100.00	8	Cellulose microcrystalline (Avicel™ PH101)	100.00
–	9	Alcohol SD 3A (200 proof)	QS
20.00	10	Calcium pantothenate; use racemic calcium pantothenate, USP (80 mesh; 15% excess)	46.00
11.50	12	Magnesium oxide (light powder calcined)	11.50
500.00	13	Ascorbic acid	500.00
3.83	14	Povidone (K-29–32)	3.83
–	15	Alcohol SD 3A (200 proof)	QS
4.00 μg	16	Vitamin B12; use vitamin B12 oral powder in gelatin (15% excess)	4.60
28.00	17	Acid stearic	28.00
9.60	18	Magnesium stearate	9.60

Manufacturing Directions

1. Dry-blend riboflavin, niacinamide, pyridoxine hydrochloride, thiamine mononitrate, ascorbic acid (item 5), and lactose for 10 minutes.
2. Dissolve Povidone (item 7) in 75 mL of alcohol (item 9).
3. While mixing in mass mixer, add Povidone solution to mass, and continue mixing for 10 minutes, or until a satisfactory granule mass is obtained.
4. Additional alcohol may be added, if required.
5. Granulate the mass through a 15.9-mm screen using a comminuting mill (knives forward, slow speed) or a 4-mm screen on an oscillating granulator.
6. Dry the granules between 41°C and 49°C in a hot air oven (for approximately 8 hours) or fluid-bed dryer until moisture content is below 1.5%.
7. Dry-screen the granule through a 1-mm screen on an oscillating granulator.
8. Dry-blend the calcium pantothenate and magnesium oxide in a suitable mixer for 10 minutes.
9. Dissolve Povidone (item 14) in 20 mL alcohol (item 15).
10. While mixing, add Povidone solution, and mix to produce a suitable mass.
11. Additional alcohol may be added, if required.
12. Granulate the mass through a 15.9-mm aperture screen using a comminuting mill (knives forward, slow speed) or a 4-mm screen on a oscillating granulator.
13. Dry the granule at 45°C in a hot air oven until moisture content is below 1.5%.
14. Dry-screen granule through a 1.0-mm screen on an oscillating granulator.
15. Mix the two granules made separately in a suitable mixer.
16. Add vitamin B12 powder, and blend for 10 minutes. If necessary, screen the stearic acid and magnesium stearate through a 250-μm screen.
17. Add the remainder of the granule together with magnesium stearate and stearic acid to the mixer and blend for 10 minutes.
18. Compress and coat. (See Appendix.)

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Riboflavin	10.00
100.00	2	Niacinamide (white powder)	100.00
5.00	3	Pyridoxine hydrochloride (15% excess)	5.75
15.00	4	Thiamine mononitrate (powder) (5% excess)	15.75
40.00	7	Povidone (K-29–32)	40.00
25.00	8	Povidone (K-29–32)	25.00
–	9	Alcohol SD 3 A (200 proof)	QS
13.50	10	Stearic acid (fine powder)	13.50
2.70	11	Magnesium stearate	2.70

Manufacturing Directions

1. Mill niacinamide, riboflavin, pyridoxine hydrochloride, and thiamine mononitrate through a 500-μm screen on a comminuting mill (impact forward, slow speed).
2. Load screened material from previous step into a mass mixer, add Povidone (item 7) and cellulose microcrystalline, and dry blend for 5 to 15 minutes.
3. While mixing in the mass mixer, add alcohol (item 9) to mass, and continue mixing for 10 minutes or until a satisfactory granule mass is obtained.
4. If necessary, granulate the mass through a 15.9-mm screen using a comminuting mill (knives forward, slow speed) or a 4-mm screen on an oscillating granulator.
5. Dry the granule between 41°C and 49°C in a hot air oven (for approximately 8 hours) or fluid-bed dryer until moisture content is below 1.5%.
6. Dry-screen the granules through a 1.0-mm screen on an oscillating granulator.
7. Load ascorbic acid and Povidone (item 8) into the mixer and dry-blend for 10 minutes.
8. While mixing, add 15 mL of alcohol (item 9), and mix until a satisfactory mass is formed, adding more alcohol if necessary. If necessary, screen through a 4.00-mm screen and load onto trays.
9. Dry at 49°C for 8 hours.
10. Dry screen the granules through a 1.0-mm aperture screen on an oscillating granulator.
11. Screen magnesium stearate and stearic acid through a 500-μm aperture screen.
12. Mix the two granules, add the screened lubricants, and blend for 20 minutes.
13. Coat with a protective subcoat, a color coat, and a polish coat (see Appendix).

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Vitamin A acetate (dry powder; 500,000 IU/g)	10.00
2.20	2	Thiamine mononitrate	2.20
2.20	3	Riboflavin	2.20
16.50	4	Nicotinamide	16.50
11.50	5	Calcium D-pantothenate	11.50
2.20	6	Pyridoxine hydrochloride	2.20
6.00	7	Cyanocobalamin (dry powder, 0.1%)	6.00
85.00	8	Ascorbic acid (powder)	85.00
31.00	9	Vitamin E acetate (dry powder; SD 50)	31.00
321.00	10	Ludipress®[a]	321.00
21.00	11	Kollidon® VA 64	21.00
3.00	12	Magnesium stearate	3.00
7.20	13	Orange flavor	7.20
2.50	14	Saccharin sodium	2.50

[a]Can be replaced with 300 g of microcrystalline cellulose (Vitacel®).

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, mix, and press with medium-compression force (15 kN).
2. Compress into 500 mg tablets, using 12-mm biplanar punches.

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.00	1	Thiamine hydrochloride	2.20
2.20	2	Riboflavin	2.20
11.00	3	Calcium D-pantothenate	11.00
2.20	4	Pyridoxine hydrochloride	2.20
300.00	5	Mannitol	300.00
20.00	6	Kollidon® 30 or Kollidon® VA 64	20.00
–	7	Isopropanol	~80
5000 IU vitamin A, 500 IU vitamin D	8	Vitamin A and vitamin D; use crystallets of vitamin A acetate + vitamin D3 dry powder (500,000 + 50,000 IU/g) (10% excess)	11.00
31.00	9	Vitamin E acetate (dry powder; SD 50)	31.00
0.06	10	Cyanocobalamin; use gelatin-coated cyanocobalamin (0.1%)	6.00
80.00	11	Ascorbic acid (crystalline)	80.00
20.00	12	Nicotinamide	20.00
65.00	13	Avicel™ PH101	65.00
7.00	14	Orange flavor	7.00
2.00	15	Saccharin sodium	2.00
3.00	16	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with solution of items 6 and 9.
2. Pass through an 0.8-mm sieve, mix with items 8 to 16, and press with medium-compression force.
3. Compress into 560-mg tablets, using 12-mm biplanar punches.

Multivitamin Tablets for Dogs

Formulation: Vitamin A + D3 dry powder, 4.0 g, 500000 + 50000 IU/g; thiamine mononitrate, 0.5 g; riboflavin, 0.7 g; nicotinamide, 5.0 g; calcium D-pantothenate, 1.0 g; pyridoxine hydrochloride, 0.5 g; cyanocobalamin gelatin-coated 1%, 0.5 g; folic acid, 0.05 g; choline bitartrate, 20.0 g; vitamin E acetate dry powder SD 50, 20.0 g; Ludipress, 196.0 g; magnesium stearate, 2.0 g.

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix and press with low-compression force at 250 mg.

Multivitamin Tablets for Dogs

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2000 IU Vitamin A 200 IU Vitamin D	1	Vitamin A + vitamin D3 (dry powder; 500,000 + 50,000 IU/g)	4.00
0.50	2	Thiamine mononitrate	0.50
0.70	3	Riboflavin	0.70
5.00	4	Nicotinamide	5.00
1.00	5	Calcium D-pantothenate	1.00
0.50	6	Pyridoxine hydrochloride	0.50
0.50	7	Cyanocobalamin (gelatin-coated, 1%)	0.50
0.05	8	Folic acid	0.05
20.00	9	Choline bitartrate	20.00
20.00	10	Vitamin E acetate (dry powder, SD 50)	20.00
196.00	11	Ludipress®	196.00
2.00	12	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix, and press with low-compression force.
2. Compress into 250-mg tablets, using 8-mm biplanar punches.

Multivitamin Tablets with Beta-Carotene

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.00	1	Beta-carotene; use beta-carotene dry powder (Betavit®, 10%)	10.00
2.00	2	Thiamine mononitrate	2.00
2.00	3	Riboflavin	2.00
16.00	4	Nicotinamide	16.00
11.00	5	Calcium D-pantothenate	11.00
2.00	6	Pyridoxine hydrochloride	2.00
0.06	7	Cyanocobalmine; use cyanocobalamin dry powder (0.1%)	6.00
85.00	8	Ascorbic acid (powder)	85.00
31.00	9	Vitamin E acetate (dry powder; SD 50)	31.00
321.00	10	Ludipress®	321.00
7.00	11	Kollidon® VA 64	7.00
3.00	12	Magnesium stearate	3.00
7.00	13	Orange flavor	7.00
2.00	14	Saccharin sodium	2.00

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, mix, and press with medium-compression force.
2. Compress into 508-mg tablets, using 12-mm planar punches.

Multivitamin Tablets with Copper and Zinc

Formulation: Vitamin mixture (thiamine mononitrate), 3.9%; riboflavin, 100.0.4%; nicotinamide, 10.1%; calcium D-pantothenate, 2.9%; pyridoxine hydrochloride, 1.2%; cyanocobalamin gelatin coated 0.1%, 2.6%; folic acid, 0.1%; ascorbic acid fine powder, 63.4%; vitamin E acetate dry powder 500 SD, 9.1%; copper oxide, 0.3%; zinc sulfate 6.0%, 1000 g; Aerosil, 200.5 g; Ludipress, 150 g; Avicel PH102 [5], 120 g; Kollidon VA64 [1], 25 g; magnesium stearate,10 g; talc, 10 g.

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with high-compression force at 1350 mg.

Multivitamin Tablets, DC (1–2 RDA of Vitamins)

Formulation: Vitamin A acetate dry powder, 10.0 g, 500,000 IU/g; thiamine mononitrate, 2.2 g; Riboflavin, 2.2 g; nicotinamide, 16.5 g; calcium D-pantothenate, 11.5 g; pyridoxine hydrochloride, 2.2 g; cyanocobalamin 0.1% dry powder, 6.0 g; ascorbic acid, powder, 85.0 g; vitamin E acetate dry powder SD 50, 31.0 g; Ludipress, 321.0 g; magnesium stearate, 3.0 g; orange flavor, 7.2 g; saccharin sodium, 2.5 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, mix, and press with medium-compression force (15 kN).

Multivitamin with Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.85 IU	1	Vitamin A acetate (dry powder; 500,000 IU/g)	5.47
5.00	2	Beta-carotene; use beta-carotene dry powder (Betavit®, 10%)	50.00
15.34	3	Thiamine mononitrate	15.34
4.13	4	Riboflavin	4.13
50.00	5	Nicotinamide	50.00
8.23	6	Calcium D-pantothenate	8.23
5.00	7	Pyridoxine hydrochloride	5.00
0.04	8	Cyanocobalamin; use gelatin-coated cyanocobalamin (1%)	4.00
0.04	9	D-biotin; use 1% trituration	4.00
0.38	10	Folic acid	0.38
165	11	Ascorbic acid	165
327	12	Vitamin D3 (dry powder; 100000 IU/g)	3.27
122.00	13	Vitamin E acetate (dry powder; SD 50)	122.00
0.41	14	Phytomenadione; use phytomenadione dry powder (5% GFP)	0.82

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix, and press with high-compression force.
2. Compress into 432-mg tablets, using 12-mm biplanar punches.

Multivitamin with Zinc Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Niacin; use niacinamide (white powder)	99.20
750.00	2	Ascorbic acid; use microcrystalline sodium ascorbate[a]	843.68
20.00	3	Vitamin B6; use pyridoxine hydrochloride	34.03
QS	4	Povidone	40.00
15.00	5	Thiamine hydrochloride; use thiamine mononitrate (powder)	17.47
15.00	6	Riboflavin	16.50
20.00	7	Pantothenic acid; use calcium pantothenate	32.60
0.49	8	Folic acid (powder)	0.52
12.00 μg	9	Vitamin B12; use cyanocobalamin oral powder in gelatin 1:1000	15.00
60.00	10	Vitamin E (*d,l*-α-tocopherol acetate)	60.00
–	11	Alcohol SD 3A (200 proof)	138 mL 23 mL
22.50	12	Elemental zinc (pure zinc sulfate powder)	55.61
4.00	13	Povidone	4.00
–	14	Alcohol SD 3A (200 proof)	4 mL
–	15	Alcohol SD 3A (200 proof)	9 mL
10.80	16	Magnesium stearate	10.80
40.00	17	Cellulose microcrystalline	40.00
3.20	18	Silicon dioxide colloidal	3.20
6.00	19	Colloidal silicon dioxide	6.00

[a]May use ascorbic acid (750.00 g) instead.
The quantity of Povidone is reduced to 6.34 g, and the amount of alcohol SD used is adjusted.

Manufacturing Directions

1. Mill niacinamide, sodium ascorbate, pyridoxine, Povidone (item 4), and thiamine through a comminuting mill with hammers (impact forward) at high speed and fitted with a 0 band (686-μm aperture, or similar) screen.
2. Charge millings into mass mixer.
3. Screen riboflavin, calcium pantothenate, folic acid, vitamin B12, and vitamin E through 840-μm screen.
4. Charge into mass mixer, and dry mix for 5 to 10 minutes.
5. Add 89 mL alcohol to powder while mixing.
6. Add additional alcohol, if required (approximately 49 mL), to achieve satisfactory granulation.
7. Pass wet mass through 5/8- in. band (15.88-mm aperture, or similar) screen and spread out on paper-lined trays.
8. Dry granulation at 49°C, and dry until LOD is not more than 1.5%.
9. Sift dry granule through 1.19-mm screen, and coarse grind granule through a No. 2 band (1.59-mm aperture, or similar) screen fitted on a comminuting mill (knives forward, medium speed) to polyethylene-lined drums.
10. Mill zinc sulfate and Povidone through a comminuting mill fitted with a 0 band (686-μm aperture, or similar) screen at high speed with impact (hammers) forward.
11. Charge millings into mass mixer for 5 to 10 minutes.
12. Add 3.3 mL alcohol (item 14) to powders from first step while mixing.
13. If necessary, use additional alcohol (up to 0.83 mL) to achieve satisfactory granulation.
14. Granulate wet mass through 5/8- in. band (15.88-mm aperture, or similar) screen, and spread out on paper-lined trays.
15. Dry granule at 49°C, and dry until LOD is not more than 1.5%.
16. Sift dry granule through 1.19-mm screen, and coarse grind granule through a No. 2 band (1.59-mm aperture, or similar) screen fitted on a comminuting mill (knives forward, medium speed) and transfer to polyethylene-lined drums.
17. Charge approximately 1/10th of vitamin granulation into blender.
18. Premix magnesium stearate, microcrystalline cellulose, and silicon dioxide in a bowl, and sift through 840-μm screen into blender.
19. Charge another 1/10th more of vitamin granulation into blender, and blend for 5 minutes.
20. Discharge a portion of granulation from the blender, and check for white lumps.
21. If lumps are present, discharge entire granulation through a 1.68-mm aperture screen to break lumps, then return it to blender.
22. Charge zinc granulation into the blender.
23. Charge remaining vitamin granulation into blender, and blend for 15 minutes.
24. Discharge blender into polyethylene-lined drums, tie liners, close and seal drums, and deliver to storage area.
25. Compress and coat (see Appendix).

Nalidixic Acid Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Nalidixic acid	500.00
20.00	2	Lactose monohydrate	20.00
25.00	3	Starch (maize)	25.00
30.00	4	Starch (maize)	30.00
0.10	5	Propyl paraben	0.10
0.40	6	Methyl paraben	0.40
0.80	7	Sodium starch glycolate	0.80
2.50	8	Magnesium stearate	2.50
1.00	9	Talc	1.00
0.20	10	Aerosil 200	0.20
2.00	11	Starch (maize), dried	3.00
–	12	Water, purified, ca	400 mL

Manufacturing Directions

1. Sift items 1 and 2 through a #40-mesh sieve into a suitable blending vessel.
2. Sift item 3 through #80-mesh sieve, add to step 1, and mix for 10 minutes.
3. In a separate vessel, sift item 4 through #80 mesh, add items 5 and 6, and mix for 5 minutes. Add item 12 at 80°C to prepare a 30% starch paste that is smooth and lump-free.
4. Add step 3 into step 2, and make a wet mass suitable for granulation.
5. Pass the wet mass through a 10-mm sieve in a mill, and dry in a fluid-bed dryer at 50°C for 1 hour to an LOD of not more than 3%. Transfer to a blending vessel.
6. Sift items 7 to 11 through a 250-μm sieve screen, and add to step 5. Blend for 1 minute only.
7. Compress into 575-mg tablets, using 13-mm punches.

Nalidixic Acid Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Nalidixic acid	500.00
15.00	2	Kollidon 30	15.00
–	3	Water, purified	125.00
25.00	4	Kollidon CL	25.00
5.00	5	Magnesium stearate	5.00

Manufacturing Directions

1. Granulate item 1 with the solution of item 2 in item 3. Dry, and pass through a 0.8-mm sieve. Add the mixture of items 4 and 5, mix during 10 minutes, pass again through a 0.8-mm sieve, and press with low-compression force (10 kN).
2. Compress into 545-mg tablets, using 12-mm biplanar punches.

Naproxen Tablets (250 mg)

Naproxen tablets for oral administration each contain 250, 375, or 500 mg of naproxen. Naproxen is a member of the arylacetic acid group of nonsteroidal anti-inflammatory drugs.

Naproxen Tablets

Bill of Materials			
Scale (mg/tablet)	item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Naproxen	250.00
6.00	2	Kollidon 90F	6.00
4.00	3	Kollidon 90F	4.00
4.00	4	Cremophor RH40	4.00
–	5	Water	41.00
150.00	6	Tablettose	150.00
1.00	7	Stearic acid	1.00
10.00	8	Ac-Di-Sol	10.00
1.00	9	Magnesium stearate	1.00
10.00	10	Polyethylene glycol 6000 powder	10.00

Manufacturing Directions

1. Granulate the mixture of items 1 and 2 with a solution of items 3 to 5, dry, pass through a 0.8-mm sieve, add items 6 to 9, and press with low-compression force.
2. Compress into 441-mg tablets, using 12-mm biplanar punches.

Naproxen Tablets (250 mg/500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Naproxen	250.00
78.40	2	Lactose monohydrate	78.40
7.00	3	Starch (corn)	7.00
4.00	4	Sodium starch glycolate	4.00
0.60	5	Yellow dye	0.60
5.00	6	Povidone K 29–32	5.00
5.00	7	Polysorbate 80	5.00
QS	8	Isopropyl alcohol, ca	200.00 mL
3.70	9	Talc	3.70
3.30	10	Magnesium stearate	3.30

Note: For 500-mg strength, use the same formula with higher fill weight.

Manufacturing Directions

1. Granulation
   a. Pass naproxen and lactose through a 16-mesh (1.2-mm aperture) screen into a planetary mixer (or something similar). Mix these items for 10 minutes.
   b. To a suitable blender, add starch (corn), sodium starch glycolate, and yellow dye. Blend these items for 10 minutes.
   c. Incorporate the blended powders from step 1b into the blend in step 1a. Mix for 10 minutes.
   d. Dissolve povidone and polysorbate 80 in alcohol isopropyl. The solution must be complete.
   e. While mixing the blended powders from step 1c, add the solution from step 1d. When all the solution is added, continue mixing for 2 minutes, until a characteristic mass is obtained. Add more alcohol isopropyl, if required. Record the additional amount of alcohol isopropyl.
   f. Pass the wet mass through an 8-mesh (2.38-mm aperture) screen by hand. Load the granular mass onto paper-lined trays, and oven dry at 49°C until the LOD is between 1.5% and 2.5%.
   g. Pass the dried granules through a FitzMill fitted with a 2A band (knives forward, medium speed) into tared, polyethylenelined drums.
2. Lubrication
   a. Transfer the dried granules from step 1 g to a suitable blender.
   b. Screen talc and magnesium stearate through a 30-mesh (595-μm aperture) screen, and add this to the blender. Blend this mixture for 10 minutes.
   c. Discharge the granules into clean, tared, polyethylenelined drums. Then seal the drums, and weigh for yield.
3. Compression: Compress on a suitable compression machine using 9.5-mm round, standard concave punches—tablet weight: 352 mg.

Naproxen Tablets (450 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
450.00	1	Naproxen	457.50
10.00	2	Kollidon CL	10.00
25.00	3	Kollidon 30	25.00
–	4	Water, purified	90.00
2.50	5	Magnesium stearate	2.50

Manufacturing Directions

1. Granulate the mixture of items 1 and 2 with a solution of items 3 and 4, pass through a 0.8-mm sieve, add item 5, and press to tablets with low-compression force.
2. Compress into 496-mg tablets, using 12-mm biplanar punches.

Nelfinavir Mesylate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
730.62	1	Nelfinavir mesylate	730.62
240.00	2	Crospovidone	240.00
217.37	3	Calcium silicate	217.37
Qs	4	Purified water	Qs
12.00	5	Magnesium stearate	12.00

Manufacturing Directions

Wet granulation is used to prepare the compression mix, dried (to remove water), mixed with item 5, and then compressed.

Neomycin Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Neomycin sulfate	250.00
334.00	2	Ludipress	334.00
6.00	3	Magnesium stearate	6.00
10.00	4	Aerosil 200	10.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press to tablets with low-compression force.
2. Compress into 600-mg tablets, using 12-mm biplanar punches.

Niacin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1000.00	1	Niacin	1000.00
40.00	2	Polyvinylpyrrolidone	40.00
10.00	3	Silicon dioxide	10.00
15.00	4	Sodium stearyl fumarate	15.00
400.00	5	Water	400.00

Manufacturing Directions

1. Niacin and lactose are placed in a fluidized bed apparatus.
2. An aqueous PVP solution (in 85 g of water) is sprayed to get granules.
3. The granules thus obtained are subsequently dried and passed through a sieve (1-mm mesh) and sodium stearyl fumarate is weighed, added and blended in a drum mixer.
4. The resulting mixture is pressed into tablets 1065.00 mg.
5. These tablet cores are then coated with the following formulation: ethylcellulose (Ethocel), 10.10; polyvinylpyrrolidone (Povidone), 5.50 mg; stearic acid, 2.40 mg.
6. Ethocel, povidone, and stearic acid are first dissolved in denatured alcohol (180 g).
7. The coating solution is then sprayed onto the tablet cores in a coating pan.

Nicardipine Hydrochloride Sustained-Release Tablets

Manufacturing Directions

1. First, 1200 g nicardipine hydrochloride and 1200 g hydroxypropylmethyl cellulose are dissolved in a mixture of 4800 g methanol and 4800 g dichloromethane.
2. 300 g of silicon dioxide (mean particle diameter of approximately 48 μm, particle diameter of 75 μm or smaller) is introduced to a fluidized bed granulator and coated with this solution by the side spraying method (spraying liquid volume 18 g/min, spraying air pressure 3 kg/cm^2, product temperature 30°C, inlet temperature 70°C) to obtain nicardipine hydrochloride particles.
3. Separately, 54 g of ethyl cellulose and 6 g of hydroxypropylmethyl cellulose are dissolved in a mixture of 57 g of purified water and 1083 g of methanol.
4. Nicardipine hydrochloride particles (300 g) are introduced to a fluidized bed granulator and coated with this solution by side spraying (spraying liquid volume of 8 g/min, spraying air pressure of 2.5 kg/cm^2, product temperature of 39°C, inlet temperature of 70°C) to obtain sustained-release fine particles.
5. 60 g of these sustained-release fine particles, 254.4 g mannitol, 63.6 g lactose that had been pulverized with a pin mill pulverizing device, and 12 g erythritol are granulated (spraying liquid volume 15 g/min, spraying air pressure of 0.5 kg/cm^2, product temperature of 39°C, inlet temperature of 50°C, spraying cycle of 5 seconds spraying-15 seconds drying) with an aqueous 5% w/w solution containing 8 g copolyvidone (Kollidon VA64) in a fluidized bed granulator to obtain the composition of the present invention. The ratio of ungranulated fine particles is 7.9%.
6. After further mixing 2 g of magnesium stearate with the composition that is obtained, 400-mg tablets containing 20 mg of nicardipine hydrochloride per tablet are made under an initial hardness of 0.6 kPa using a rotary tabletting machine.
7. Next, these tablets are heated for 10 minutes at 130°C using a program oven.
8. Then they are cooled at room temperature for 30 minutes. The tablets that are obtained showed a hardness of 3.7 kPa ($n = 5$), friability of 0.1% or less (100 rounds), and disintegration time in the buccal cavity of 20 seconds.

Nicotinamide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Nicotinamide (Degussa)	320.00
160.00	2	Avicel™ PH101	160.00
16.00	3	Kollidon® VA 64	16.00
3.00	4	Magnesium stearate	3.00
3.00	5	Aerosil® 200	3.00

Manufacturing Directions

With medium-compression force, compress into 506-mg tablets, using 12-mm biplanar punches.

Nicotinic Acid (Niacin) Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Nicotinic acid	200.00
200.00	2	Ludipress®	200.00
5.00	3	Kollidon® CL	5.00
1.50	4	Magnesium stearate	1.50
3.00	5	Aerosil® 200	3.00
10.00	6	PEG-6000	10.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve.
2. Mix and press with very low-compression force.
3. Compress into 410-mg tablets, using 12-mm biplanar punches.

Nicotinic Acid (=Niacin) Tablets (200 mg)

Formulation: Nicotinic acid (Lonza), 200.0 g; Ludipress, 200.0 g; Kollidon CL, 5.0 g; magnesium stearate, 1.5 g; Aerosil 200, 3.0 g; polyethylene glycol 6000, powder, 10.0 g.

Manufacturing Directions

Pass all components through a 0.5-mm sieve, mix, and press with very low-compression force at 419 mg.

Nicotinic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
375.00	1	Nicotinic acid	375.00
188.70	2	Hydroxypropyl methyl cellulose E10 M premium	188.70
12.90	3	Povidone K90	12.90
5.80	4	Stearic acid (Hystrene 5016)	5.80

Manufacturing Directions

1. Charge one half of the quantity of item 1 and items 2 and 3 and the powder bed is dry mixed in a Littleford granulator, with choppers on, for approximately 1 minute.
2. At the completion of the 1-minute premix cycle, an appropriate quantity about three times the quantity of item 3 and sprayed slowly for a period of 5 minutes.
3. The granulated unit is discharged into double polyethylene-lined containers and then manually loaded into a Glatt bowl while being passed through a #4-mesh screen, the Glatt bowl is loaded into a Glatt fluid-bed dryer with an inlet air temperature setting of about 70 ± 5°C.
4. The unit is dried until a moisture level of approximately 1.0% is obtained as determined using a Computrac® Moisture Analyzer.
5. The dried granulation is discharged into appropriately labeled, double polyethylene-lined drums and reconciled.
6. The dried and reconciled granulation is passed through a Kemutec BetaGrind mill equipped with an l.5-mm screen and running at approximately 1500 RPM.
7. The milled granulation is collected into appropriately labeled, double polyethylene-lined drums and reconciled.
8. The milled granulation is sampled and tested by quality control and released prior to further processing.
9. The released granulation units are charged to a Patterson-Kelley 20 ft^3 V-blender after which they are blended together for about 10 ± 1 minutes and then discharged to appropriately labeled, double polyethylene-lined containers.
10. Add item 4 blend and compress at 582.40 mg in caplet-shaped punches; compress 727.50 for 500-mg strength and 990.50 mg for 750-mg strength.

Nifedipine Coprecipitate Tablet

1. kg of nifedipine and 1.0 kg of polyvinylpyrrolidone are dissolved in 18 L of methylene chloride at room temperature.
2. The obtained solution is treated in a spray-dryer plant at a temperature equal to 90°C with double fluid nozzle with external mixing.
3. A solid coprecipitate having a ratio by weight between nifedipine and polyvinylpyrrolidone equal to 1:1 and a granulometry lower than 100 μm is obtained.
4. A tablet composition is prepared using the coprecipitate of nifedipine and polyvinylpyrrolidone 1:1, having a granulometry lower than 100 μm.
5. A granulate is first prepared introducing in a fluid-bed dryer hydroxypropylmethylcellulose, carboxypolymethylene, and talc, in addition to the coprecipitate of nifedipine and polyvinylpyrrolidone. Purified water is used in order to obtain the granules which, mixed with magnesium stearate and colloidal silica, allow to obtain some tablets, which are subsequently coated with an opaque, protective film.
6. In the final composition the proportion of all ingredients is as follows (by weight%): nifedipine 15.96%; polyvinylpyrrolidone 15.96%; talc 30.31%; hydroxypropylmethylcellulose 31.91%; carboxypolymethylene 1.60%; magnesium stearate 1.06%; colloidal silica 1.60%.
7. Substances of the coating: (by weight%): talc 0.49%; magnesium stearate 0.24%; titanium dioxide 0.37%; iron oxide 0.04%; acrylic acid copolymer 0.37%; polyethylene glycol 4000 0.08%.
8. The tablets had an average weight equal to 188 mg.

Nifedipine Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Nifedipine	5.00
60.00	2	Starch (maize)	60.00
40.00	3	Lactose monohydrate	40.00
40.00	4	Dicalcium phosphate	40.00
4.00	5	Polyvinylpyrrolidone K30	4.00
0.04	6	Isopropyl alcohol	40 mL
2.00	7	Magnesium stearate	2.00
1.00	8	Talc	1.00

Manufacturing Directions

1. Sift item 1 through #40 mesh into a suitable mixing vessel. Sift items 2 to 4 through a 250-μm sieve into the same vessel, portion by portion, mixing with item 1 to achieve geometric dilution. Dry the mix for 15 minutes.
2. In a separate vessel, prepare the binding solution by dissolving item 5 and item 6.
3. Add the binding solution from step 2 into step 1 slowly, and mix until a suitable mass is obtained.
4. Pass the wet mass through a #6 sieve onto trays, and dry it overnight in a dehumidified room.
5. Pass dried granules through a #18-mesh sieve. Load into a blending vessel.
6. Sift items 7 and 8 through a 250-μm sieve, and add to step 5. Blend for 1 minute.
7. Compress into 150-mg tablets, using 7-mm punches.
8. Coat with an HPMC organic coating. (See Appendix.)

Nifedipine Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Nifedipine	10.00
40.00	2	Kollidon 25	40.00
—	3	Methylene chloride	180.00
105.00	4	Microcrystalline cellulose (Avicel PH 102)	105.00
20.00	5	Starch (maize)	20.00
25.00	6	Kollidon CL	25.00
0.40	7	Magnesium stearate	0.40

Manufacturing Directions

1. Dissolve a mixture of items 1 and 2 in item 3. Granulate the mixture of items 4 to 6 with the solution prepared previously, then sieve, dry the obtained coprecipitate, add item 7, and press with low- to medium-compression force.
2. Compress into 223-mg tablets, using 8-mm punches.

Nimesulide-Dispersible Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Nimesulide	100.00
120.00	2	Lactose monohydrate	120.00
100.00	3	Starch (maize)	100.00
0.40	4	Sodium metabisulfite	0.40
0.40	5	Propyl paraben	0.40
30.00	6	Starch (maize)	30.00
5.00	7	Talc	5.00
1.50	8	Magnesium stearate	1.50
2.50	9	Flavor	2.50
11.20	10	Sodium starch glycolate	11.20
–	11	Water, purified	QS

Manufacturing Directions

1. Sift items 1 to 3 through a #40-mesh sieve into a suitable mixer, and mix for 15 minutes.
2. In a separate vessel, prepare the binding paste by taking an appropriate quantity of item 11, heating it to 90°C, adding item 5, and dissolving. Add item 4 and dissolve. Finally, add item 6, and make a smooth slurry (30% starch).
3. Add step 2 into step 1, and form a lump-free mass.
4. Pass the wet mass through an 8-mm sieve, and load onto trays. Dry the mass at 50°C, overnight, to less than 2% moisture.
5. Pass the dried granules through a #18-mesh sieve into a blending vessel.
6. Sift items 7 to 10 through a 250-μm sieve into step 4, and blend for 1 minute.
7. Compress into 358-mm tablets, using 40-mm punches.

Nitrendipine Tablets (25 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Nitrendipine	26.00
53.00	2	Ludipress	53.00
1.50	3	Kollidon CL	1.50
0.50	4	Magnesium stearate	0.50

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with low-compression force.
2. Compress into 82-mg tablets, using 6-mm biplanar punches.

Nitrofurantoin Tablets

Formulations: Nitrofurantoin sodium hydrate, 238 mg (equivalent to 200 mg nitrofurantoin); microcrystalline cellulose, 175 mg; sodium starch glycollate, 25 mg; cornstarch, 25 mg; talc, 20 mg; magnesium stearate, 1 mg.

Manufacturing Directions

1. The ingredients are mixed and screened and 488-mg convex core tablets compressed by direct compression using a suitable tablet press yielding tablets approximately 11 mm in diameter and 5.4 mm in height.
2. Coating solution: Eudragit-S 12.5% Isopropanol Suspension 45.7 Polyethylene glycol 6000 33% Aqueous Solution 3.5 Talc 2.5 Isopropanol/Acetone 1:1 48.3.
3. Use solution from step 2 to enteric coat by spraying the Eudragit-S suspension onto their surfaces as tablets rotate in a conventional coating pan. Coating thickness required to produce an even, uninterrupted surface distribution varies between 4.0 and 7.2 mg/cm^2 a lacquer dry substance. Coat thickness may vary beyond this range depending upon production scale and process equipment. Air suspension coating techniques are also applicable.

Nitrofurantoin Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Nitrofurantoin	100.00
20.00	2	Starch (maize)	20.00
38.00	3	Lactose monohydrate	38.00
10.00	4	Kollidon 30	10.00
–	5	Water, purified	QS
5.00	6	Kollidon CL	5.00
8.00	7	Starch (maize)	8.00
4.00	8	Talc	4.00
1.00	9	Magnesium stearate	1.00

Manufacturing Directions

1. Granulate a mixture of items 1 to 3 with a solution of items 4 and 5, dry, sieve, mix with items 6 to 9, and press.
2. Compress into 180-mg tablets, using 8-mm punches.

Nitrofurantoin Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Nitrofurantoin	100.00
200.00	2	Ludipress	200.00
2.00	3	Magnesium stearate	2.00
3.00	4	Aerosil 200	3.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress into 307-mg tablets, using 12-mm punches.

Nitroglycerin and Isosorbide Mononitrate Sustained-Release Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
30.00	1	Isosorbide mononitrate	30.00
100.00	2	Hydroxypropyl methylcellulose	100.00
40.00	3	Lactose monohydrate	40.00
40.00	4	Ethylcellulose	40.00
18.00	5	Polyvinylpyrrolidone	18.00
2.00	6	Silicon dioxide	2.00
1.00	7	Magnesium stearate	1.00
8.00	8	Eudragit L100–55	8.00
1.80	9	Triethyl citrate	1.80
4.50	10	Talc	4.50
1.47	11	Polyethylene glycol 6000	1.47
0.29	12	Sodium hydroxide	0.29
Qs	13	Water	Qs
14.00	14	Eudragit EPO	14.00
8.00	15	Citric acid	8.00
Qs	16	Water	Qs
0.30	17	Nitroglycerin	0.30
65.00	18	Lactose fine powder	65.00
5.00	19	Sucrose fine powder	5.00
2.00	20	Flavor optional	2.00
0.10	21	Polyvinylpyrrolidone	0.10
qs	22	Ethyl alcohol 95%	qs

Manufacturing Directions

1. Blend isosorbide mononitrate, hyproxypropyl methylcellulose, ethylcellulose, and lactose to form a uniform blend.
2. Prepare polyvinylpyrrolidone in water or a mixture of water and ethanol solution.
3. Granulate step 1 with solution from step 2.
4. Dry the granulation and screen or mill to desired particle size.
5. Add silicon dioxide, stearic acid, and magnesium stearate and blend for additional 5 to 10 minutes.
6. Compress tablets at 233 mg.
7. Prepare the coating solution by mixing water, Eudragit L100-55, sodium hydroxide, PEG 6000, triethyl citrate, and talc to form a uniform dispersion.
8. Coat isosorbide mononitrate tablets with Eudragit L coating solution using a coating pan or a fluid-bed coater until a desired coat weight is achieved (259.50 g).
9. Prepare a coating solution containing Eudragit E and citric acid in water.
10. Coat isosorbide mononitrate enteric-coated tablets with the above coating solution in a coating pan or a fluid-bed coater until a desired coating weight is obtained (291 mg).
11. Prepare the solvent mixture containing polyvinylpyrrolidone, ethyl alcohol, and water.
12. Blend nitroglycerin, lactose, sucrose, and the flavoring agent. Screen to break lumps.
13. Add the mixture of step 11 to step 12 until a moistened powder blend is achieved.
14. Compress isosorbide mononitrate tablet (281.06 mg) with moistened nitroglycerin triturate (72.4 mg) in a tabletting machine for the total weight of 353.46 mg. The product contains 0.3 mg of nitroglycerin in the molded triturate tablet for intraoral release and 30 mg of isosorbide mononitrate as a sustained-release form, which releases isosorbide for a duration of 8 to 12 hours.

Nitroglycerin Retard Tablets

Manufacturing Directions

Formulation: Cetyl alcohol, 15.0% w/w; hydroxy ethyl cellulose, 5.0% w/w; lactose, 45.5% w/w; talc, 15.0% w/w; nitroglycerin 1:10, 16.0% w/w; talc and magnesium stearate q.s., 100.0% w/w.

1. Melt cetyl alcohol in a water jacketed tank fitted with a stirrer; add the lactose and blend. Granulate the free flowing mass through a No. 16 stainless steel screen.
2. Hydrate hydroxy ethyl cellulose with three volumes of water for each part by weight of hydroxy ethyl cellulose, and stir until a granular paste is obtained.
3. Add the granules from step 1 to the paste obtained from step 2. Continue the blend and add the talc and nitroglycerin powder. Blend until a uniform granular mass is obtained.
4. The granules are then dried at 45°C for 30 minutes and after drying, granulated through a No. 16 standard mesh screen.
5. The tablet lubricants (magnesium stearate and talc) are then added in suitable quantity and the mixture compressed into tablets.

Compression Data: tablet weight is 400 mg; punch size: 3/8 in.; flat bevelled edge.

Nitroglycerine Tablets (0.3 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.30	1	Nitroglycerin, use 1.95% mixture (diluted nitroglycerin)[a]	15.38
0.61	2	Glyceryl monostearate	0.61
16.37	3	Lactose monohydrate	16.37
0.065	4	Silicon dioxide colloidal	0.065
2.10	5	Pregelatinized starch	2.10
0.10	6	Calcium stearate	0.105

Adjust quantity based on assay with item 3. Do not add any excess.

Manufacturing Directions

1. Mill glyceryl monostearate (Myvaplex 600P) and lactose monohydrate in a suitable mixing vessel equipped with an intensifier bar.
2. Separately mill silicon dioxide and lactose monohydrate together.
3. Add diluted nitroglycerin USP to step 1. Blend for 10 minutes, with the intensifier bar set to "on."
4. Add step 2 into step 3, and mix for 3 minutes.
5. Add item 5 after passing through a 250-μm sieve to step 4, and mix for another 5 minutes, with the intensifier bar set to "on."
6. Add calcium stearate to the blend in step 5, and blend for 5 minutes.
7. Compress a suitable quantity into tablets.

Noramidopyrine Methansulfonate and Dicyclomine Hydrochloride Tablets (500 mg/10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Noramidopyrine methansulfonate	500.00
10.00	2	Dicyclomine hydrochloride	10.00
4.00	3	Lactose monohydrate	4.00
12.50	4	Starch (maize)	12.50
1.50	5	Gelatin	1.50
1.50	6	Magnesium stearate	1.50
1.50	7	Talc	1.50
1.50	8	Methyl carboxycellulose	1.50
1.50	9	Aerosil 200	1.50
1.50	10	Sodium metabisulfite	1.50
0.22	11	Methyl paraben	0.22
0.02	12	Propyl paraben	0.02
–	13	Isopropyl alcohol	QS
–	14	Water, purified	QS

Manufacturing Directions

1. Charge items 1 and 3 in a suitable mixing vessel, and 7 g of item 4, and mix for 5 minutes.
2. In a separate vessel, take a sufficient quantity of item 14, bring it to a boil, and dissolve in it items 11 and 12. Allow the mixture to cool to 50°C, add items 5 and 10, and dissolve. Add the balance of item 4, and mix well to prepare a smooth paste.
3. Add step 2 into step 1, and form a smooth wet mass. Pass the mass through a 2.38-mm sieve screen over paper-lined trays, and dry at 60°C, overnight, to an LOD of not more than 3%.
4. Pass the dried granules through a #16 mesh into a blending vessel.
5. Granulate item 2 with a sufficient quantity of item 13 (optionally containing a dye).
6. Dry the granules in step 4 in a dehumidified room.
7. Add step 6 into step 5, and mix for 5 minutes.
8. Sift items 6 to 9 through a 500-mm screen, and blend for 2 minutes.
9. Compress 625 mg in a suitable punch.

Norephedrine and Terfenidine Tablet

Formulation: 1(-)-norephedrine hydrochloride, 37.5 mg; terfenadine, 30.0 mg; lactose, 65.0 mg; hydroxypropylmethylcellulose, 15.0 mg; croscarmellose sodium, 5.0 mg; talc, 10.0 mg; hydrogenated castor oil, 8.0 mg. Total 70.5 mg.

Manufacturing Directions

The tablet is made by wet granulating l(-)-norephedrine hydrochloride, terfenadine, and lactose with a solution of hydroxypropylmethylcellulose. The granulation is dried, sized, and the remaining ingredients are sequentially dry blended and then compressed into tablets.

Norethindrone and Ethinyl Estradiol Tablets (0.75 mg/0.035 mg; 0.50 mg/0.035 mg; 1.0 mg/0.035 mg)

Each of the following products is a combination oral contraceptive containing the progestational compound norethindrone and the estrogenic compound ethinyl estradiol:

- Ortho-Novum 7/7/7—Each white tablet contains 0.5 mg of norethindrone and 0.035 mg of ethinyl estradiol. The inactive ingredients are lactose, magnesium stearate, and pregelatinized starch. Each light peach tablet contains 0.75 mg of norethindrone and 0.035 mg of ethinyl estradiol. The inactive ingredients are FD&C Yellow No. 6, lactose, magnesium stearate, and pregelatinized starch. Each peach tablet contains 1 mg of norethindrone and 0.035 of ethinyl estradiol. The inactive ingredients are FD&C Yellow No. 6, lactose, magnesium stearate, and pregelatinized starch. Each green tablet in the Ortho-Novum 7/7/7 28 package contains only inert ingredients, as follows: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.
- Ortho-Novum 10/11—Each white tablet contains 0.5 mg of norethindrone and 0.035 mg of ethinyl estradiol. The inactive ingredients are lactose, magnesium stearate, and pregelatinized starch. Each peach tablet contains 1 mg of norethindrone and 0.035 of ethinyl estradiol. The inactive ingredients are FD&C Yellow No. 6, lactose, magnesium stearate, and pregelatinized starch. Each green tablet in the Ortho-Novum 10/11 28 package contains only inert ingredients, as listed under the green tablets in the Ortho-Novum 7/7/7 28 package.
- Ortho-Novum 1/35—Each peach tablet contains 1 mg of norethindrone and 0.035 mg of ethinyl estradiol. The inactive ingredients are FD&C Yellow No. 6, lactose, magnesium stearate, and pregelatinized starch. Each green tablet

in the Ortho-Novum 1/35 28 package contains only inert ingredients, as listed under green tablets in the Ortho-Novum 7/7/7 28 package.

- Modicon—Each white tablet contains 0.5 mg of norethindrone and 0.035 mg of ethinyl estradiol. The inactive ingredients are lactose, magnesium stearate, and pregelatinized starch. Each green tablet in the Modicon 28 package contains only inert ingredients, as listed under the green tablets in the Ortho-Novum 7/7/7 28 package.

Norfloxacin Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Norfloxacin	400.00
90.00	2	Microcrystalline cellulose (Avicel PH 112)	90.00
26.00	3	Croscarmellose sodium (Ac-Di-Sol)	26.00
4.00	4	Magnesium stearate	4.00
–	5	Absolute alcohol (ethanol, dehydrated alcohol)	60.00

Manufacturing Directions

Note: Avoid overmixing lubricants, or hardness may be reduced.

1. Sieving and kneading
   a. Sift item 1 through a 900-μm sieve. Load it into the mixer.
   b. Add item 5 to step 1a, while mixing at low speed. Scrape sides and blades. Mix and chop at low speed for 2 minutes. Check the end point of granulation. If required, add additional absolute alcohol to get the end point. (The end point of the granulation is the point where there are little or no lumps in the granulation.)
2. Drying: Dry the wet granules in an oven at 55°C for 6 hours. After 2 hours of drying, scrape the semidried granules to break the lumps for uniform drying.
3. Check the LOD. The limit is 0.7% to 1%. If required, dry further at 55°C for 1 hour. Check the LOD.
4. Transfer the dried granules to stainless steel drums.
5. Grinding: Grind the dried granules through a 1.25-mm sieve, using a granulator at medium speed. Collect the granules in stainless steel drums. Load the granules into the blender.
6. Lubrication
   a. Sift items 2 and 3 through a 500-μm sieve, and add it to the blender. Mix the blend for 2 minutes.
   b. Sift item 4 through a 250-μm sieve. Add 5- to 100-g granules from bulk (see the previous step). Mix in a polythene bag for 1 minute. Then, add to the blender. Blend for 1 minute.
   c. Unload in stainless steel drums.
7. Compression
   a. Check the temperature and humidity before starting compression. The limits are that the temperature cannot exceed 25°C, and the relative humidity should be between 45% and 50%.
   b. Compress the granules using a rotary tabletting machine (diameter: 16.2 × 8.3 mm, compression weight: 520 mg).
8. Tablet coating: Coat with an HPMC solution. (See Appendix.)

Norfloxacin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Norfloxacin	400.00
48.56	2	Microcrystalline cellulose	48.56
47.12	3	Starch 1500	47.12
5.15	4	Stearic acid	5.15
2.58	5	Fumed silica	2.58
10.30	6	Croscarmellose sodium	10.30
1.29	7	Magnesium stearate	1.29

Manufacturing Directions

1. Pass Starch 1500 and fumed silica together through a 40-mesh screen.
2. Add norfloxacin, microcrystalline cellulose, stearic acid, and croscarmellose sodium to the material from step 1 and blend for 15 minutes in a twin-shell blender.
3. Add the magnesium stearate to the material from step 2 and blend for an additional 5 minutes.
4. Compress into 515-mg tablets.

Norgestimate and Ethinyl Estradiol Tablets (0.18 mg/0.035 mg; 0.215 mg/0.035; 0.25 mg/0.035 mg)

Each of the following products is a combination oral contraceptive containing the progestational compound norgestimate and the estrogenic compound ethinyl estradiol.

1. Ortho Tri-Cyclen® 21 Tablets and Ortho Tri-Cyclen® 28 Tablets
   a. Each white tablet contains 0.180 mg of the progestational compound, norgestimate (18,19-dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include lactose, magnesium stearate, and pregelatinized starch.
   b. Each light blue tablet contains 0.215 mg of the progestational compound, norgestimate (18,19-dinor-17-pregn-4-en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17α-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch.
   c. Each blue tablet contains 0.250 mg of the progestational compound, norgestimate (18,19-dinor-17-pregn-4- en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17α)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17a-pregna,1,3,5 (10)-trien-20-yne-3,17-diol). Inactive ingredients include FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch.
   d. Each green tablet in the Ortho Tri-Cyclen 28 package contains only inert ingredients, as follows: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.
2. Ortho-Cyclen 21 Tablets and Ortho-Cyclen 28 Tablets
   a. Each blue tablet contains 0.25 mg of the progestational compound, norgestimate (18,19-dinor-17-pregn-4- en-20-yn-3-one,17-(acetyloxy)-13-ethyl-,oxime,(17a)-(+)-) and 0.035 mg of the estrogenic compound, ethinyl estradiol (19-nor-17a-pregna,1,3,5(10)-trien-20-yne-3,17-diol). Inactive ingredients include FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, and pregelatinized starch.
   b. Each green tablet in the Ortho-Cyclen 28 package contains only inert ingredients, as follows: D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, lactose, magnesium stearate, microcrystalline cellulose, and pregelatinized starch.

Nystatin Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Nystatin	55.00
110.00	2	Ludipress	110.00
1.00	3	Aerosil 200	1.00
1.30	4	Magnesium stearate	1.30

Manufacturing Directions

1. Mix the components, and pass through a 0.8-mm sieve.
2. Press with very low-compression force.
3. Compress into 175-mg tablets, using 8-mm punches. For 100-mg strength, compress into 350-mg tablets using 10-mm punches.

Nystatin Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Nystatin	200.00
51.00	2	Lactose monohydrate	51.00
–	3	Isopropyl alcohol	40 mL
10.00	4	Kollidon CL	10.00
3.00	5	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate a mixture of items 1 and 2 with a solution of items 3 and 4. Dry, pass through a 0.8-mm sieve, add item 5, and press with medium-compression force.
2. Compress into 270-mg tablets, using 9-mm punches.

Olanzapine Orally Disintegrating Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Olanzapine	5.00
92.97	2	Mannitol DC Grade	92.97
0.50	3	Gelatin	0.50
0.50	4	Aspartame	0.50
0.02	5	Sodium methylparaben	0.02
0.01	6	sodium propylparaben	0.01
1.00	7	Colloidal silicon Dioxide (Aerosil-200)	1.00

For all other strengths adjust the total weight with item 2.

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1 and items 3 to 6 through 0.5-mm sieve and collect in a container.
4. Add 15% (=6.9 g) Mannitol from step 1 to step 3 and mix well.
5. Transfer step 4 into step 2.
6. Transfer balance quantity of step 1 into step 2.
7. Mix step 2 for 20 minutes using tumbler.
8. Pass item 7 through 0.500-mm sieve and add to step 7.
9. Mix step 8 for 2 minutes.
10. Compress into 100-mg tablets, using a suitable punch (5.5 mm, round).

Olanzapine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Olanzapine	10.00
200.00	2	Pregelatinized starch	200.00
25.00	3	Microcrystalline cellulose (Avicel PH 101)	25.00
15.00	4	Povidone	15.00
10.00	5	Croscamellose	10.00
3.75	6	Magnesium stearate	3.75
2.50	7	FD&C Yellow No. 2 Lake	2.50
–	8	Water, purified, ca	5 mL

Manufacturing Directions

1. Charge items 1 to 3, 5, and 7 in a suitable blender, and mix them.
2. In a separate vessel, prepare a binding solution using items 4 and 8.
3. Add to step 1 and granulate. Dry granules in trays at 40°C under vacuum.
4. Pass the dried granules through 60 mesh.
5. Add and blend item 6, and compress.

Olanzapine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.50	1	Olanzapine	2.50
49.20	2	Lactose Spray Dried	49.20
35.00	3	Microcrystalline cellulose (Avicel PH102)	35.00
2.0	4	Crospovidone	2.00
0.50	5	Hydroxypropyl cellulose	0.50
0.80	6	Magnesium stearate	0.80
2.00	7	Hypromellose	2.00
0.45	8	Polyethylene Glycol 4000	0.45
0.60	9	Titanium dioxide	0.60
0.20	10	FD&C Blue No. 2 Aluminum Lake	0.20
–	11	Water, purified	30.00

Note: For all other strengths, adjust the total quantity with item 2.

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and charge in a tumbler.
2. Pass items 1, 4, and 5 through 0.5-mm sieve and collect in a stainless steel container.
3. Add 5.0% (=2.5 g) lactose from step 1 to step 2 and mix well.
4. Add 10.0% (=4.9 g) lactose from step 1 to step 3 and mix well.
5. Transfer step 4 into step 1.
6. Pass item 3 through 0.7-mm sieve and charge to step 1.
7. Mix step 1 for 20 minutes using tumbler.
8. Pass item 6 through 0.250-mm sieve and add to step 7.
9. Mix step 8 for 2 minutes.
10. Compress into 90-mg tablets, using a suitable punch (5.5 mm, round, imprinted 2.5).
11. Charge item 11 in a stainless steel vessel. Add item 7 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hypromellose.
12. Add items 8 to 10 one by one to step 11 with stirring. Stir for 5 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
13. Load core tablets from step 10 in coating pan and apply coating dispersion from step 12 to get 2.5% to 3.0% weight gain.

Olanzapine Tablets Zyprexa

Each Zyprexa® tablet contains olanzapine equivalent to 2.5 mg (8 μmol), 5 mg (16 μmol), 7.5 mg (24 μmol), or 10 mg (32 μmol). The inactive ingredients are carnauba wax, color mixture white, crospovidone, FD&C Blue No. 2 Aluminum Lake, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients.

Omeprazole and Ibuprofen Tablets (10 mg/400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Omeprazole, use magnesium omeprazole	12.00
12.00	2	Nonpareil cores	12.00
1.80	3	Hydroxypropyl methylcellulose	1.80
–	4	Water, purified	35.40
23.50	5	Hydroxypropyl cellulose	2.35
4.03	6	Talc	4.03
–	7	Water, purified	48.00
38.70	8	Methacrylic acid copolymer (30% suspension)	38.70
3.48	9	Triethyl citrate	3.48
0.58	10	Mono- and diglycerides	0.58
0.06	11	Polysorbate 80	0.06
–	12	Purified water	22.68
400.00	13	Ibuprofen	400.00
273.60	14	Microcrystalline cellulose	273.60
100.40	15	Polyvinylpyrrolidone cross-linked	100.40
33.30	16	Polyvinylpyrrolidone K-25	33.30
26.70	17	Sodium lauryl sulfate	26.70
–	18	Water, purified	297.00
4.0	19	Sodium stearyl fumarate	4.00

Manufacturing Directions

Note: The formulation and manufacturing directions given here can be used to formulate combinations of omeprazole with other NSAIDs, such as naproxen (250 mg) or piroxicam (20 mg). Omeprazole can be replaced with pantoprazole or lansoprazole.

1. Prepare a solution of items 1 and 3 in item 4, and spray onto item 2 to prepare nonpareil cores in a fluid-bed dryer.
2. Prepare a solution of items 5 to 7 and 8 to 12 separately. Alternate application of these solutions on step 1 to provide enteric properties to the cores.
3. Pass the enteric-coated cores through a sieve.
4. Prepare a granulating solution using items 16 to 18.
5. Dry blend items 13, 15 (one-tenth), and 16, and add step 4 to this step to granulate. Add more of item 18 to the mass. Pass granules through #8 mesh, and dry at 60°C for 6 hours. Pass dried granules through a 0.8-mm sieve.
6. Add step 3 and the balance of item 15, and blend for 10 minutes.
7. Compress into 886-mg tablets, using 15-mm punches. There is a disintegration time of less than 1 minute in simulated gastric juice (USP without enzymes).

Omeprazole Effervescent Tablets

Manufacturing Directions

1. Core material : magnesium omeprazole, 12.00 kg; non-pareil cores, 12.00 kg; hydroxypropyl methylcellulose, 1.8 kg; water purified, 35.4 kg. Suspension layering is performed in a fluid-bed apparatus. Magnesium omeprazole is sprayed onto inert suger seeds (non-pareil cores) from a water suspension containing the dissolved binder.
2. Separating layer core material (step 1), 23.50 kg; hydroxypropyl cellulose, 2.35 kg; talc, 4.03 kg; magnesium stearate, 0.34 kg; water purified, 48.00 kg. The prepared core material is coating layered with a separating layer in a fluid-bed apparatus with a hydroxypropyl cellulose solution containing talc and magnesium stearate.
3. Enteric coating layer pellets with the layer (step 2), 29.00 kg; methacrylic acid copolymer (30% suspension), 38.70 kg; triethyl citrate, 3.48 kg; mono- and diglycerides (NF), 0.58 kg; polysorbate 80, 0.06 kg; water purified, 22.68 kg. The enteric coating layer consisting of methacrylic acid copolymer, mono- and diglycerides, triethylcitrate, and polysorbate is sprayed onto the pellets (layered with a separating layer) in a fluid-bed apparatus. In the same type of apparatus the enteric coating layered pellets are coated with hydroxypropyl methylcellulose/Mg-stearate suspension.
4. Over-coating layer enteric-coated pellets (step 3), 44.7 kg; hydroxypropyl methylcellulose, 0.58 kg; mg-stearate, 0.02 kg; water purified, 11.6 kg. The pellets covered by an over-coating layer are classified by sieving.
5. The obtained enteric coating layered pellets are mixed with prepared granules and other components as described below and thereafter compressed to effevescent tablets.
6. Granulation (1000 tablets): citric acid anhydrous, 605 g; Mannitol dried, 200 g; riboflavin, 0.1 g; polyvinylpyrrolidone K-25 (PVP K-25), 6.0 g; EtOH 99% (w/v), 90 g.
7. PVP K-25 is dissolved in ethanol to give the granulating solution. In this solution riboflavin is dispersed. Citric acid and mannitol are mixed and the liquid is added and the mass further mixed. Then the mass is put on a tray and dried in a drying oven for approximately 2 hours at 55°C. The granulate is milled to pass sieve 1.0 mm.
8. A premix consisting of the following is prepared by dry mixing in a mixer: Sodium carbonate anhydrous, 36 g; sodium dodecyl sulfate, 1 g; sodium stearylfumarate, 14 g; essence orange, 2.0 g; saccharine sodium, 2.0 g; polyvinyl pyrrolidone cross-linked, 70 g; enteric-coated pellets from above, 95.7 g.
9. Final mixing: Granulate from above, 811.1 g, premix from above, 220.7 g, sodium bicarbonate, 453 g. The final mixing time is 4 minutes.
10. Compression to tablets is done on a tabletting machine equipped with punches giving 20-mm diameter flat tablets with bevelled edges. Tablet weight is 1485 mg.

Omeprazole Fast-Disintegrating Tablets

Manufacturing Directions

1. Croscarmellose sodium 300 g is added to the vortex of a rapidly stirred beaker containing 3.0 kg of deionized water.
2. This slurry of step 1 is mixed for 10 minutes.
3. Omeprazole 90 g (powdered) is placed in the bowl of a Hobart mixer. After mixing, the slurry of croscarmellose sodium is added slowly to the omeprazole in the mixer bowl, forming a granulation, which is then placed in trays and dried at 70°C for 3 hours.
4. The dry granulation is then placed in a blender, and 1500 g of Avicel AC-815 (85% microcrystalline cellulose coprocessed with 15% of a calcium, sodium alginate complex) and 1500 g of Avicel PH-302 (microcrystalline cellulose) are added.
5. After the mixture of step 4 is thoroughly blended, 35 g of magnesium stearate is added and mixed for 5 minutes.
6. The resulting mixture of step 5 is compressed into tablets on a standard tablet press with an average weight of about 0.75 g, and contain about 20 mg omeprazole.

Omeprazole Fast-Dissolving Tablets

Manufacturing Directions

1. Croscarmellose sodium (300 g) is added to the vortex of a rapidly stirred beaker containing 3.0 kg of deionized water.
2. The slurry in step 1 is mixed for 10 minutes.
3. 90 g of Omeprazole (powdered) is placed in the bowl of a Hobart mixer. After mixing, the slurry of croscarmellose sodium is added slowly to the omeprazole in the mixer bowl, forming a granulation which is then placed in trays and dried at 70°C for 3 hours.
4. The dry granulation is then placed in a blender, and to it is added 1500 g of Avicel AC-815 (85% microcrystalline cellulose coprocessed with 15% of a calcium, sodium alginate complex) and 1500 g of Avicel PH-302 (microcrystalline cellulose).
5. After the above mixture is thoroughly blended, 35 g of magnesium stearate is added and mixed for 5 minutes.
6. The resulting mixture is compressed into tablets on a standard tablet press with average weight of about 1.5 g that contains about 20 mg omeprazole. These tablets have low friability and rapid disintegration time. This formulation may be dissolved in an aqueous solution containing a buffering agent for immediate oral administration. Alternatively, the suspension tablet may be swallowed whole with a solution of buffering agent. In both cases, the preferred solution is sodium bicarbonate 8.4%. As a further alternative, sodium bicarbonate powder (about 975 mg per 20 mg dose of omeprazole (or an equipotent amount of other PPI)) is compounded directly into the tablet. Such tablets are then dissolved in water or sodium bicarbonate 8.4%, or swallowed whole with an aqueous diluent.

Omeprazole Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Omeprazole	20.00
200.00	2	Poloxamer (Pluronic PE 6800)	200.00
7.00	3	Colloidal silicon dioxide	7.00
10.00	4	Magnesium carbonate	10.00
12.00	5	Sodium starch glycollate	12.00
100.00	6	Titanium dioxide	100.00
226.00	7	Ludipress	226.00
25.00	8	Sodium stearyl fumarate	25.00
Enteric coating layer			
75.00	9	Polyvinyl acetate phthalate	75.00
0.25 mg	10	Antifoam emulsion	0.25 mg
12.00	11	Sodium hydroxide	12.00

Manufacturing Directions

1. The poloxamer is melted at a temperature of 80°C.
2. Omeprazole, together with 2 mg of colloidal silicon dioxide, 8 mg of magnesium carbonate, titanium dioxide, and 6 mg of sodium starch glycolate are added and mixed thoroughly. Mixing is continued until the melt solidified.
3. The melt is granulated and the rest of the ingredients added to the granulate. The granulate is then compressed into tablets containing 20-mg Omeprazole.
4. These tablets, which formed the substrate of the composition, are then transferred into a conventional coating pan and coated with the enteric coating layer, prepared in the following manner.
   a. First, the antifoam emulsion is dissolved in water to form an aqueous solution. Polyvinyl acetate phthalate is then stirred into this solution for a final concentration of about 10% weight per volume before sodium hydroxide is added.
   b. Sodium hydroxide (1 M solution) is then added to adjust the pH value of the solution to about 8, thereby obtaining a basic solution of the enteric coating material.
   c. This solution is then sprayed onto the tablets with an incoming air temperature of 40°C. The omeprazole cores can be alternately coated using hydroxypropyl methyl cellulose acetate succinate (HPMCAS) as the enteric coating layer.

Omeprazole Tablets (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Omeprazole	10.00
200.00	2	Calcium glycerophosphate	200.00
400.00	3	Sodium bicarbonate	400.00
12.00	4	Croscarmellose sodium	12.00
3.00	5	Pregelatinized starch	3.00

Omeprazole Tablets (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Omeprazole	10.00
175.00	2	Calcium glycerophosphate	175.00
175.00	3	Calcium lactate	175.00
250.00	4	Sodium bicarbonate	250.00
20.00	5	Polyethylene glycol 6000	20.00
12.00	6	Croscarmellose sodium	12.00
3.00	7	Peppermint flavor	3.00
1.00	8	Magnesium silicate	1.00
1.00	9	Magnesium stearate	1.00

Omeprazole Tablets, Chewable (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Omeprazole	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
250.00	4	Sodium bicarbonate	250.00
0.50	5	Aspartame calcium	0.50
12.00	6	Silicon dioxide colloidal	12.00
15.00	7	Starch (maize)	15.00
12.00	8	Croscarmellose sodium	12.00
10.00	9	Dextrose anhydrous	10.00
3.00	10	Peppermint flavor	3.00
3.00	11	Maltodextrin	3.00
3.00	12	Mannitol	3.00
3.00	13	Pregelatinized starch	3.00

Manufacturing Directions

1. Pass all ingredients through a 250-μm mesh, and blend in a suitable blender.
2. Compress into 672-mg tablets, using 15-mm biplanar punches. For 20-mg tablets, increase the quantity of item 1 and compress an additional 10 mg.

Omeprazole Tablets, Rapid Dissolution (20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Omeprazole	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
500.00	4	Sodium bicarbonate	500.00
50.00	5	Calcium hydroxide	50.00
12.00	6	Croscarmellose sodium	12.00

Omega Fatty Acids Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
140.00 g	1	Omega fatty acids dry N-3	140.00
140.00 g	2	Avicel™ PH101	140.00
8.40 g	3	Kollidon® VA 64	8.40
2.00 g	4	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix, and press with high-compression force.
2. Compress into 289-mg tablets, using 9-mm biconvex punches.
3. The dry powder omega fatty acids dry N-3 contains 25% fish oil; this fish oil consists of about 30% EPA+DHA.
4. These tablet cores could be coated with an enteric coating of Kollicoat MAE 30 D. (See Appendix for more choices.)

Orlistat Chewable Tablets

Manufacturing Directions

1. Orlistat (60 g) and myristic acid (30 g) are melted together at 50°C.
2. Mannitol (400 g) and lactose (400 g) are added and the mixture is cooled to room temperature under continuously stirring.
3. Talcum (10 g) is added and homogeneously distributed.
4. The powder is pressed into tablets of 960 mg weight (=orlistat content of 120 mg).

Orlistat Chewable Tablets

Manufacturing Directions

1. Orlistat (120 g) and myristic acid (30 g) are melted together at 50°C.
2. Sucrose palmitate (PEG40 stearate, 12 g) and lactose (15 g) are added and the mixture is cooled to room temperature under continuously stirring.
3. The powder is pressed into tablets of 960 mg weight (=orlistat content of 120 mg).

Orlistat Chewable Tablets

Manufacturing Directions

1. Mix together orlistat (120 g), sodium laurate (30 g), mannitol (80 g), and HPMC 3cp (60 g) with stepwise addition of a (50:50% m/m) ethanol/water mixture (0.2 mL/g).
2. The formed granules are dried in vacuum at 30°C to constant weight and pressed into tablets (each containing 120 mg orlistat).

Oxprenolol Retard Tablets

Manufacturing Directions

1. 15.6 kg of 3-(4-chloro-3-sulfamoylphenyl)-3-hydroxy-isoindolin-1-one (chlortalidone), 3.0 kg of microcrystalline cellulose, 6.456 kg of dicalcium phosphate, 0.9 kg of cornstarch, 0.024 kg of iron yellow, and 0.120 kg of magnesium stearate are homogeneously mixed.
2. The pressing of the two active substance mixtures to form capsule-shaped tablets is carried out as described in Example 2. The tablets have a length of 18.0 mm, a width of 5.5 mm, a depth of approximately 5.6 mm, and a radius of curvature of 3.5 mm; the depth of the dividing notches provided on both sides is 1.47 mm in each case.

Oxprenolol Retard Tablets

Manufacturing Directions

1. A mixture of 9.6 kg of the ground hydrochloride of 1-(2-allyloxyphenoxy)-3-isopropylaminopropan-2-ol (oxprenolol) and 6.98 kg of ground lactose is granulated together with 16.0 kg of a 30% aqueous dispersion of the 70:30 copolymer of ethyl acrylate and methyl methacrylate in the fluidized bed; the spraying-in speed is 0.7 L/min and the temperature of the supply air is 38°C. The mixture is then dried in the same apparatus for 25 minutes at a supply air temperature of 40°C. With the simultaneous addition of 0.12 kg of colloidal silicon dioxide, 0.3 kg of calcium stearate, and 4.0 kg of stearic acid, the granulate is forced through a sieve of 1-mm mesh width and then mixed in a planetary mixer for 15 minutes.

2. The pressing of the granulate to form capsule-shaped biconvex tablets each weighing 410 mg is carried out on a tablet press having guided dies (the two opposing dies being provided with wedges for forming the dividing notches) having the following dimensions: length = 16.5 mm, width = 6.0 mm, and radius of curvature = 3.6 mm. The tapering dividing notches provided on both sides are each 1.47 mm in depth; the depth of the compact is approximately 5.4 mm.
3. Coating is carried out in a coating vessel of 55 cm diameter, which is equipped with baffle plates. With the aid of a binary nozzle 5 kg of compacts are sprayed continuously with a coating solution or suspension of the following composition. 0.1 kg of hydroxypropyl methylcellulose (viscosity 5 cps) are dissolved in 1.2 kg of demineralized water.
4. To this there are added while stirring, 0.005 kg of polysorbate 80, 0.05 kg of talc, and 0.1 kg of a 20% homogeneous suspension of titanium dioxide in a solution of 0.007 kg of hydroxypropyl methylcellulose (5 cps) in 90% ethanol. The supply air temperature is 60°C; the temperature of the compacts in the vessel is maintained at approximately 35°C. The amount of film coating sprayed on is 19 mg (dry weight) per compact.

Oxprenolol Retard Tablets

Manufacturing Directions

1. 15.6 kg of 3-(4-chloro-3-sulfamoylphenyl)-3-hydroxyisoindolin-1-one (chlortalidone), 3.0 kg of microcrystalline cellulose, 6.456 kg of dicalcium phosphate, 0.9 kg of cornstarch, 0.024 kg of iron yellow, and 0.120 kg of magnesium stearate are homogeneously mixed.
2. The pressing of the two active substance mixtures to form capsule-shaped tablets is carried out as described in Example 2. The tablets have a length of 18.0 mm, a width of 5.5 mm, a depth of approximately 5.6 mm, and a radius of curvature of 3.5 mm; the depth of the dividing notches provided on both sides is 1.47 mm in each case.

Oxybutynin Chloride Tablets (5 mg/10 mg) Ditropan

Each Ditropan XL extended-release tablet contains 5 or 10 mg of oxybutynin chloride USP, formulated as a once-a-day controlled-release tablet for oral administration. Ditropan XL also contains the following inert ingredients: cellulose acetate, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycol, polyethylene oxide, synthetic iron oxides, titanium dioxide, polysorbate 80, sodium chloride, and butylated hydroxytoluene.

Ditropan XL uses osmotic pressure to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The system, which resembles a conventional tablet in appearance, comprises an osmotically active bilayer core surrounded by a semipermeable membrane. The bilayer core is composed of a drug layer containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser-drilled orifice in the semipermeable membrane on the drug-layer side of the tablet. In an aqueous environment, such as the gastrointestinal tract, water permeates through the membrane into the tablet core, causing the drug to go into suspension and the push layer to expand. This expansion pushes the suspended drug out through the orifice. The semipermeable membrane controls the rate at which water permeates into the tablet core, that in turn, controls the rate of drug delivery. The controlled rate of drug delivery into the gastrointestinal lumen is thus independent of pH or gastrointestinal motility. The function of Ditropan XL depends on the existence of an osmotic gradient between the contents of the bilayer core and the fluid in the gastrointestinal tract. Because the osmotic gradient remains constant, drug delivery remains essentially constant. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the feces as an insoluble shell.

Oxybutynin Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Oxybutynin hydrochloride	15.00
15.00	2	Polyvinylpyrrolidone	15.00
3.00	3	Silicon dioxide	3.00
100.00	4	Lactose	100.00
30.00	5	Fumaric acid	30.00
1.50	6	Sodium stearyl fumarate	1.50

Manufacturing Directions

1. Oxybutynin hydrochloride, fumaric acid, and lactose are placed in a fluidized bed apparatus.
2. An aqueous PVP solution (in 85 g of water) is sprayed to get granules.
3. The granules thus obtained are subsequently dried and passed through a sieve (1-mm mesh), and sodium stearyl fumarate is weighed, added, and blended in a drum mixer.
4. The resulting mixture is pressed into tablets (7-mm diameter and 7-mm curvature) with average hardness being between 60 and 120 N and a total weight of 164.50 mg.
5. These tablet cores are then coated with the following formulation: ethyl cellulose (Ethocel), 10.10; polyvinylpyrrolidone (Povidone), 5.50 mg; stearic acid, 2.40 mg; for total weight of 182.50 mg.
6. Ethocel, povidone, and stearic acid are first dissolved in denatured alcohol (180 g). The coating solution is then sprayed onto the tablet cores in a coating pan.

Oxybutynin Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Oxybutynin hydrochloride	10.00
15.00	2	Polyvinyl pyrrolidone	15.00
3.00	3	Silicon dioxide colloidal	3.00
100.00	4	Lactose	100.00
30.00	5	Fumaric acid	30.00
1.50	6	Sodium stearyl fumarate	1.50
–	7	Water, purified	85.00

Manufacturing Directions

1. Charge oxybutynin hydrochloride, fumaric acid, and lactose in fluidized-bed equipment.
2. Prepare in a separate container an aqueous PVP solution (in 85 g of water).
3. Spray the solution in step 2 into step 1 to form granules at a typical setting using a fluid-bed dryer: Airflow = 100 to 110 m^3/h; liquid flow (g/min) = 6 to 7 g/min; inlet temperature = 65; and spraying pressure = 2.8 bar.
4. Pass dried granules through a sieve (1-mm mesh). Sodium stearyl fumarate is weighed, added, and blended in a drum mixer.
5. Compress using 7-mm punches at 164 mg.
6. Coat the tablets using the following formula per tablet: ethylcellulose (Ethocel), 10.10; polyvinylpyrrolidone (Povidone), 5.50; stearic acid, 2.40; and the total weight (dry weight of coated tablet) is 182.50.

Oxycodone Hydrochloride and Acetaminophen Tablets (5 mg/325 mg) Percocet

Each tablet of Percocet contains acetaminophen, 325 mg, and oxycodone HCl, 5 mg (5 mg oxycodone HCl is equivalent to 4.4815 mg oxycodone.) The inactive ingredients are microcrystalline cellulose, povidone, pregelatinized starch, stearic acid, and other ingredients.

Oxycodone and Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
325.00	1	Acetaminophen powder	325.00
4.48	2	Oxycodone, use oxycodone hydrochloride	5.00
6.00	3	Colloidal silicon dioxide	6.00
77.00	4	Microcrystalline cellulose	77.00
32.00	5	Croscarmellose sodium	32.00
13.00	6	Hydroxypropyl methylcellulose	13.00
62.00	7	Starch (maize)	62.00
2.00	8	Magnesium stearate	2.00
–	9	Water, purified	QS

Manufacturing Directions

1. Pass hydrocodone bitartrate through a #20 mesh, and pass acetaminophen and colloidal silicon dioxide (50%) through a Frewitt SG Turbo Sieve equipped with a 1.0-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-line collecting drum at speed setting 5 (approximately 1030 rpm).
2. Pass microcrystalline cellulose (50%), croscarmellose sodium (50%), cornstarch (66%), and hydroxypropyl methylcellulose through the Turbosieve at the same settings as in step 2. Charge screened powders into a Lodige MGT-600 mixer, and mix for 5 minutes with the plow speed at approximately 103 rpm and no choppers.
3. Add water to the mixer over a 10-minute period, using a stainless steel transfer container with a valve, while mixing with the plows at about 103 rpm and the choppers at slow speed.
4. Mix the wet mass for another 15 minutes until a Wattmeter reading of 15 to 16 MkW is reached.
5. Dry the material. Preheat a Glatt fluid-bed dryer by running it for 2.5 minutes at 60°C inlet air temperature at 3500 m^3/h. Set the exhaust blower bypass speed at about 40%, the filter shaking interval for about 2 minutes and the filter shake duration of 5 seconds. Transfer the material in the dryer for drying. Decrease the inlet air to 2500 m^3/h and the inlet air temperature to 55°C after 30 minutes. Dry the material until an LOD of less than 0.5% is reached.
6. Pass the dried granulation through a FitzMill using a #20 mesh wire screen, with knives forward, at medium speed.
7. Pass the remaining microcrystalline cellulose and the colloidal silicon dioxide through a sieve equipped with a 1-mm round-hole screen, an angle bar, a cloth skirt, and a polyethylene-lined collecting drum.
8. Add magnesium stearate, and mix for 3 minutes.
9. Compress using a 13/32 ± round tooling.

Oxycodone Hydrochloride Tablets (5 mg)

Each tablet contains oxycodone hydrochloride, 5 mg. The tablets also contain microcrystalline cellulose and stearic acid. The oral solution contains alcohol, FD&C Red No. 40, flavoring, glycol, sorbitol, water, and other ingredients.

Oxytetracycline Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Oxytetracycline hydrochloride	250.00
230.00	2	Ludipress	230.00
6.00	3	Magnesium stearate	6.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with very low-compression force.
2. Compress into 495-mg tablets, using 12-mm biplanar punches.

Pancreatin and Cholic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
130.00	1	Pancreatin	130.00
2.00	2	Cholic acid	2.00
127.00	3	Avicel™ PH101	127.00
56.00	4	Lactose monohydrate	56.00
2.00	5	Magnesium stearate	2.00
3.00	6	Aerosil® 200	3.00

Manufacturing Directions

1. Mix the components, and press with high-compression force.
2. Compress into 324-mg tablets, using 9-mm biconvex punches.
3. Coat by enteric coating. (See Appendix.)

Pancreatin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
30.00	1	Pancreatin	30.00
308.00	2	Ludipress®	308.00
10.00	3	Kollidon® CL	10.00
2.00	4	Magnesium stearate	2.00

Manufacturing Directions

1. Mix the components, pass through an 0.8-mm sieve, and press with low-compression force.
2. Compress into 355-mg tablets, using 8-mm biconvex punches.
3. Coat by enteric coating. (See Appendix.)

Pancreatin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Pancreatin	300.00
290.00	2	Ludipress®	290.00
25.00	3	Kollidon® CL	25.00
3.00	4	Magnesium stearate	3.00

Manufacturing Directions

1. Mix the components, pass through an 0.8-mm sieve, and press to tablets with low-compression force.
2. Compress into 615-mg tablets, using 11-mm biconvex punches.
3. Coat by enteric coating. (See Appendix.)

Pantoprazole Tablets Protonix

Protonix is supplied as a delayed-release tablet for oral administration, available in two strengths. Each delayed-release tablet contains 45.1 or 22.6 mg of pantoprazole sodium sesquihydrate (equivalent to 40 or 20 mg of pantoprazole, respectively), with the following inactive ingredients: calcium stearate, crospovidone, hydroxypropyl methylcellulose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate.

Pantoprazole Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Pantoprazole	10.00
200.00	2	Calcium glycerophosphate	200.00
400.00	3	Sodium bicarbonate	400.00
12.00	4	Croscarmellose sodium	12.00
3.00	5	Pregelatinized starch	3.00

Pantoprazole Tablets (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Pantoprozole	10.00
175.00	2	Calcium glycerophosphate	175.00
175.00	3	Calcium lactate	175.00
250.00	4	Sodium bicarbonate	250.00
20.00	5	Polyethylene glycol 6000	20.00
12.00	6	Croscarmellose sodium	12.00
3.00	7	Peppermint flavor	3.00
1.00	8	Magnesium silicate	1.00
1.00	9	Magnesium stearate	1.00

Pantoprazole Tablets, Chewable (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Pantoprazole	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
250.00	4	Sodium bicarbonate	250.00
0.50	5	Aspartame calcium	0.50
12.00	6	Silicon dioxide colloidal	12.00
15.00	7	Starch (maize)	15.00
12.00	8	Croscarmellose sodium	12.00
10.00	9	Dextrose anhydrous	10.00
3.00	10	Peppermint flavor	3.00
3.00	11	Maltodextrin	3.00
3.00	12	Mannitol	3.00
3.00	13	Pregelatinized starch	3.00

Manufacturing Directions

1. Pass all ingredients through a 250-μm mesh, and blend in a suitable blender.
2. Compress into 672-mg tablets, using 15-mm biplanar punches. For 20-mg tablets, increase the quantity of item 1, and compress an additional 10 mg.

Pantoprazole Tablets, Rapid Dissolution (20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Pantoprazole	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
500.00	4	Sodium bicarbonate	500.00
50.00	5	Calcium hydroxide	50.00
12.00	6	Croscarmellose sodium	12.00

Papain Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.00	1	Papain	1.00
150.00	2	Lycasin	150.00
17.40	3	Hydrogenated vegetable oil	17.40
9.60	4	Water	9.60
5.8	5	Gelatin (40% solution)	5.8
17.4	6	Starch-coated dicalcium phosphate	17.4
1.60	7	Monodiglyceride mixture	1.60
0.60	8	Lecithin	0.60
0.10	9	Aspartame	0.10
0.10	10	Vanillin	0.10
0.20	11	Glycerin	0.20
0.20	12	Sodium bicarbonate	0.20
0.38	13	Mint flavor	0.38

Manufacturing Directions

1. Boil Isomalt, Lycasin, water, fat, mono- and diglyceride mixture, glycerin, and lecithin to 131°C.
2. Glycerin is added and the mixture is cooled to 60°C.
3. Thereafter sodium bicarbonate, papain, dicalcium phosphate, and the remaining ingredients are added.
4. Thereafter the mixture is cooled to room temperature and is ground into powder and compressed into a 205 mg tablet by using a tablet press.

Papaverine Hydrochloride Retard Tablet

Formulation: Cetyl alcohol, 10 g; hydroxyethyl cellulose, 5 g; papaverine hydrochloride, 75 g; talc, 10 g.

Manufacturing Directions

1. Melt cetyl alcohol in a jacketed vessel and incorporate papaverine hydrochloride, blend well, and granulate through a #16 standard mesh sieve. Dry at room temperature.
2. Hydrate the hydroxyethyl cellulose with 15 g of water.
3. Blend the granules obtained as a result of step 1 with the hydrated cellulose component of step 2 and mix well.
4. Granulate the whole through a #16 standard mesh sieve and dry.
5. Compress into tablets of suitable size and shape.

Para Amino Salicylic Acid Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Calcium para amino salicylic acid	500.00
280.00	2	Ludipress	280.00
35.00	3	Kollidon 35	35.00
–	4	Isopropyl alcohol	QS
5.00	5	Magnesium stearate	5.00
5.00	6	Talc	5.00

Manufacturing Directions

1. Granulate items 1 and 2 with a solution of items 3 and 4. Dry the granules, and lubricate with items 5 and 6.
2. Compress into 825-mg tablets, using 16-mm biplanar punches.

Paroxetine Hydrochloride Tablets (10 mg/20 mg/ 30 mg/40 mg) Paxil

1. Immediate-release tablets—Each film-coated Paxil® tablet contains paroxetine HCl equivalent to paroxetine as follows. *10 mg:* yellow; *20 mg:* pink (scored); 30 mg: blue; and *40 mg:* green. Inactive ingredients consist of dibasic calcium phosphate dihydrate, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycols, polysorbate80, sodium starch glycolate, titanium dioxide, and one or more of the following: D&C Red No. 30, D&C Yellow No. 10, FD&C Blue No. 2, and FD&C Yellow No. 6.
2. Controlled-release tablets—Each enteric, film-coated, bilayer, controlled-release Paxil tablet contains paroxetine HCl equivalent to paroxetine as follows: 12.5 mg and 25 mg. One layer of the tablet consists of a degradable barrier layer, and the other contains the active material in a hydrophilic matrix. The barrier layer is pale yellow and pink for the 12.5- and 25-mg strength tablets, respectively; the active layer is white. Inactive ingredients consist of hydroxypropyl methylcellulose, polyvinylpyrrolidone, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, glyceryl behenate, methacrylic acid copolymer type C, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, and one or more of the following colorants: yellow ferric oxide or red ferric oxide.

Paroxetine Hydrochloride Hemihydrate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Paroxetine hydrochloride hemihydrates	22.76
160.24	2	Dibasic calcium phosphate hemihydrates	160.24
8.00	3	Povidone anhydrous PVP K30	8.00
6.00	4	Sodium starch glycolate	6.00
3.00	5	Magnesium stearate	3.00
qs	6	Water	qs

Manufacturing Directions

1. Paroxetine hydrochloride hemihydrate, dibasic calcium phosphate anhydrous, sodium starch glycolate and povidone are premixed and granulated with water;
2. The granulate, after drying and milling through a 0.6-mm sieve, is mixed with dibasic calcium phosphate anhydrous and sodium starch glycolate in a dry state for 20 minutes. Then magnesium stearate is added, followed by mixing for a further 5 minutes;
3. Tablets are pressed (approximately 206 mg) from the resulting mixture, and coated with a coating suspension of Opadry containing the composition (%w/w) titanium dioxide, 31.250; hydroxypropyl methylcellulose, 29.875 (Methocel E3 Premium); Hydropropyl methylcellulose, 29.875 (Methocel E5 Premium); Polyethylene Glycol 400, 8.000; Polysorbate 80 (Tween), 1.000).

Paroxetine Hydrochloride Hemihydrate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
22.76	1	Paroxetine Hydrochloride 22.76	22.76
160.24	2	Hemihydrate Dibasic Calcium Phosphate Anhydrous	160.24
8.00	3	Anhydrous Povidone (PVP K-30)	8.00
6.00	4	Sodium starch Glycolate	6.00
3.00	5	Magnesium Stearate	3.00
QS	6	Purified water Q.S.	QS

Manufacturing Directions

1. Paroxetine hydrochloride hemihydrate, dibasic calcium phosphate anhydrous, sodium starch glycolate, and povidone are premixed and granulated with water;
2. The granulate, after drying and milling through a 0.6-mm sieve, is mixed with dibasic calcium phosphate anhydrous and sodium starch glycolate in a dry state for 20 minutes. Then magnesium stearate is added, followed by mixing for a further 5 minutes;
3. Tablets are pressed from the resulting mixture, and coated with a coating suspension of Opadry Coating Suspension (Opadry 6.0) Composition: (%w/w) titanium dioxide, 31.250%; hydroxypropyl methylcellulose, 29.875% (Methocel E3 Premium); hydropropyl methylcellulose, 29.875% (Methocel E5 Premium); polyethylene glycol 400, 8.000%; polysorbate 80 (Tween), 1.000%.
4. Tablet weight is for about 20 mg strength (approximately 206 mg).

Penicillin Chewable Tablets (125 mg)

Each tablet contains Penicillin V potassium equivalent to 250 mg (400,000 units) or 500 mg (800,000 units) Penicillin V. The tablets also contain lactose, magnesium stearate, povidone, starch, stearic acid, and other inactive ingredients.

Penicillin Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
277.16	1	Mannitol	277.16
53.00	2	Sugar	53.00
21.20	3	Sodium cyclamate	21.20
2.30	4	Saccharin sodium	2.30
125.00	5	Penicillin, use benzathine Penicillin V, 3% excess	172.83
–	6	Water, purified, ca	96.00 mL
5.50	7	Raspberry flavor	5.50
4.40	8	Polarcillin potassium (Amberlite IRP-88)	4.40
11.60	9	Talc	11.60
35.00	10	Magnesium stearate	35.00

Note: Adjust the weight of penicillin for potency, and alter the weight of mannitol to compensate. The weight of sodium citrate is 450 minus the weight of penicillin.

Manufacturing Directions

Note: Allergic reactions sometimes occur with penicillin. Avoid contact as much as possible, and use equipment dedicated to penicillin or cephalosporin products. The LOD limits are low, so use an air-conditioned area.

1. Granulation
   a. Mill mannitol, sugar, sodium cyclamate, and sodium saccharin through a 2.38-mm aperture screen using a suitable comminuting mill, with knives forward, at medium speed.
   b. Add the milled materials from step 1 to the mixer, and then add the penicillin. Mix for 10 minutes. Add the water slowly, cleaning the sides of the mixer as necessary. Mix for 10 minutes after the water is added. The final mass should have a sandy appearance.
   c. Transfer the wet granulation to the bowl of a fluid-bed dryer through a 6.7-mm aperture screen. Dry at 30°C for 20 minutes. Stir, then pass the granulation by hand through a 5.5-mm aperture screen. After that, transfer the granulation to the bowl of the fluid-bed dryer.
   d. Continue drying at 60°C, turning over after each 30 minutes, until the LOD is no more than 0.8% (drying time is approximately 60 minutes).
   e. Screen the dried granules through an 840-μm aperture screen on a suitable sieve shaker, and pass the coarse material through a 1.6-mm aperture screen on a comminuting mill, at low speed, with knives forward.
   f. Screen the flavor, polarcillin potassium, magnesium stearate, and talc through a 595-μm screen on a sieve shaker. Charge the screened powders into a suitable blender.
   g. Charge the screened and milled granules from step 5 into the blender, and blend for 30 minutes.
   h. Discharge the granulation into tared polyethylene-lined drums, and seal the bags. Weigh them for yield.
   i. Compress on 9.53-mm square punches. Note the weight according to the adjustments made (hardness: 10–12 kPa diagonally, 15–21 kPa flat).

Peptide Sublingual Tablets

Formulation: The individual component peptides each have a molecular weight of less than 20000 daltons. Thymosin fraction, 5%; water, 5.0%; sucrose/lactose, 69.5%; propylene glycol, 0.5%; silicon dioxide, 15.0%; methyl nicotinate, 0.5%.

Manufacturing Directions

The wetted mixture is formed into tablets of a desired weight and the tablets are then dried at 30°C for 36 hours.

Perfloxacin Tablets (400 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Perfloxacin, use perfloxacin mesylate	592.00
63.00	2	Lactose monohydrate	63.00
42.00	3	Dicalcium phosphate	42.00
52.00	4	Starch (maize)	52.00
22.00	5	Starch (maize)	22.00
1.00	6	Gelatin	1.00
15.60	7	Sodium starch glycolate	15.60
10.00	8	Talc	10.00
5.00	9	Magnesium stearate	5.00
3.00	10	Sodium starch glycolate	3.00
10.00	11	Starch (maize)	10.00
–	12	Water, purified	QS

Manufacturing Directions

1. Sift items 1 to 4 through a 250-μm sieve, and charge into a suitable vessel; mix it for 10 minutes.
2. In a separate vessel, charge items 5 to 7, and add hot item 12 to make a 30% starch paste.
3. Add the paste in step 2 to step 1, and form a wet mass suitable for granulating.
4. Pass the wet mass through a #8 sieve, and spread it on paper-lined trays.
5. Dry the granules at 50°C overnight until an LOD of not more than 3% is reached.
6. Pass the dried granules through a 1.19-mm sieve screen into a blending vessel.
7. Sift items 8 to 11 through a 250-μm sieve, and add to step 6. Blend for 2 minutes.
8. Compress into 815-mg tablets, using an 18.8 × 8.8-mm punch.
9. Coat the material with an HPMC methylene chloride coating. (See Appendix.)

Phenindione Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Phenindione	50.00
165.00	2	Ludipress®	165.00
2.00	3	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press with low-compression force.
2. Compress into 230-mg tablets, using 8-mm biplanar punches.

Phenindione Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Phenindione	50.00
165.00	2	Ludipress	165.00
2.00	3	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress into 230-mg tablets, using 8-mm biplanar punches.

Phendimetrazin Tablets (35 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
35.00	1	Phendimetrazin	35.00
281.00	2	Ludipress	281.00
281.00	3	Starch (maize)	281.00
3.00	4	Magnesium stearate	3.00
3.00	5	Aerosil 200	3.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium-compression force.
2. Compress into 604-mg tablets, using 12-mm biplanar punches. The amount of Ludipress and cornstarch may be reduced to obtain better disintegration times.

Phenoxymethyl Penicillin Potassium Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
58.10	1	Sodium citrate powder	68.10
250.00	2	Penicillin V acid, use phenoxymethyl potassium[a]	277.20
29.50	3	Povidone K 29–32	29.40
–	4	Alcohol SD 3A 200 proof, ca	100 mL
16.00	5	Starch (maize)	16.00
16.00	6	Talc	16.00
6.10	7	Magnesium stearate	6.10

[a]Adjust the quantity based on the factored potency and adjusted by sodium citrate. Starch must be dried. The amount of sodium citrate is 345.30-weight of item 2.

Manufacturing Directions

Note: Allergic reactions sometimes occur with penicillin. Avoid contact as much as possible, and use equipment dedicated to penicillin or cephalosporin products. The LOD limits are low, so use an air-conditioned area.

1. Granulation
   Note: Dried cornstarch must be used for lubrication. Dry the starch at 80°C for 36 hours prior to its use in manufacturing. Check the LOD of starch. The LOD must be less than 2%.
   a. Mill separately the sodium citrate through a 595-μm aperture screen using a suitable comminuting mill, at medium speed, with impact forward, and the penicillin through a 595-μm aperture screen with knives forward, at high speed. In a suitable mixer, mix them for 5 minutes.
   b. Dissolve Povidone in 100 mL of alcohol in a dry stainless steel bucket.
   c. Add PVP-alcohol slowly to the mixer, and mix for 30 minutes or until balls form in the sandy mixture. Add and record extra alcohol if required.
   d. Pass the mass through a 9.52-mm aperture screen, place into a fluid-bed dryer bowl, and dry at 50°C for 1 hour. Turn over as necessary. The LOD should not be more than 0.7%.
   e. Mill the granules through a 1.59-mm aperture screen using a suitable comminuting mill, with knives forward, at medium speed. Put the granules into tared polyethylene-lined drums, then seal, and weigh.
2. Lubrication
   a. Transfer the dried granulation to a suitable blender.
   b. Screen the dried starch and talcum through a 595-μm aperture screen on a sieve shaker, and add to the blender. Blend this mixture for 30 minutes.
   c. Screen the magnesium stearate through a 595-μm aperture screen on a sieve shaker, and add it to the blender. Blend this for 30 minutes.
   d. Discharge the granules into polyethylene-lined drums. Then, seal and weigh for yield.
3. Compression
   a. Compress using 10.32-mm round, standard concave punches.
   b. Compress to calculated weight after adjustments, with a variation not more than 3%; thickness between 4.4 and 4.6 mm (range not more than ±5%); hardness between 10 and 14 kPa, and disintegration time no more than 15 minutes in water.
4. Coating: Coat by a methocel subcoat, color coat, and polishing coat. (See Appendix.)

Phenolphthalein Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Phenolphthalein	200.00
150.00	2	Dibasic calcium phosphate	150.00
11.00	3	Kollidon® 30	11.00
–	4	Isopropanol or ethanol (96%)	QS
19.00	5	Kollidon® CL	19.00
3.00	6	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 3 and 4, mix with items 5 and 6, pass through an 0.8-mm sieve, and press with low-compression force.
2. Compress into 385-mg tablets, using 9-mm biconvex punches.

Phenolphthalein Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
90.00	1	Yellow phenolphthalein	90.00
64.80	2	Microcrystalline cellulose	64.80
187.20	3	Dicalcium phosphate	187.20
3.60	4	Croscarmellose sodium	3.60
3.60	5	Fumed silica	3.60
7.20	6	Stearic acid	7.20
3.60	7	Magnesium stearate	3.60

Manufacturing Directions

1. Screen items 6 and 7 through a 40-mesh sieve.
2. Blend items 1 and 5 in a V-blender for 3 minutes.
3. Add items 2 and 4 to the blender, and mix for 5 minutes.
4. Add item 3 to the blender, and mix for 12 minutes.
5. Add item 6 and blend for 3 minutes.
6. Add item 7 and mix for another 5 minutes.
7. Compress using 3/8- in., flat, bevel-edged punches to hardness of 10 kPa; average tablet weight is 360 mg.

Phenylpropanolamine and Bromopheniramine Fast-Dissolving Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
6.25	1	Phenylpropanomaine hydrochloride	6.25
1.00	2	Brompheniramine maleate	1.00
6.00	3	Citric acid	6.00
1.80	4	Magnasweet 135	1.80
4.50	5	Aspartame	4.50
3.60	6	Cherry flavor	3.60
21.00	7	Croscarmellose sodium	21.00
3.00	8	Lecitihin	3.00
30.00	9	Cornstarch	30.00
3.00	10	Silicon dioxide	3.00
2.10	11	Magnesium stearate	2.10
219.25	12	Fast-dissolving granulation (see below)	219.25

Manufacturing Directions

1. Fast-dissolving granulation is made by combining 400 g of melted PEG 900 with fructose powder (100 g) in a planetary mixer (low-shear mixer) and mixing until the granules formed.
2. The granulations are allowed to cool, and are then screened.
3. All ingredients are mixed in a V-blender.
4. Tablets are compressed (301.5 mg) at approximately 3 kN.
5. Tablet hardness is 0.2 to 0.5 kPa and disintegration time 10 seconds.

Phenylpropanolamine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Phenylpropanolamine hydrochloride, USP	60.00
180.00	2	Calcium sulfate dihydrate	180.00
—	3	Starch paste10%	QS
12.00	4	Starch 1500 (StarX)	12.00
6.00	5	Magnesium stearate	6.00

Manufacturing Directions

1. Add starch in 1:10 ratio to cold water, heat to boil with constant stirring until a thick, translucent white paste is formed.
2. Keep it for use in granulation below.
3. Mix the phenylpropanolamine hydrochloride with the calcium sulfate in a Sigma blade mixer for 15 minutes.
4. Add starch paste in sufficient quantity to form a suitable wet mass of desirable consistency.
5. Allow to mix for 30 minutes.
6. Pass the wet mass through a #14 screen and distribute on drying trays.
7. Dry in a forced-air oven at 49°C to 54°C or in a fluid-bed dryer.
8. Pass the dried granules through a #18 mesh screen.
9. Transfer granules to a twin-sell blender, add items 4 and 5, and blend for 6 to 8 minutes.
10. Compress the granulation in a rotary press using 3/8- in. standard punches. Tablet weight is 260 mg.

Phenylpropanolamine Hydrochloride Tablets (60 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Phenylpropanolamine hydrochloride	60.00
180.00	2	Calcium sulfate dihydrate	180.00
QS	3	Starch paste (10%)	QS
12.00	4	Starch 1500 (StaRx)	12.00
6.00	5	Magnesium stearate	6.00

Manufacturing Directions

1. Starch paste: Add starch with a 1:10 ratio to cold water. Heat to a boil, with constant stirring, until a thick, translucent white paste is formed. Keep it for use in step 2.
2. Granulation
   a. Mix the phenylpropanolamine hydrochloride with the calcium sulfate in a sigma blade mixer for 15 minutes.
   b. Add starch paste from step 1 in sufficient quantity to form a wet mass suitable of desirable consistency.
   c. Allow to mix for 30 minutes.
   d. Pass the wet mass through a #14 screen and distribute on drying trays.
   e. Dry in a forced-air oven at 120°F to 130°F or in a fluid-bed dryer.
   f. Pass the dried granules through a #18 mesh screen.
3. Lubrication
   a. Transfer granules to a twin-sell blender, add Starch 1500 and magnesium stearate, and blend for 6 to 8 minutes.
4. Compression: Compress the granulation in a rotary press using 9.5-mm standard punches. The tablet weight should be 260 mg.

Phenylbutazone Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Phenylbutazone	100.00
3.33	2	Lactose monohydrate	3.33
3.33	3	Mannitol	3.33
162.00	4	Starch (maize)	162.00
10.00	5	Starch (maize)	10.00
0.66	6	Polyvinylpyrrolidone potassium 30	0.66
0.28	7	Propyl paraben	0.28
0.28	8	Methyl paraben	0.28
5.00	9	Talc	5.00
3.00	10	Magnesium stearate	3.00
7.00	11	Sodium starch glycolate	7.00
–	12	Water, purified	QS

Manufacturing Directions

1. Sift items 1 to 4 through #40 mesh into a suitable mixing vessel. Mix for 10 minutes.
2. In a separate vessel, heat item 12 to boiling and add and dissolve items 7 and 8. Allow this blend to cool to 60°C, then add item 6, and dissolve. Finally, add item 5, and stir well to make a smooth paste of 30% starch.
3. Add the starch paste from step 2 into step 1, and mix to form a suitable wet mass.
4. Pass the wet mass in step 3 through #18 mesh onto trays. Then, dry at 60°C overnight to an LOD of not more than 2.8%. Transfer to a blending vessel.
5. Sift items 9 to 11 through a 250-μm sieve. Add to step 4, and blend for 1 minute.
6. Compress into 280-mg tablets, using a 5-mm punch.
7. Coat the tablets with a sealing coat and a color coat (HPMC). (See Appendix.)

Phenytoin Sodium Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Phenytoin sodium	100.00
235.00	2	Ludipress	235.00
10.00	3	Magnesium stearate	10.00
8.00	4	Kollidon CL	8.00
5.00	5	Aerosil 200	5.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress into 346-mg tablets, using 12-mm biplanar punches.

Phenytoin Sodium Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Phenytoin sodium	100.00
50.00	2	Dicalcium phosphate	50.00
45.00	3	Sucrose crystalline	45.00
10.00	4	Kollidon 25	10.00
–	5	Isopropyl alcohol + ethanol (1:1)	30.00
5.00	6	Kollidon CL	5.00
2.00	7	Magnesium stearate	2.00

Manufacturing Directions

1. Granulate the mixture of items 1 to 3 with a solution of items 4 and 5; dry. Pass through a 0.8-mm sieve, mix with items 6 and 7, and press with high-compression force.
2. Compress into 209-mg tablets, using 8-mm biplanar punches.

Phenytoin Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Phenytoin base	100.00
235.00	2	Ludipress	235.00
2.00	3	Magnesium stearate	2.00
2.00	4	Stearic acid	2.00
8.00	5	Kollidon CL	8.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress into 351-mg tablets, using 12-mm biplanar punches.

Pioglitazone Hydrochloride Tablets (15 mg/30 mg/ 45 mg) Actos

Actos is available as a tablet for oral administration containing 15, 30, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropyl cellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.

Pipemidic Acid Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Pipemidic acid, use pipemidic acid trihydrate	236.00
16.00	2	Calcium carboxymethyl cellulose	16.00
4.00	3	Hydroxypropyl cellulose	4.00
8.00	4	Cellulose microcrystalline	8.00
2.40	5	Silicon dioxide colloidal	2.40
5.60	6	Magnesium stearate	5.60
QS	7	Water, purified, ca	80.00 mL

Manufacturing Directions

Caution: Wear a mask and gloves during all operations.

1. Granulation
   a. Pass pipemidic acid (item 1) and calcium carboxymethyl cellulose (item 2) through a 24-mesh (0.6-mm) screen attached to an oscillating granulator. Charge into a planetary mixer, and blend for 10 minutes.
   b. Dissolve the hydroxypropyl cellulose (item 3) in 80 mL of water, using continuous mechanical stirring.
   c. Add the binder solution to the mixed powder from step 1, and blend for 10 minutes to form a suitable mass. More water should be added, if necessary, to complete granulation and densification.
   d. The granules should then be screened through an 8-mesh (2-mm) screen.
   e. Spread the moist granules on trays, and dry at 50°C (122°F) for 16 hours or until moisture level is within the range of 11% to 16%.
2. Lubrication
   a. Using an oscillating granulator, pass the dried granules through a 12-mesh (1.4-mm) screen.
   b. Pass the cellulose microcrystalline (item 4), maize starch (item 5), silicon dioxide colloidal (item 6), and magnesium stearate (item 7) through a 12-mesh (1.4 mm) screen.
   c. Charge the items from step 2b into planetary blender. Add half of the dried granule from step 2a and blend for 5 minutes. Then add the remainder of the dried granule, and blend for an additional 15 minutes at a nominal speed of 30 rpm.
   d. Load the lubricated granule into tared, polyethylene-lined drums, and weigh for yield.
3. Compression: Compress on a suitable machine using ovaloid tooling, 12.5 mm × 6.5 mm; the compression weight is 280 mg. For 400-mg strength, 9.1 × 15.5-mm punches and 560-mg weight.
4. Coating: Coat using a methocel/ethocel coating. (See Appendix.)

Pipobroman Tablets (25 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Pipobroman	25.00
100.00	2	Lactose monohydrate powder	100.00
5.00	3	Povidone K 29–32	5.00
QS	4	Water, purified, ca	12 mL
2.00	5	Starch (corn)	2.00
1.10	6	Magnesium stearate	1.10

Manufacturing Directions

1. Granulation
   a. Pass pipobroman, lactose, and povidone through an 840-μm aperture screen using a FitzMill or something similar, with impact forward and high speed.
   b. Charge milled granulation into a mixer. Mix for approximately 5 minutes, and then add 12 mL of purified water to the mass. Pass granulation through a FitzMill or a similar method using a no. 5 (12.7-mm) band, with knives forward and at slow speed.
   c. Pass granulation thinly on paper-lined trays, set the oven at 50°C, and dry overnight, or until the LOD is less than 2% (1 hour Brabender at 105°C).
   d. Sift dried granulation through an 840-μm aperture screen and FitzMill the coarse granules through a 1-mm aperture screen, with knives forward, at a slow speed.
2. Lubrication
   a. Charge one-half of the base granulation into a Glen mixer or a similar mixing method.
   b. Mix cornstarch and magnesium stearate. Screen this mixture through a 595-μm aperture screen into a mixer.
   c. Charge the remaining granulation into the mixer. Blend for approximately 5 minutes.
   d. Discharge into polyethylene-lined drums. The theoretical lubricated weight is 133.1 g.
3. Compression: Compress using 9/32-in. standard concave punches, with a compression weight of 133 mg.

Piroxicam Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.40	1	Piroxicam	150.40
6.70	2	Sodium dodecyl sulfate	6.70
18.00	3	Sodium starch glycolate	18.00
44.90	4	Hydroxypropyl methyl cellulose	44.90
228.00	5	Cellulose lactose	228.00

Manufacturing Directions

1. Compress tablet.
2. Coat with co-polymer of the methacrylic acid triethylcitrate (150 mg) and simethicone 30% emulsion (15 mg).

Piroxicam Water-Dispersible Tablets (20 mg)

Formulation: Piroxicam, 20 g; cornstarch, 150 g; Ludipress, 50 g; Kollidon CL, 8 g; polyethylene glycol 6000 powder, 10 g; Aerosil 200, 1 to 2 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press with low- to medium-compression force at 238 mg.

Placebo Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
299.70	1	Ludipress®	299.70
0.30	2	Magnesium stearate	0.30

Manufacturing Directions

1. Mix the components, sieve, and press.
2. For this formulation, compress 300 mg.
3. The compression force determines hardness and friability.
4. At 7 kN, the hardness is 45 N; at 22 kN, the hardness is 160 N.
5. The disintegration time increases from 1 to 4 minutes.

Placebo Tablets

Formulation: Ludipress, 99.9%; magnesium stearate, 0.1%.

Manufacturing Directions

1. Mix the components, sieve, and press.
2. Tablet weight is 300 mg.

Plaroxetine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Paroxetine, use paroxetine hydrochloride hemihydrate	22.67
83.34	2	Dicalcium phosphate (Ditab)	83.84
50.67	3	Microcrystalline cellulose (Avicel PH 102)	50.67
8.34	4	Sodium starch glycolate (Explotab)	8.34
1.67	5	Magnesium stearate	1.67

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
30.00	1	Paroxetine, use paroxetine hydrochloride hemihydrate	34.00
125.00	2	Dicalcium phosphate (Ditab)	125.00
76.00	3	Microcrystalline cellulose (Avicel PH 102)	76.00
12.50	4	Sodium starch glycolate (Explotab)	12.50
2.50	5	Magnesium stearate	2.50

Manufacturing Directions

1. Pass item 2 through a screen, and weigh it into a planetary mixer.
2. Add 30-mesh paroxetine to the bowl.
3. Add 20-mesh Avicel and Explotab, and mix all the powders for 10 minutes.
4. Add magnesium stearate, and mix for 5 minutes.
5. Compress into pentagonal tablets using 9.5-mm punches for 30-mg tablets and 8.25 mg for 20-mg tablets. Compress 250 and 166.7 mg, respectively.

Potassium Bicarbonate-Coated Tablet

Manufacturing Directions

1. Preparation of potassium bicarbonate crystals: US Patent 5445805 describes how to prepare crystals of size within the range of 800 to 900 μm, a B.E.T. surface area of 0.004 to 0.01 m^2/g and particle distributions such that over 90% by weight of the crystals are within the range of 700 to 1000 μm. (At least 90% of the crystals are retained on a 25-mesh screen [707 μm] and less than 10% are retained on an 18-mesh screen [1000 μm]).
2. Preparation and application of controlled release coating lacquers—Coating lacquer composition: CUTINA HR, 23.45 g; ETHOCEL, 163.45 g; acetyl tributyl citrate, 8.75 g; isopropyl alcohol, 3304.35 g. Total = 3500.00 g.
3. Coating conditions: process air flow = 100 to 171 m^3/h; spray period = 135 minutes; spray temperature = 60.1°C to 68.1°C; spray pressure = 2.0 bars; liquid flow rate = 26 to 28 g/min; product temperature = 46°C to 52°C. Coated crystals: theoretical yield = 3191.1 g; actual yield around 98% giving w/w dry matter of 6.37% (coated/uncoated crystals).
4. Hydrogenated castor oil (CUTINA HR), ethylcellulose (ETHOCEL Standard 100 premium), and acetyl tributyl citrate are dissolved in isopropyl alcohol to provide the controlled release coating lacquers.
5. CUTINA HR, ETHOCEL, and acetyl tributyl citrate are dissolved in the isopropyl alcohol solvent by heating in a mixer equipped with a heating jacket set at 60°C to 70°C with vigorous agitation. The agitation is continued for about 1 hour. When dissolved, the mixture is clear to translucent.
6. The coating lacquer composition is maintained at temperatures of 60°C to 70°C.
7. The lacquers are coated on the potassium bicarbonate particles by co-current flow through a fluidized bed in which the moisture content is controlled. The coating lacquer is sprayed from a spray nozzle positioned at the bottom of a GLATT fluidized bed apparatus equipped with a Wurster tube.
8. The potassium bicarbonate crystals are fluidized and the warm coating lacquer is sprayed on the crystals in multiple coating cycles.
9. The process air flow rate is adjusted as necessary to provide adequate movement of the crystals through the fluidized bed as they are coated. During the coating process, the isopropyl alcohol solvent is flash-evaporated from the crystals as they cycled through the fluidized bed.
10. After completing the application of the coating lacquer to the crystals, any trace residual solvent remaining on the coated crystals is removed by cycling in the fluidized bed without lacquer spray for 10 minutes.
11. Following the residual solvent removal, the coated crystals are cooled in the bed.
12. The amount of coating lacquer applied on the crystals is calculated as the % w/w of the dry matter of the respective coatings, relative to the uncoated potassium bicarbonate crystals.
13. Compression: potassium 85.00% bicarbonate coated crystals, CUTINA HR 1.50%; AVICEL PH 7.68%, cornstarch 5.12%, SYLOID 0.40%, LUBRITAB 0.30%. Compress tablets of 1500 mg of potassium bicarbonate.

Potassium Chloride Retard Tablet

Formulation: Cetyl alcohol, 14.00 g; potassium chloride, 82.00 g; hydroxy ethyl cellulose, 4.50 g; talc, 1.50 g.

Manufacturing Directions

1. To 10 g of water at 50°C, contained in a suitable vessel, fitted with a stirrer, add the hydroxy ethyl cellulose. Blend until a uniformly hydrated granular mass is formed.
2. Add to the hydrated cellulose granules, with constant stirring, the potassium chloride. Continue mixing until a free-flowing uniform granule blend is obtained.
3. Dry the cellulose-potassium chloride granules for 30 minutes at 50°C. Granulate the dried granules through a No. 16 stainless steel standard mesh screen.
4. Melt the cetyl alcohol in a water jacketed tank fitted with an efficient stirrer. Hold the melt at 50°C to 60°C and incorporate the granules from step 3. Continue stirring until a free-flowing granular mass is obtained. Allow the mass to cool and granulate through a No. 16 standard mesh stainless steel screen.
5. Lubricate the granules with talc and compress into cores. Core Compression Data: Core weight, 750.0 mg; punch size, 7/16th in. deep concave
6. The cores are then pan-coated using normal coating techniques.

Potassium Chloride Tablets (30 mg), Klor

Potassium chloride extended-release capsules, USP, are a solid oral dosage form of potassium chloride containing 10 mEq (750 mg) of potassium chloride (equivalent to 10 mEq [390 mg] of potassium and 10 mEq [360 mg] of chloride) in a microencapsulated capsule. This formulation is intended to release potassium so that the likelihood of a high localized concentration of potassium chloride within the gastrointestinal tract is reduced. The inactive ingredients are calcium stearate, gelatin, pharmaceutical glaze, povidone, sugar spheres, and talc.

Klor-Con extended-release tablets, USP, are a solid oral dosage form of potassium chloride. Each contains 600 or 750 mg of potassium chloride equivalent to 8 or 10 mEq of potassium in a wax matrix tablet.

Potassium Chloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
30.00	1	Potassium chloride	30.00
150.00	2	Gelatin powder	150.00
2.00	3	Croscarmellose sodium	2.00
5.00	4	Talc	5.00
3.00	5	Magnesium stearate	3.00

Manufacturing Directions

1. Accurately weigh potassium chloride, gelatin, croscarmellose sodium, talc, and magnesium stearate.
2. Add potassium chloride, gelatin, and croscarmellose sodium, one item at a time, in a suitable blender, and mix for 15 minutes. Add talc and magnesium stearate, and mix for an additional 5 minutes.
3. Compress into 200-mg tablets, using 6-mm punches.

Povidone–Iodine Effervescent Vaginal Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
350.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06, with excess	360.00
1450.00	2	Ludipress®	1450.00
360.00	3	Tartaric acid	360.00
265.00	4	Sodium bicarbonate	265.00
19.00	5	Talc	19.00
2.00	6	Calcium arachinate	2.00
2.00	7	Aerosil® 200	2.00

Manufacturing Directions

1. Dry the mixture of items 2 to 4 for 4 hours at 60°C, mix with item 1 and items 5 to 7, and press to tablets.
2. Compress into 2.5-g tablet, using 20-mm biplanar punches.
3. The tablet is dissolved in water to obtain a vaginal douche solution.

Povidone–Iodine Lozenges

Bill of Materials			
Scale (mg/Lozenge)	Item	Material Name	Quantity/1000 Lozenges (g)
5.00	1	Polyvinylpyrrolidone (PVP)–iodine 30/06	5.00
150.00	2	Sorbitol (crystallized)	150.00
4.00–5.00	3	Menthol (crystalline)	4.00–5.00
4.00–5.00	4	Eucalyptol (crystalline)	4.00–5.00
1.00	5	Aspartame, potassium	1.00
0.10	6	Saccharine sodium	0.10
1.00	7	Aerosil® 200	1.00
1.00	8	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press with medium-compression force.
2. Compress into 176-mg tablets, using 8-mm biplanar punches.

Pravastatin Sodium Tablets (10–40 mg), Pravachol

Pravachol is available for oral administration as 10-, 20-, and 40-mg tablets. Inactive ingredients include croscarmellose sodium, lactose, magnesium oxide, magnesium stearate, microcrystalline cellulose, and povidone. The 10-mg tablet also contains red ferric oxide; the 20-mg tablet also contains yellow ferric oxide; and the 40-mg tablet also contains green lake blend (mixture of D&C Yellow No. 10 Aluminum Lake and FD&C Blue No. 1 Aluminum Lake).

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Pravastatin sodium	10.00
12.00	2	Crospovidone	12.00
77.00	3	Lactose, spray dried	77.00
1.00	4	Magnesium stearate	1.00

Manufacturing Directions

1. Charge pravastatin sodium and polyplasdone in a blender after passing through a 250-μm sieve.
2. Add item 3, and mix for 20 minutes at moderate speed.
3. Add item 4, and blend for 5 minutes at low speed.
4. Compress in a suitable punch, 100 mg for 10-mg strength, and proportionally for strengths up to 40 mg.

Pravastatin Tablets

Formulation: Pravastatin, 6.7%; lactose, 67%; microcrystalline cellulose, 20%; croscarmellose sodium, 2%; magnesium stearate, 1%; magnesium oxide, 3.3%.

Manufacturing Directions

1. Pravastatin, magnesium oxide, and a fraction (30%) of lactose are mixed together for 2 to 10 minutes employing a suitable mixer. The resulting mixture is passed through a #12 to #40 mesh size screen.
2. Microcrystalline cellulose, croscarmellose sodium, and the remaining lactose are added and the mixture is mixed for 2 to 10 minutes. Thereafter, magnesium stearate is added and mixing is continued for 1 to 3 minutes.
3. The resulting homogeneous mixture is then compressed into tablets each containing 5, 10, 20, or 40 mg of pravastatin. A dispersion of the tablets in water had a pH of about 10.

Prazosin Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Prazosin hydrochloride, anhydrous[a]	5.00
94.00	2	Ludipress	94.00
1.00	3	Magnesium stearate	1.00

[a]If using polyhydrate, increase the amount to 6.00, and adjust with item 2.

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with high-compression force.
2. Compress into 109-mg tablets, using 8-mm biplanar punches.

Prednisolone Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Prednisolone	5.00
60.00	2	Lactose monohydrate	60.00
32.50	3	Starch (maize)	32.50
6.00	4	Starch (maize)	6.00
4.00	5	Starch (maize, dried)[a]	4.00
2.00	6	Talc (fine powder)	2.00
0.50	7	Magnesium stearate	0.50
–	8	Purified water	18.00

LOD: not more than 4.5% when dried at 120°C for 4 hours.

Manufacturing Directions

Precautions: The binding solution contains maize starch, and, therefore, it is possible to have microbiological growth. Thus, prepare the solution directly before the granulation process. Prednisolone is a potent corticosteroid, and, therefore, use a mask, gloves, and goggles during the whole process.

1. Preparation of binding solution
   a. Prepare an homogeneous slurry of item 4 using 8 g of item 8 (25–30°C). Check that it is free of lumps.
   b. Charge this slurry into 10 g of item 8 heated to 90°C in the vessel (Giusti). Stir until there is complete gelatinization.
   c. Check the weight. The theoretical weight is 24 g.
   d. Leave the starch paste to cool to 40°C to 50°C.
   Note: Compensate any loss of weight due to vaporization by adding item 8.
2. Dry mixing: Pass items 1 to 3 through a 630-μm sieve using a sifter. Load this powder to the mixer, and mix for 15 minutes at high speed.
3. Wet massing: Add starch paste cooled to 40°C to 50°C from step 1d. Mix for 10 minutes at high speed. Add purified water if required.
4. Pass the wet granules through sieve 24205 using the FitzMill.
5. Drying: Spread the wet granules onto the trays. Load the trolleys to the dryer. Dry the granules at 60°C for 14 hours.
6. Grinding: Pass the dried granules through a 1-mm sieve using a granulator.
7. Lubrication
   a. Pass items 5 and 6 through a 250-μm sieve using a sifter. Collect the material in a stainless steel drum.
   b. Load the sieved material from step 6 into the blender.
   c. Load the sieved lubricant powders from step 7a into the blender.
   d. Blend the powders for 5 minutes.
8. Blending
   a. Pass item 7 through a 250-μm sieve using a sifter. Load the sieved powder into the blender. Mix the powder for 1 minute.
   b. Unload the lubricated granules in stainless steel drums.
9. Check and record the weight of the granules.
10. Compression: Compress 110 mg of the granules using a rotary tabletting machine in 7.1-mm punches.

Prednisolone Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Prednisolone, use as prednisolone micronized	10.50
49.50	2	Microcrystalline cellulose (Avicel PH 102)	49.50
7.50	3	Sodium starch glycolate (Primojel)	7.50
105.00	4	Lactose (spray dried)	105.00
25.00	5	Starch (maize), dried	25.00
1.00	6	Colloidal silicon dioxide (Aerosil 200)	1.00
1.50	7	Magnesium stearate	1.50

Manufacturing Directions

See the manufacturing directions for the 5-mg strength tablet.

Prednisolone Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Prednisolone micronized	21.00
60.00	2	Microcrystalline cellulose (Avicel PH 102)	60.00
9.00	3	Sodium starch glycolate (Primojel)	9.00
127.00	4	Lactose (spray dried)	127.00
30.00	5	Starch (maize, dried)	30.00
1.00	6	Colloidal silicon dioxide (Aerosil 200)	1.00
2.00	7	Magnesium stearate	2.00

Manufacturing Directions

See the manufacturing directions for the 5-mg strength tablet.

Prednisolone Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Prednisolone	20.00
155.00	2	Lactose monohydrate	155.00
10.00	3	Kollidon VA 64	10.00
8.00	4	Kollidon CL	8.00
5.00	5	Magnesium stearate	5.00
2.00	6	Aerosil 200	2.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress into 212-mg tablets, using 8-mm biplanar punches.

Prednisone Tablets (10 mg)

Deltasone tablets contain prednisone, which is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, that are readily absorbed from the gastrointestinal tract. Prednisone is a white to practically white, odorless, crystalline powder. It is very slightly soluble in water and slightly soluble in alcohol, in chloroform, in dioxane, and in methanol. The chemical name for prednisone is pregna-1,4-diene-3,11,20-trione,17,21-dihydroxy-. Its molecular weight is 358.43.

Deltasone tablets are available in five strengths: 2.5, 5, 10, 20, and 50 mg. The inactive ingredients are as follows. *2.5 mg:* calcium stearate, cornstarch, erythrosine sodium, lactose, mineral oil, sorbic acid, and sucrose; *5 mg:* calcium stearate, cornstarch, lactose, mineral oil, sorbic acid, and sucrose; *10 mg:* calcium stearate, cornstarch, lactose, sorbic acid, and sucrose; *20 mg:* calcium stearate, cornstarch, FD&C Yellow No. 6, lactose, sorbic acid, and sucrose; *50 mg:* cornstarch, lactose, magnesium stearate, sorbic acid, sucrose, and talc.

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Prednisone	10.00
208.00	2	Ludipress	208.00
2.00	3	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all components, pass through a sieve, and press with low-compression force.
2. Compress into 223-mg tablets, using 8-mm biplanar punches.

Pregabaline-Coated Granule Fast-Crumbling Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Pregabaline	150.00
6.43	2	Corpovidone potassium	6.43
7.50	3	Acesulfam	7.50
4.28	4	Precipitated silicat	4.28
39.64	5	Ethylcellulose AGM	39.64
6.43	6	Crospovidone	6.43

Manufacturing Directions

1. A suspension is obtained by mixing ethylcellulose, 80% precipitated silica, and 50% acesulfamin ethyl alcohol, until a homogeneous suspension is obtained.
2. The powder mixture consisting of pregabaline, item 6, 70% aspartame, and 20% precipitated silica is then fluidized.
3. The granulation is then started by spraying the mixture for about 15 to 20 minutes at a spraying rate of 25 g/min and a suspension atomization pressure of 0.8 bar.
4. The actual coating is then performed by spraying the remainder of the mixture over about 1 hour 30 minutes at a spraying rate of 15 to 20 g/min and a suspension atomization pressure of 1.5 bar.
5. 15% of the mixture is sprayed during the granulation step, the remainder to 100% being sprayed during the coating step.
6. The granules obtained are then formulated as fast-crumbling multiparticulate tablets, the composition of which is as follows: Coated granules (150 mg), Mannitol (474 mg), Cropovidone (80 mg), aspartame (14 mg), flavoring (8 mg), and magnesium stearate (8 mg).

Probenecid Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Probenecid	500.00
130.00	2	Starch (maize)	130.00
10.00	3	Kollidon 30	10.00
–	4	Alcohol	70.00 mL
25.00	5	Kollidon CL	25.00
3.00	6	Aerosil 200	3.00
3.00	7	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate a mixture of items 1 and 2 with a solution of items 3 and 4. Pass this mixture through a 0.8-mm sieve. Add items 5 to 7, and press with low-compression force.
2. Compress into 674-mg tablets, using 12-mm biplanar punches.

Promethazine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Promethazine HCl	10.50
41.95	2	Lactose monohydrate	41.95
20.00	3	Maize starch	20.00
0.05	4	Sodium metabisulfite (sodium disulfite)	0.05
2.00	5	Povidone (PVP K-30)	2.00
5.00	6	Maize starch (dried)	5.00
0.50	7	Magnesium stearate	0.50
–	8	Alcohol (ethanol, 95%)	6.07
–	9	Purified water	8.67

Manufacturing Directions

Note: Avoid over-mixing of lubricants; otherwise, hardness will be reduced.

1. Mix items 9 and 8 in a stainless steel container.
2. Dissolve items 4 and 5 by slow stirring with stirrer until mixture becomes clear.
3. Sift items 1 to 3 through a stainless steel 500-μm sieve in sifter.
4. Load into mixer, and mix for 5 minutes at low speed.
5. Add binding solution at a rate of 5 to 7 g/min to the dry powders, while mixing at low speed.
6. After addition is complete, scrape sides and blades.
7. Mix further for 2 minutes using a mixer and chopper at low speed.
8. Scrape sides and blades.
9. Check for the end point of granulation, which is the point where the granulation consists of few or no lumps.
10. If required, add purified water.
11. Dry the wet granules with the air circulation heater off to expel alcohol for 2 hours.
12. Then, dry at 55°C for 14 hours.
13. After 4 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying.
14. Check the LOD (limit: 1.0–1.5%).
15. If required, dry further at 55°C for 2 hours.
16. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed.
17. Collect in stainless steel drums.
18. Load granules into the blender.
19. Sift item 6 material through a 500-μm sieve using a sifter, and add it into blender.
20. Mix for 3 minutes.
21. Sift item 7 through a 500-μm sieve, and add 1 to 2 g of granules from above.
22. Mix in polyethylene bag for 1 minute.
23. Add to blender.
24. Mix for 30 seconds.
25. Compress 0.80 g.
26. Coat using one of the HPMC coatings given in the Appendix.

Promethazine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Promethazine HCl	26.00
103.75	2	Lactose monohydrate	103.75
50.00	3	Maize starch	52.50
1.50	4	Sodium metabisulfite (sodium disulfite)	1.50
5.00	5	Povidone (PVP K-30)	5.00
12.50	6	Maize starch (dried)	12.50
1.25	7	Magnesium stearate	1.25
–	8	Alcohol (ethanol, 95%)	15.00
–	9	Purified water	21.67

Manufacturing Directions

Note: Avoid over mixing of lubricants; otherwise, hardness will be reduced.

1. Mix items 9 and 8 in a stainless steel container.
2. Dissolve items 4 and 5 by slow stirring with stirrer until mixture becomes clear.
3. Sift items 1 to 3 through a stainless steel 500-μm sieve in sifter.
4. Load into mixer, and mix for 5 minutes at low speed.
5. Add binding solution at a rate of 5 to 7 g/min to the dry powders, while mixing at low speed.
6. After addition is complete, scrape sides and blades.
7. Mix further for 2 minutes using a mixer and chopper at low speed.
8. Scrape sides and blades.
9. Check for the end point of granulation, which is the point where the granulation consists of few or no lumps.
10. If required, add purified water.
11. Dry the wet granules with the air circulation heater off to expel alcohol for 2 hours.
12. Then, dry at 55°C for 14 hours.
13. After 4 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying.
14. Check the LOD (limit: 1.0–1.5%).
15. If required, dry further at 55°C for 2 hours.
16. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed.
17. Collect in stainless steel drums.
18. Load granules into the blender.
19. Sift item 6 material through a 500-μm sieve using a sifter, and add it into blender.
20. Mix for 3 minutes.
21. Sift item 7 through a 500-μm sieve, and add 1 to 2 g of granules from above.
22. Mix in polyethylene bag for 1 minute.
23. Add to blender.
24. Mix for 30 seconds.
25. Compress 0.80 g.
26. Coat using one of the HPMC coatings in the Appendix.

Promethazine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Promethazine HCl[a]	10.50
41.95	2	Lactose monohydrate	41.95
20.00	3	Starch (maize)	20.00
0.05	4	Sodium metabisulfite (sodium disulfite)	0.05
2.00	5	Povidone (PVP K-30)	2.00
5.00	6	Starch (maize), dried[b]	5.00
0.50	7	Magnesium stearate	0.50
–	8	Alcohol (ethanol 95%)	6.07
–	9	Purified water	8.67

[a]0.5-mg promethazine HCl/tablet added extra, considering the assay and LOD of the material (assay 97–101.5%, calculated on the dried basis LOD NMT 0.5%).
[b]LOD: NMT 4.5% when dried at 120°C for 4 hours.

Manufacturing Directions

1. Avoid over mixing lubricants, or hardness may be reduced.
2. Mix items 9 and 8 in a stainless steel container.
3. Dissolve items 4 and 5 by slow stirring with a stirrer until the mixture becomes clear.
4. Sift items 1 to 3 through a stainless steel 500-μm sieve in a sifter. Load into a mixer, and mix for 5 minutes at low speed.
5. Add a binding solution 5 to 7 g/min to the dry powders while mixing at low speed. After addition is over, scrape sides and blades. Mix an additional 2 minutes using a mixer and chopper at low speed. Scrape sides and blades.
6. Check for the end point of granulation. The end point is the point of granulation that consists of little or no lumps. If required, add purified water.
7. Dry the wet granules with the air circulation heater off, to expel alcohol for 2 hours. Then dry at 55°C for 14 hours. After 4 hours of drying, scrape the semidried granules to break the lumps for uniform drying.
8. Check the LOD. The limit is 1% to 1.5%. If required, dry further at 55°C for 2 hours.
9. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect the granules in stainless steel drums.
10. Load the granules into the blender. Sift the item 6 material through a 500-μm sieve using a sifter, and add it into the blender. Mix the blend for 3 minutes.
11. Sift item 7 through a 500-μm sieve. Add 1 to 2 g granules from step 10. Mix in a polythene bag for 1 minute. Add to the blender. Mix for 30 seconds.
12. Compress 0.80 g. Coat using one of the HPMC coatings. (See Appendix.)

Promethazine Hydrochloride Tablets (25 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Promethazine HCl	26.00
103.75	2	Lactose monohydrate	103.75
50.00	3	Starch (maize)	52.50
1.50	4	Sodium metabisulfite (sodium disulfite)	1.50
5.00	5	Povidone (PVP K-30)	5.00
12.50	6	Starch (maize), dried	12.50
1.25	7	Magnesium stearate	1.25
–	8	Alcohol (ethanol 95%)	15.00
–	9	Purified water	21.67

Promethazine Hydrochloride Tablets (10 mg) Phenergan

Each tablet of phenergan contains 12.5, 25, or 50 mg of promethazine hydrochloride. The inactive ingredients present are lactose, magnesium stearate, and methylcellulose. Each dosage strength also contains the following: *12.5 mg*—FD&C Yellow No. 6 and saccharin sodium; *25 mg*—saccharin sodium; and *50 mg*—FD&C Red No. 40.

Propranolol Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
120.00	1	Propranolol hydrochloride	120.00
4.00	2	Polyvinylpyrrolidone	4.00
2.00	3	Silicon dioxide	2.00
80.00	4	Lactose	80.00
2.00	5	Sodium stearyl fumarate	2.00
QS	6	Water qs	QS

Manufacturing Directions

1. Propranolol hydrochloride and lactose are placed in a fluidized bed apparatus.
2. An aqueous PVP solution (in 85 g of water) is sprayed to get granules.
3. The granules thus obtained are subsequently dried and passed through a sieve (1-mm mesh) and sodium stearyl fumarate is weighed, added, and blended in a drum mixer.
4. The resulting mixture is pressed into tablets 208.00 mg.
5. These tablet cores are then coated with the following formulation: ethylcellulose (Ethocel) 10.10 polyvinylpyrrolidone (Povidone) 5.50 mg, stearic acid 2.40 mg.
6. Ethocel, povidone, and stearic acid are first dissolved in denatured alcohol (180 g). The coating solution is then sprayed onto the tablet cores in a coating pan.

Propranolol Hydrochloride Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Propranolol hydrochloride	10.00
490.00	2	Ludipress	490.00
2.50	3	Magnesium stearate	2.50

Note: For 50-mg and 100-mg strengths, adjust with item 2.

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force.
2. Compress 514 mg for 10-mg strength, 496 mg for 50-mg strength, and 505 mg for 100-mg strengths, using 12-mm biplanar punches.

Propranolol Hydrochloride Tablets (10 mg)

Propranolol HCl is available as 10-, 20-, 40-, 60-, and 80-mg tablets. The inactive ingredients contained in propranolol HCl tablets are lactose, magnesium stearate, microcrystalline cellulose, and stearic acid. In addition, propranolol HCl 10-mg and 80-mg tablets contain FD&C Yellow No. 6 and D&C Yellow No. 10; propranolol HCl 20-mg tablets contain FD&C Blue No. 1; propranolol HCl 40-mg tablets contain FD&C Blue No. 1, FD&C Yellow No. 6, and D&C Yellow No. 10; and propranolol HCl 60-mg tablets contain D&C Red No. 30.

Propranolol Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (kg)
10.00	1	Propranolol hydrochloride	10.00
2.00	2	Maize starch	2.00
4.00	3	Lactose	4.00
0.20	4	Soluble starch	0.20
15.00	5	Purified water	15.00
3.00	6	Primojel	3.00
9.00	7	Microcrystalline cellulose	9.00
0.50	8	Magnesium stearate	0.50

Manufacturing Directions

1. Pass items 1 to 3 through a FitzMill sieve 24228 at medium speed, and mix for 15 minutes.
2. Bring to boil 1.25 kg of purified water (item 5), and dissolve in it item 4. Add the remaining water and allow boiling for a few minutes, allowing the mixture to cool to room temperature.
3. Make a uniform mass of step 2 with step 1 solution, and pass it through a FitzMill sieve 24183, adding water if necessary.
4. Dry granules at 35°C for 14 hours. Pass the granules through a FitzMill sieve 24228 at low speed.
5. Pass items 6 to 8 through a FitzMill sieve 24228 and at medium speed.
6. Compress.
7. Coat in a pan at 25°C to 30°C under a flow of warm air using the Opaspary coating. (See Appendix.) After coating, polish the film-coated tablet.

Propranolol HCl Substained-Release Pellets Releasing Tablets (MUPS-Formulation)

Formulation (for 500 g of tablets): Propranolol HCl/ Kollicoat® SR 30D pellets, 250.0 g; microcrystalline cellulose Vivapur® 200, 250.0 g; magnesium stearate, 2.5 g

Manufacturing Directions

Mix the ingredients together, pass through a 0.8-mm sieve, and compress into tablets with a force of about 15kN at 400 mg.

Propranolol Tablets (40 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
40.00	1	Propranolol	40.00
108.00	2	Ludipress	108.00
0.30	3	Magnesium stearate	0.30
0.40	4	Stearic acid	0.40

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with high-compression force.
2. Compress into 150-mg tablets, using 8-mm biconvex punches.

Proton Pump Inhibitor Dispersible Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Lansoprazole or another PPI equipotent	10.00
175.00	2	Calcium acetate	175.00
175.00	3	Calcium glycerophospate	175.00
250.00	4	Sodium bicarbonate	250.00
20.00	5	Polyethylene glycol	20.00
12.00	6	Croscarmellose sodium	12.00
3.00	7	Peppermint	3.00
1.00	8	Magnesium silicate	1.00
1.00	9	Magnesium stearate	1.00

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Lansoprazole or another PPI equipotent	10.00
175.00	2	Calcium lactate	175.00
175.00	3	Calcium glycerophosphate	175.00
250.00	4	Sodium bicarbonate	250.00
20.00	5	Polyethyle glycol	20.00
12.00	6	Croscarmellose sodium	12.00
3.00	7	Peppermint	3.00
1.00	8	Magnesium stearate	1.00
1.00	9	Magnesium silicate	1.00

Proton Pump Inhibitor Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00 (or equipotent)	1	Proton pump inhibitor	10.00 (or equipotent)
175.00	2	Calcium lactate	175.00
250.00	3	Sodium bicarbonate	250.00
175.00	4	Calcium glycerophosphate	175.00
0.50	5	Phenylalanine (aspartame calcium)	0.50
12.00	6	Colloidal silicon dioxide	12.00
15.00	7	Cornstarch	15.00
12.00	8	Croscarmellose sodium	12.00
10.00	9	Dextrose	10.00
3.00	10	Peppermint	3.00
3.00	11	Maltodextrin	3.00
3.00	12	Mannitol	3.00
3.00	13	Pregelatinized Starch	3.00

Manufacturing Directions

1. Compress.
2. May be used for 20 mg or equivalent quantity of the active without any change in other ingredients.

Pseudoephedrine Hydrochloride Fast-Disintegrating Tablets

1. To the vortex of a rapidly stirred vessel containing 345 g of deionized water is added 30 g of croscarmellose sodium.
2. This slurry is mixed for 10 minutes.
3. Concurrently, 300 g of pseudoephedrine hydrochloride and 300 g of microcrystalline cellulose (Avicel PH-101) are placed in the bowl of a mixer.
4. This mixture is stirred for 10 minutes.
5. At the conclusion of the mixing time, the slurry is added slowly to the contents of the mixing bowl, forming a granulation which is then placed in trays and dried in a 65°C oven for 3 hours.
6. The dried granulation is passed through a US Standard 16 mesh screen (1190 μm).
7. The dried granulation is then placed in a twin-shell blender, and 300 g of Avicel AC-815 (85% microcrystalline cellulose coprocessed with 15% of a calcium, sodium alginate complex) and 300 g of microcrystalline cellulose (Avicel PH-102) are added.
8. This is thoroughly blended for 10 minutes, after which 10.05 g of magnesium stearate is added and mixed for an additional 5 minutes.
9. Prior to being added to the blender the magnesium stearate had been passed through a US Standard 30 mesh screen.
10. The resulting blend is compressed into tablets using 6.35 mm (0.25 in.) round standard concave tooling to give average weight of 0.1299 g and an average thickness of 4.864 mm (0.1915 in.).
11. The hardness of these tablets averaged 1.38 kPa.
12. Friability is measured at 0.077% after 4 minutes.
13. The average disintegration time is 15 seconds in 10 mL of deionized water, forming a suspension with minimal shaking.

Pseudoephedrine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Pseudoephedrine HCl[a]	63.00
120.20	2	Lactose monohydrate	120.20
25.00	3	Maize starch	25.00
1.00	4	Povidone (PVP K-30)	1.00
4.00	5	Povidone (PVP K-30)	4.00
1.80	6	Magnesium stearate	1.80
–	7	Alcohol (ethanol, 95%)	29.00

[a]Pseudoephedrine HCl 3.0 mg/tab can be added in excess to compensate for moisture and handling loss.

Manufacturing Directions

Note: Avoid over-mixing of lubricants; otherwise, hardness is reduced.

1. Dissolve item 5 in item 7 while mixing at slow speed using a stirrer.
2. Sift items 1 to 4 through a 500-µm sieve.
3. Load into mixer, and mix for 5 minutes at low speed.
4. Add binding solution to the dry powders while mixing at low speed for 2 minutes.
5. After addition is complete, mix further for 1 minute using mixer and chopper at low speed.
6. Scrape sides and blade.
7. Check for the end point of granulation, which is when the granulation consists of wet granules with few or no lumps.
8. If required, add ethanol 95% to achieve desired granules.
9. Record extra quantity of ethanol 95% used.
10. Dry the wet mass at 55°C for 7 hours.
11. After 4 hours of drying, scrape the semidried granules to break the lumps to promote uniform drying.
12. Check the moisture content (limit: 1.5–2.5%).
13. Sift the dried granules through a 1.25-mm sieve using a granulator at medium speed.
14. Collect in stainless steel drums.
15. Load granules into the drum blender.
16. Sift item 6 through a stainless steel 250-µm sieve in sifter.
17. Add 8 to 12 g granules in mixer to sieved item 6.
18. Mix manually for 1 minute.
19. Add to drum blender, and blend for 1 minute.
20. Compress into 215-mg tablets, using 8-mm round punches.

Pseudoephedrine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	(+) Pseudoephedrine hydrochloride	60.00
95.00	2	Dicalcium phosphate (Di-Tab)	95.00
5.00	3	Kollidon® 30	5.00
–	4	Water	QS
20.00	5	PEG-6000 (powder)	20.00
2.00	6	Aerosil® 200	2.00

Manufacturing Directions

1. Granulate dicalcium phosphate with solution of items 3 and 4, dry, pass through an 0.8-mm sieve, and mix with item 1.
2. Add items 5 and 6, and press with low-compression force.
3. Compress into 192-mg tablets, using 8-mm biplanar punches.

Psyllium and Docusate Sodium Tablets

Formulation: Psyllium, 71.0%; ethylcellulose, 4.8%; isopropyl alcohol qs; microcrystalline cellulose, 16.7%; PVP crosslinked, 1.9%; carnuba wax, 2.3%; docusate sodium, 3.3%.

Manufacturing Directions

1. Soak ethylcellulose in isopropyl alcohol overnight.
2. Granulate psyllium with isopropyl/ethylcellulose mixture in mixer.
3. Dry at 49°C for 3 hours.
4. Mill through 12-mesh screen.
5. Mix in a mixer the following: psyllium, microcrystalline cellulose, and carnuba wax.
6. Compress the tablet per granulation specifications using a tabletting press.
7. Coat the core tablets.

Methylcellulose, polycarbophil, calcium polycarbophil, bran, malt soup extract, karaya, guar gum, or mixtures of these can be substituted for the psyllium. The amounts of psyllium and/or dioctyl sulfosuccinate can be varied. Dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, can be substituted for the dioctyl sodium sulfosuccinate, or two or three of these can be combined.

Psyllium Husk Tablets

Manufacturing Directions

1. Raw, unmilled psyllium seed husk (2 g) is stirred with 0.2 N sodium hydroxide (400 mL) containing sodium borohydride (400 mg) in a nitrogen atmosphere at ambient temperature for 90 minutes.
2. The pH of the solution is from 10 to 11.
3. The solution is passed through a pasteurizer at a temperature of 100°C for a period of 50 seconds.
4. Once pasteurized, the mixture is centrifuged for 20 minutes at 23500 × *g*.
5. The supernatant is decanted from an insoluble fraction that settles out in the centrifuge bottle.
6. The insoluble fraction is mixed with fresh sodium hydroxide/sodium borohydride solution (100 mL) and recentrifuged for 15 minutes to increase yield of the soluble fraction.
7. The pH of the supernatant is adjusted to 5.5 by the addition of acetic acid at ambient temperature with stirring, forming a gel.
8. The gel is desiccated with isopropanol added with high shear mixing.
9. The isopropanol solution is then decanted from the gel.
10. The solids content of the gel is 30%.
11. The gel material is passed through an extruder and extruded into individual particles with an average particle size of 500 μm.
12. The extruded particles enter a fluidized bed dryer fitted with a cyclonic airflow screen, such as a Conidur screen.
13. The air temperature is maintained at 80°C.
14. The gel temperature remains below 70°C throughout the drying process.
15. The particles are dried to a powder, with 90% of the water being removed.
16. The yield of the gel-forming polysaccharide is 85%.
17. Chewable tablets, total weight 2.5 g, are manufactured while step 8 is dry blended with sorbitol for 10 minutes, each component having an average particle size of about 500 μm.
18. The premix, if desired, is added and the mixture is blended for an additional 10 minutes.
19. Magnesium stearate is added and the composition is blended for another 5 minutes.
20. The mixture is directly compressed into tablets using pressures of from 2000 to 4000 psi.
21. The final compositions comprise the following components by weight: gel-forming, 50.0%; polysaccharide sorbitol Neosorb P20, 48.16%; magnesium stearate, 0.5%; flavorant, 0.4%; colorant, 0.14%; citric acid, 0.8%.
22. Optionally, the coating can be applied directly to a chewable tablet containing the gel-forming polysaccharide.
23. Additionally, it may be desired to include a flavorant within the coating composition: ethanol, 94%; polyethylene glycol, 5%; flavorant, 1%

Pyrazinamide Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Pyrazinamide	500.00
134.50	2	Ludipress	134.50
12.00	3	Kollidon CL	12.00
3.50	4	Aerosil 200	3.50

Manufacturing Directions

1. Mix all components, sieve through a 0.8-mm screen, and press with medium-compression force.
2. Compress into 652-mg tablets, using 12-mm biplanar punches.

Pyrazinamide Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Pyrazinamide	500.00
50.00	2	Starch (maize)	50.00
20.00	3	Kollidon 30	20.00
–	4	Alcohol, ca	200 mL
5.00	5	Kollidon CL	5.00
6.00	6	Magnesium stearate	6.00

Manufacturing Directions

1. Granulate mixture items 1 and 2 with a solution of items 3 and 4. Pass through a 0.8-mm sieve, mix with items 5 and 6, and press with low-compression force.
2. Compress into 605-mg tablets, using 12-mm biplanar punches.
3. The quantity of items 5 can be increased to 10 mg if there is a problem in compressing tablets.

Pyrazinamide Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Pyrazinamide	500.00
125.00	2	Mannitol	125.00
–	3	Water, purified	50.00 mL
25.00	4	Starch (maize)	35.00
QS	5	Water, purified	150 mL
10.00	6	Talc	10.00
6.00	7	Magnesium stearate	6.00

Manufacturing Directions

Note: Carry out all operations subsequent to drying at a relative humidity below 50% and temperature below 26°C.

1. Granulation
   a. Pass the pyrazinamide and mannitol through a 1.2-mm aperture stainless steel screen on a sieve shaker, transfer them to a suitable mass mixer, and mix for 5 minutes.
   b. Add the starch to the water (item 3) and mix until a smooth slurry, free from lumps, is formed.
   c. Heat the water (item 5) to boiling. Reduce the heat, then, while mixing, add the slurry from step 1b. Continue mixing well, until a smooth translucent paste is formed. Allow this paste to cool to 50°C before using it in step 1d.
   d. Add one-half of the starch paste from step 1c to the blended powders in the mixer, and mix for 1 minute. Stop mixing, and scrape the blades and sides of the mixer. Add the second half of the starch paste and mix for another 1 minute. Stop mixing, scrape the blades and sides of the mixer, and examine the mass.
   e. If necessary, add more water at 50°C in small quantities, mixing for 1 minute after each addition, until a good, wet, holding mass is formed. Record extra water used. *Note:* Do not overwet or overmix the mass.
   f. Pass the wet mass through a 4.76-mm aperture stainless steel screen by hand, spread on paper-lined trays, and dry in a hot-air oven at 50°C, turning the granules every 20 minutes, to an LOD of 1% to 1.5% (3 hours at 60°C under maximum vacuum).
2. Lubrication
   a. Pass the granules through a 1.2-mm aperture stainless steel screen on a sieve shaker, and transfer the fines to a blender.
   b. Pass the coarse granules through an 840-μm aperture stainless steel screen on an oscillating granulator, and then transfer the granules to the blender.
   c. Screen the talc and sodium starch glycolate through a 595-μm aperture stainless steel screen on a sieve shaker, and add the mixture to the blender. Blend it for 15 minutes.
   d. Screen the magnesium stearate through a 595-μm aperture stainless steel screen on a siever shaker, and add to the blender. Blend for 2 minutes only.
   e. Discharge into polyethylene-lined drums, and then seal and weigh.
3. Compression: Compress using 12.5-mm round, concave bisected punches; disintegration time is not more than 15 minutes in water.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
40.00	1	Pyridoxine hydrochloride	40.00
150.00	2	Lactose monohydrate	150.00
150.00	3	Avicel™ PH101	150.00
15.00	4	Kollidon® VA 64	15.00
10.00	5	Kollidon® CL	10.00
1.00	6	Magnesium stearate	1.00
1.00	7	Aerosil® 200	1.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with high-compression force.
2. Compress into 361-mg tablets, using 12-mm biplanar punches; items marked with asterisk can be deleted when the compression weight becomes 340 mg.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
40.00	1	Pyridoxine hydrochloride	40.00
300.00	2	Cornstarch	300.00
15.00	3	Kollidon® 30	15.00
80.00	4	Water + isopropanol	80.00
1.00	5	Magnesium stearate	1.00
2.00	6	Aerosil® 200	2.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 3 and 4, dry, pass through an 0.8-mm sieve, mix with items 5 and 6, and press with high-compression force.
2. Compress into 354-mg tablets, using 12-mm biplanar punches.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Pyridoxine hydrochloride	100.00
200.00	2	Tabletlose®	200.00
10.00	3	Kollidon® VA 64	10.00
3.00	4	Kollidon® CL	3.00
1.00	5	Magnesium stearate	1.00
1.00	6	Aerosil® 200	1.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix, and press with medium-compression force.
2. Compress into 363-mg tablets, using 12-mm biplanar punches.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Pyridoxine hydrochloride	100.00
150.00	2	Lactose monohydrate	150.00
83.00	3	Avicel™ PH101	83.00
10.00	4	Kollidon® VA 64	10.00
3.00	5	Kollidon® CL	3.00
1.00	6	Magnesium stearate	1.00
1.00	7	Aerosil® 200	1.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix and press with medium-compression force.
2. Compress into 360-mg tablets, using 12 mm-biplanar punches.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Pyridoxine hydrochloride	250.00
100.00	2	Avicel™ PH101	100.00
12.00	3	Kollidon® VA 64	12.00
5.00	4	Magnesium stearate	5.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix, and press with high-compression force.
2. Compress into 361-mg tablets, using 12-mm biplanar punches.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Pyridoxine hydrochloride	300.00
100.00	2	Lactose monohydrate D 20	100.00
20.00	3	Kollidon® 30	20.00
QS	4	Isopropanol + water (1+1)	60.00
10.00	5	Kollidon® CL	10.00
2.00	6	Aerosil® 200	2.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 3 to 6, dry, and sieve through an 0.8-mm screen.
2. Press with medium-compression force.
3. Compress into 440-mg tablets, using 12-mm biplanar punches.

Pyridostigmine Bromide Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Pyridostigmine bromide	10.00
96.00	2	Starch (maize)	96.00
8.50	3	Silicic acid (Aerosil 200)	8.50
1.50	4	Prejel PA5	1.50
30.00	5	Lactose powder anhydrous	30.00
3.70	6	Talc	3.70
0.23	7	Magnesium stearate	0.23
QS	8	Water, purified, ca	39.70 mL

Manufacturing Directions

1. Mix 5% of item 2 and equal amounts of item 8 in a suitable vessel, at boiling. Mix and allow the paste to cool to 40°C.
2. Mix item 1 into the paste in step 1, in portions, and then add items 4 and 3, avoiding large lumps; mix to homogenous mix.
3. Add the following to item 5 (passed through a sieve), the balance of item 8 (at 40°C), and item 2, and mix to obtain a good mass; add more item 8 if necessary.
4. Pass the through a 10-mm screen in a granulator.
5. Dry the granules at 50°C until the relative humidity over the granules is 30% to 40%.
6. Crush granules in an oscillating granulator with 1-mm perforation place.
7. Blend the granules with items 6 and 7, and pass through a 1-mm sieve.
8. Blend for 10 minutes.
9. Compress to 150-mg weight.

Pyrilamine Tannate and Phenylephrine Tannate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Pyrilamine Tannate	60.00
25.00	2	Phenylephrine Tannate	28.75*
94.00	3	Starch	94.00
150.00	4	Methylcellulose USP 1500cps	150.00
32.00	5	Polygalactouronic acid	32.00
97.00	6	Calclium phosphate dehydrate	97.00
2.60	7	Magnesium stearate	2.60

*Manufacturing excess.

Quetiapine Fumarate Tablets (25 mg/100 mg/200 mg) Seroquel

Seroquel is supplied for oral administration as 25-mg (peach), 100-mg (yellow), and 200-mg (white) tablets. The inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, and titanium dioxide. The 25-mg tablets contain red ferric oxide and yellow ferric oxide, and the 100-mg tablets contain only yellow ferric oxide.

Quinine Sulfate Tablets (300 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Quinine sulfate	300.00
20.00	2	Starch (maize)	20.00
25.00	3	Lactose monohydrate	25.00
5.00	4	Sodium starch glycolate	5.00
0.80	5	Methyl paraben	0.80
0.10	6	Propyl paraben	0.10
2.00	7	Gelatin	2.00
20.00	8	Starch (maize)	20.00
3.00	9	Talc	3.00
1.50	10	Aerosil 200	1.50
2.00	11	Magnesium stearate	2.00
–	12	Water, purified	QS

Manufacturing Directions

1. Sift items 1 to 4 through a 250-μm sieve into a suitable mixing vessel.
2. In a separate vessel, take the appropriate quantity of item 12, and heat it to a boil. Add and dissolve items 5 and 6. Cool to 50°C, and add items 7 and 8. Then mix to form a 30% starch paste.
3. Add the paste from step 2 into step 1, and mix the paste to form a suitable mass for granulation.
4. Pass the wet mass through a 2.38-mm sieve onto paper-lined trays; dry at 60°C overnight.
5. Pass the dried granules through #18 mesh into a blending vessel. Sift items 9 to 11 through a 250-μm sieve, and the pieces add to step 5, and blend for 2 minutes. Compress into 375-mg tablets, using 9.5-mm punches.
6. Coat the tablets using HPMC and methylene chloride. (See Appendix.)

Quinapril Hydrochloride Tablets (5 mg/10 mg/20 mg/40 mg) Accupril

Accupril tablets contain 5, 10, 20, or 40 mg of quinapril for oral administration. Each tablet also contains candelilla wax, crospovidone, gelatin, lactose, magnesium carbonate, magnesium stearate, synthetic red iron oxide, and titanium dioxide.

Quinapril Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Quinapril, use quinapril hydrochloride	22.00
108.00	2	Lactose monohydrate	108.00
55.00	3	Magnesium carbonate	55.00
10.50	4	Crospovidone	10.50
4.00	5	Povidone K-30	4.00
0.50	6	Magnesium stearate	0.50
QS	7	Purified water	QS

Manufacturing Directions

1. Sift quinapril hydrochloride, lactose monohydrate, magnesium carbonate, and crospovidone through a 0.9-mm sieve.
2. Load sifted powder from step 1 to a mixer granulator and mix for 5 minutes.
3. Dissolve povidone K-30 in purified water under slow stirring until the solution becomes clear.
4. Add the binding solution from step 3 to step 2, and mix for a few minutes until the proper granules are formed.
5. Unload the granules, and dry at 55°C in an oven to get the desired LOD of 2.5%.
6. Grind the dried granules to get granules of the desired particle size of #16 mesh.
7. Add crospovidone and magnesium stearate to ground granules in a blender, and blend for 3 minutes.
8. Compress 200 mg of the lubricated granules into tablets (12 mm).
9. Use appropriate coating materials (HPMC). (See Appendix.)

Quinolone Antibiotic Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Quinolone antibiotic[a]	100.00
23.50	2	Microcrystalline cellulose	23.50
15.00	3	Starch (maize)	15.00
6.50	4	L-Hydroxypropylcellulose	6.50
3.50	5	Magnesium stearate	3.50
1.50	6	Colloidal anhydrous silica (Aerosil 200)	1.50

[a]Applicable to most quinolone antibiotics.

Manufacturing Directions

1. The manufacturing process described is for the 100-mg tablet. Adjust the weights of all components based on the quantity used. When calculating, factor in for salt form, moisture, and activity.
2. Sift items 1 to 4.
3. Mix these (use two-thirds of item 4) at this stage in a blender. Add screened item 6, and mix at a slow speed.
4. Run the mixture through a compacting mill, and collect graded granules in a blender.
5. Add screened item 6 and the balance of item 4, and blend. Add the screened magnesium stearate in the rotating-shell blender. Mix at 6 rpm for 5 minutes. The final mixture is obtained.
6. Compress into 8-mm tablets or 10-mm tablets (for 200-mg tablets).
7. Coat using an HPMC coating. (See Appendix.)

Rabeprazole Sodium Tablets (20 mg) Aciphex

The active ingredient in Aciphex™ delayed-release tablets is rabeprazole sodium Aciphex is available for oral administration as delayed-release, enteric-coated tablets containing 20 mg of rabeprazole sodium. The inactive ingredients are mannitol, hydroxypropyl cellulose, magnesium oxide, low-substituted hydroxypropyl cellulose, magnesium stearate, ethylcellulose, hydroxypropyl methylcellulose phthalate, diacetylated monoglycerides, talc, titanium dioxide, carnauba wax, and ferric oxide (yellow) as a coloring agent.

Rabeprazole Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Rabeprazole	20.00
50.00	2	Precipitated calcium carbonate	50.00
40.00	3	Starch (maize)	40.00
73.40	4	Lactose monohydrate	73.40
6.00	5	Hydroxypropyl cellulose	6.00
2.00	6	Magnesium stearate	2.00
–	7	Water, purified	QS

Manufacturing Directions

1. Mix *R*(+) rabeprazole, precipitated calcium carbonate, cornstarch, lactose, and hydroxypropyl-cellulose together.
2. Add water, and knead the mixture. Then dry in vacuum at 40°C for 16 hours.
3. Pass the granules through a 16-mesh sieve to give granules.
4. Add item 6, and blend.
5. Compress.

Raloxifene Tablets (60 mg) Evista

Evista is supplied in a tablet dosage form for oral administration. Each Evista tablet contains 60 mg of raloxifene HCl, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include anhydrous lactose, carnauba wax, crospovidone, FD&C Blue No. 2 Aluminum Lake, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, modified pharmaceutical glaze, polyethylene glycol, polysorbate 80, povidone, propylene glycol, and titanium dioxide.

Raloxifene Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Raloxifene HCl	60.00
156.00	2	Lactose anhydrous	156.00
7.20	3	Polyvinyl pyrrolidone	7.20
7.20	4	Polysorbate 80	7.20
7.20	5	Cross-linked polyvinyl pyrrolidone	7.20
2.40	6	Magnesium stearate	2.40

Manufacturing Directions

1. Granulate the mixture of raloxifene HCl, lactose anhydrous, and cross-linked polyvinyl-pyrrolidone with an aqueous solution of polyvinylpyrrolidone and polysorbate 80.
2. Dry the granules, and reduce to a suitable size.
3. Mix and blend magnesium stearate.
4. Compress into 240-mg tablets.

Ranitidine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Ranitidine; use Ranitidine HCl	88.88
65.00	2	Microcrystalline cellulose, NF	65.00
1.12	3	Magnesium stearate, NF	1.12

Manufacturing Directions

1. Pass ranitidine and microcrystalline cellulose through a 595-μm screen, and transfer to a suitable mixer.
2. Mix for 10 minutes.
3. Screen magnesium stearate through a 400-μm screen and add to the blender.
4. Blend for 2 minutes.
5. Compress using slightly convex round punches at hardness 8 ppi and disintegration time of not more than 15 minutes in water.
6. Coat using a methocel-ethocel coating solution (see Appendix).

Ranitidine Hydrochloride Tablets (150 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Ranitidine, use ranitidine hydrochloride	167.68
129.75	2	Microcrystalline cellulose	129.75
9.00	3	Hydroxypropyl methyl cellulose 2910	9.00

Manufacturing Directions

1. Granulation: Pass ranitidine and microcrystalline cellulose through a 595-μm aperture screen, transfer to a suitable mixer, and mix for 10 minutes.
2. Lubrication
   a. Screen magnesium stearate through a 400-μm aperture screen and add to the blender. Blend for 2 minutes.
   b. Discharge the granule into polyethylene-lined drums. Seal the drums, and weigh for yield.
3. Compression: Compress using slightly convex round punches. The weight of 10 tablets should be about 2.07 g, with not more than 3% variation. Disintegration time is not more than 15 minutes in water.
4. Coating: Use opaque methocel–ethocel coating. (See Appendix.)

Ranitidine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Ranitidine	150.00
147.00	2	Ludipress	147.00
3.00	3	Magnesium stearate	3.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm screen, and press with low-compression force.
2. Compress into 305-mg tablets, using 8-mm biconvex punches.
3. If the flowability of the tabletting mixture is not sufficient, add about 1% Aerosil 200. For 300-mg strength, use proportion weight, and increase fill weight; the use of 1% Aerosil 200 is required.

Ranitidine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
167.39	1	Ranitidine HCl USP [Orchev Pharma]	167.39
78.28	2	Microcrystalline cellulose NF [Avicel® PH-102, FMC]	78.28
62.00	3	Pregelatinized starch NF [Starch 1500®, Colorcon]	62.00
1.55	4	Fumed silica NF [Aerosil® 200, Degussa AG]	1.55
0.78	5	Magnesium stearate NF [Peter Greven]	0.78

Manufacturing Directions

1. All materials, with the exception of magnesium stearate, are blended for 10 minutes in a blender.
2. Magnesium stearate is added and blended for an additional 2 minutes.
3. Tablets compressed at 310 mg.

Ranitidine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Ranitidine; use Ranitidine HCl[a]	85.00
95.00	2	Microcrystalline cellulose (Avicel™ PH102)	95.00
7.00	3	Croscarmellose sodium (Ac-Di-Sol)	7.00
6.60	4	Microcrystalline cellulose (Avicel™ PH102)	6.60
1.40	5	Magnesium stearate	1.40

[a]Ranitidine HCl (1.5%) is added to compensate LOD and process loss.

Manufacturing Directions

1. Process the product in an area where the relative humidity is 40% to 45% and temperature does not exceed 25°C.
2. Store the bulk tablets in polyethylene-lined stainless steel containers at a controlled relative humidity of 45% to 50% and temperature not exceeding 25°C.
3. Pass items 2, 3, and 1 through a sifter using a 900-μm sieve.
4. Load into a blender, and mix for 3 minutes.
5. Manually mix items 4 and 5 in a polyethylene bag for 1 minute.
6. Pass through a sifter using a 500-μm sieve.
7. Collect in a polyethylene bag.
8. Add to blender, and blend for 1 minute.
9. Check temperature and humidity before start of slugging (at a temperature not exceeding 25°C and a relative humidity of 40% to 45%).
10. Slug 240.0 g of mixed powder in a rotary tabletting machine.
11. Grind the slugs in a granulator using a 3.0-mm sieve followed by a 1.00-mm sieve.
12. Compress 195 mg using oblong biconvex punches.
13. Check temperature and humidity before start of compression (limit: temperature not exceeding 25°C and relative humidity of 40% to 45%).
14. Coat using a hydroalcoholic HPMC coating.

Ranitidine Tablets (75 mg)

Bill of Materials			
Scale(mg/tablet)	Item	Material Name	Quantity/1000 Tabs (g)
75.00	1	Ranitidine, use ranitidine HCl[a]	85.00
95.00	2	Microcrystalline cellulose (Avicel PH 102)	95.00
7.00	3	Croscarmellose sodium (Ac-Di-Sol)	7.00
6.60	4	Microcrystalline cellulose (Avicel PH 102)	6.60
1.40	5	Magnesium stearate	1.40

[a]Ranitidine HCl 1.5% is added as an extra to compensate LOD and process loss.

Manufacturing Directions

1. Process the product in an area where the RH is between 40% and 45%, and the temperature does not exceed 25°C. Store the bulk tablets in polythene-lined stainless steel containers at a controlled RH 45% to 50% and a temperature not exceeding 25°C.
2. Pass items 2, 3, and 1 through a sifter using a 900-μm sieve.
3. Load into blender, and mix for 3 minutes. Mix items 4 and 5 in a polythene bag manually for 1 minute. Pass through a sifter using a 500-μm sieve.
4. Collect in a polythene bag. Add to the blender, and blend for 1 minute.
5. Check temperature and humidity before starting to get sluggish. (Temperature not exceeding 25°C, RH 40–45%.)
6. Slug 240.0 g of mixed powder in a rotary tablet-ting machine. Grind the slugs in the granulator, using a 3-mm sieve followed by a 1-mm sieve.
7. Compress into 195-mg tablets, using oblong biconvex punches. Check the temperature and humidity before starting the compression. The limitation is that the temperature should not exceed 25°C, and the RH should be 40% to 45%.
8. Coat using a hydroalcoholic HPMC coating.

Ranitidine Tablets (300 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Ranitidine use as ranitidine HCl*	340.00
110.00	2	Microcrystalline cellulose (Avicel PH 102)	110.00
10.00	3	Croscarmellose sodium (Ac-Di-Sol)	10.00
16.00	4	Microcrystalline cellulose (Avicel PH 102)	16.00
4.00	5	Magnesium stearate	4.00

*Anhydrous; adjust for moisture.

Manufacturing Directions

Precautions: Process the product in an area where the relative humidity is between 40% and 45%, and the temperature should not exceed 25°C. Store the bulk tablets in polythene-lined stainless steel containers at a controlled relative humidity of 45% to 50% and at temperatures not exceeding 25°C.

1. Dry powder sieving and mixing: Pass items 2, 3, and 1 through a sifter, using a 900-μm sieve. Load into the blender, and mix for 3 minutes.
2. Lubrication
   a. Mix manually items 4 and 5 in a polythene bag for 1 minute. Pass through a sifter using a 500-μm sieve. Collect in a polythene bag. Add to the blender (step 1), and blend for 1 minute.
   b. Unload in stainless steel drums. Check and record the weight of powder mix.
3. Slugging
   a. Check the temperature and humidity before the start of slugging. Limits: temperature not exceeding 25°C; relative humidity of 40% to 45%.
   b. Slug 240.0 g of the mixed powder in a rotary tabletting machine using the following parameters. Keep the rest of the quantity in a stainless steel drum.
4. Grinding: Grind the slugs in a granulator using a 3-mm sieve followed by a 1-mm sieve.
5. Mixing: Ground granules, 240 g, from step 2, and 240 g of the lubricated granules from step 3a. Load into blender and mix for 1/2 minutes.
6. Compression: Check the temperature and humidity before starting compression. Limits: temperature not exceeding 25°C; relative humidity of 40% to 45%. Compress the granules using a rotary tabletting machine. Compress into 480-mg tablets, using 015.5 mm × 7 mm punches.

Ranitidine Tablets (150 mg), Zantac

Each Zantac 150 tablet for oral administration contains 168 mg of ranitidine HCl equivalent to 150 mg of ranitidine. Each tablet also contains the inactive ingredients FD&C Yellow No. 6 Aluminum Lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, titanium dioxide, triacetin, and yellow iron oxide.

Each Zantac 300 tablet for oral administration contains 336 mg of ranitidine HCl equivalent to 300 mg of ranitidine. Each tablet also contains the inactive ingredients croscarmellose sodium, D&C Yellow No. 10 Aluminum Lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

Zantac 150 EFFERdose tablets and Zantac 150 EFFERdose granules for oral administration are effervescent formulations of ranitidine that must be dissolved in water before use. Each individual tablet or the contents of a packet contains 168 mg of ranitidine HCl equivalent to 150 mg of ranitidine and the following inactive ingredients: aspartame, monosodium citrate anhydrous, povidone, and sodium bicarbonate. Each tablet also contains sodium benzoate. The total sodium content of each tablet is 183.12 mg (7.96 mEq) per 150 mg of ranitidine, and the total sodium content of each packet of granules is 173.54 mg (7.55 mEq) per 150 mg of ranitidine.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
3.00	1	Riboflavin	3.00
195.00	2	Ludipress®	195.00
2.00	3	Magnesium stearate	2.00
1.00	4	Aerosil® 200	1.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix, and press with very low-compression force (4 kN).
2. Compress into 202-mg tablets, using 8-mm biplanar punches.
3. This is a very low active ingredient formulation (3 mg).
4. If content uniformity is a problem, prepare a premix of the active ingredient with a small part of the Ludipress® or with lactose monohydrate before mixing with the other components of the formulation.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Riboflavin	10.00
75.00	2	Lactose monohydrate	75.00
20.00	3	Cornstarch	20.00
15.00	4	Avicel™ PH101	15.00
5.00	5	Kollidon® 30	5.00
25.00	6	Water	25.00
0.80	7	Aerosil® 200	0.80
2.50	8	Talc	2.50
1.70	9	Hydrogenated castor oil	1.70

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with solution of items 5 and 6, dry, pass through an 0.8-mm sieve, mix with items 7 to 9, and press with low compressive force.
2. Compress into 134-mg tablets, using 8-mm biplanar punches.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Riboflavin	75.00
375.00	2	Sorbitol (crystalline)	375.00
23.00	3	Kollidon® VA 64	23.00
4.00	4	Magnesium stearate	4.00
12.00	5	Aerosil® 200	12.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix, and press with low compressive force.
2. Compress into 493-mg tablets, using 12-mm biplanar punches.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Riboflavin	100.00
250.00	2	Sorbitol (crystalline)	250.00
19.00	3	Kollidon® VA 64	19.00
5.00	4	Magnesium stearate	5.00
10.00	5	Aerosil® 200	10.00

Manufacturing Directions

1. Pass all components through an 0.8-mm sieve, mix, and press with medium-compression force.
2. Compress into 384-mg tablets, using 12-mm biplanar punches.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Riboflavin, with excess	156.00
150.00	2	Ludipress®	150.00
4.00	3	Magnesium stearate	4.00
2.00	4	Aerosil® 200	2.00

Manufacturing Directions

1. Mix all components, pass through an 0.8-mm sieve, and press with low compressive force.
2. Compress into 308-mg tablets, using 8-mm biplanar punches.

Rifampicin, Isoniazid, Ethambutol, and Pyridoxine Tablets (300 mg/200 mg/25 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
–	1	Alcohol SD 3A, 200 proof	150.00 mL
3.00	2	Alcohol cetostearyl	3.00
300.00	3	Rifampicin powder	300.00
12.00	4	Hydroxypropyl methyl cellulose 2910, 50 cps	2.00
–	5	Alcohol SD 3A, 200 proof	QS
200.00	6	Isoniazid zisonicotinylhydrazine, 10% excess	220.00
25.00	7	Pyridoxine hydrochloride	25.00
400.00	8	Ethambutol hydrochloride	400.00
20.00	9	Povidone K 29–32	20.00
–	10	Water, purified	50.00 mL
–	11	Water, purified	QS
20.00	12	Talc	20.00
40.00	13	Sodium starch glycolate	40.00
10.00	14	Magnesium stearate	10.00

Manufacturing Directions

Note: Rifampicin and ethambutol hydrochloride are expensive raw materials, therefore, handle with care. The product should be manufactured in a separate, closed area, and all manufacturing equipment should be covered to minimize dust contamination.

1. Granulation I
   a. Charge the alcohol (item 1) into a container, and while stirring, gradually add the alcohol cetostearyl. Continue mixing until it all dissolves.
   b. Charge the rifampicin into the mixer (preferably a planetary mixer), followed by the hydroxypropyl methylcellulose. Mix together for 5 minutes.
   c. While mixing the blended powders from step 1b, pour in the alcoholic solution from this step. (Do not add too slowly or excessive evaporation will occur.) When all the solution is added, continue mixing for 1 minute.
   d. Stop the mixer, scrape the blades, walls, and bottom of the mixer, and then restart the mixer.
   e. While mixing, add extra alcohol (item 5) in portions, mixing for 30 seconds between each addition. Continue adding alcohol and mixing until the mass changes to a uniform dark reddish-brown color that exhibits good adhesion when squeezed and contains no dry powder. Stop mixing.
   f. Quickly scrape the blades, walls, and bottom of the mixer. Then pass the mass through a 4.76-mm aperture screen, spread on lined trays, and dry in a hot-air oven at 50°C to an LOD (60°C for 3 hours under vacuum) of not more than 2.5%.
   g. Sift the dried granules through a 1.2-mm screen on a sieve shaker.
   h. Pass the coarse granules from step 1g through a 1.7-mm screen. i. Transfer the siftings from step 1g and the granules from step 1h to a suitable blender.
2. Granulation II
   a. Pass successively, through a 1.2-mm aperture screen on a sieve shaker, the isoniazid followed by the pyridoxine hydrochloride. Charge the screened powders into a suitable mixer, and mix for 5 minutes.
   b. Pass the ethambutol hydrochloride through a 1.2-mm aperture screen, and transfer to the mixer. Blend all the powders together for 5 minutes.
   c. Add the water (item 10) to a stainless steel container, and add, while mixing, the povidone. Continue mixing until it all dissolves.
   d. While mixing the powders from step 2b add the aqueous solution from step 2c in a slow stream. When all the solution is added, continue mixing for 1 minute.
   e. Stop the mixer, and scrape the blades, wall, and bottom of the mixer. Start mixing again.
   f. Gradually add extra water until granulation is achieved with the formation of balls.
   g. Pass the mass through a 4.76-mm aperture screen, and spread on lined trays. Dry in a hot-air oven at 50°C for 4 hours, pass the granules through a 2.38-mm aperture screen, return to the oven, and continue drying to an LOD of less than 1% (60°C for 3 hours under vacuum).
   h. Sieve the dried granules through an 840-μm aperture screen on a suitable sieve shaker.
   i. Pass the coarse granules from step 2h through an 840-μm aperture screen.
   j. Transfer the fines from step 2h and the granules from step 2i to the blender (see step 1i).
3. Lubrication
   a. Pass the talc and sodium starch glycolate through a 595-μm aperture screen on a sieve shaker, and then transfer to the blender with Granulations I and II.
   b. Blend all the items together for 15 minutes, then stop the blender.

c. Pass the magnesium stearate through a 595- μm aperture screen on a sieve shaker, then transfer to the blender.
d. Blend the batch for 3 to 4 minutes, then stop the blender.
e. Discharge the contents of the blender into polyethylene-lined drums, and weigh.

4. Compression: Compress into 1.05-g tablets, using ovaloid punches (18.6 × 8.7 mm), with a disintegration time of not more than 20 minutes in water and a thickness of 8.4 to 8.8 mm.
5. Coating: Apply an organic methocel coating. (See Appendix.)

Rifampicin Tablets (300 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
–	1	Alcohol SD 3A, 200 proof	150.00 mL
3.00	2	Alcohol cetostearyl	3.00
300.00	3	Rifampicin powder	300.00
12.00	4	Hydroxypropyl methylcellulose 2910 50 cps	12.00
–	5	Alcohol SD 3A, 200 proof	QS
8.00	6	Talc	8.00
16.00	7	Sodium starch glycollate powder	16.00
7.50	8	Magnesium stearate	7.50

Manufacturing Directions

Caution: (1) Rifampicin is an expensive raw material; handle with care. (2) The product should be manufactured in a separate closed area, and all manufacturing equipment should be covered so as to minimize dust contamination. (3) After use, wash the manufacturing area and equipment thoroughly with water and detergent. Personnel should take a cleansing shower after exposure during manufacturing.

1. Granulation
   a. Do not over fill the mixer, because this retards penetration of the alcohol to the bottom of the bowl, leading to excessive evaporation and inadequate massing.
   b. Charge the alcohol (item 1) into a container, and while stirring gradually, add the alcohol cetostearyl. Continue mixing until all has dissolved.
   c. Charge the rifampicin into the mixer (preferably a planetary mixer), followed by the hydroxypropyl methylcellulose. Mix together for 5 minutes.
   d. While mixing the blended powders from step 1b, pour in the alcoholic solution from step 1a. (Do not add too slowly or excessive evaporation will occur.) When all the solution is added, continue mixing for 1 minute.
   e. Stop the mixer; scrape the blades, walls, and bottom of the mixer well, and then restart the mixer.
   f. While mixing, add extra alcohol (item 5) in portions, mixing for 30 seconds between each addition. Continue adding alcohol and mixing until the mass changes to a uniform dark reddish-brown color that exhibits good adhesion when squeezed and contains no dry powder. Stop mixing.
   g. Quickly scrape the blades, walls, and bottom of the mixer, and then pass the mass through a 4.76-mm aperture screen; spread on lined trays, and then dry in a hot-air oven at 50°C to an LOD not more than 2.5% (60°C for 3 hours under vacuum). Request samples.
   h. Sift the dried granules through a 1.2-mm screen on a sieve shaker.
   i. Pass the coarse granules from step g through a 1.7-mm screen on a granulator or something similar.
   j. Transfer the siftings from steps g and \ through a 1.7-mm screen on a granulator.
2. Lubrication: Pass the talc and sodium starch glycolate through a 595-μm aperture screen on a sieve shaker, and then transfer to the blender.
3. Blend all the items together for 15 minutes, then stop the blender.
   a. Pass the magnesium stearate through a 595-μm aperture screen on a sieve shaker, then transfer to the blender.
   b. Blend the batch for 3 to 4 minutes, and then stop the blender.
   c. Discharge the contents of the blender into polyethylene-lined drums, and weigh. Record the batch weight.
4. Compression: Compress the tablets on a suitable rotary tabletting machine, using round punches of 10.32 mm. The tablet weight for 10 tablets is as follows: (3.465 × 100)/(100% LOD). Hardness is 6 to 8 kPa; disintegration time should be more than 15 minutes in water; and thickness should be 5.15 to 5.25 mm.
   a. For other strengths of rifampicin, 450 and 600 mg, scale up the formula. For 450-mg tablets, use ovaloid punches of 15.2 × 7.77 mm. The tablet weight for 10 tablets is (5.145 × 100)/(100% LOD); hardness is 9 to 15 kPa; the disintegration time is not more than 15 minutes in water; and the thickness is 6.55 to 6.65 mm. The coating solution will be 200 mL—optionally add coating solution gloss methocel, 90.00 mL. (See Appendix.)
   b. For 600-mg tablets, use ovaloid punches of 18.6 × 7.8 mm. The tablet weight for 10 tablets is (6.930 × 100)/(100% LOD); hardness is 9 to 15 kPa; the disintegration time is not more than 15 minutes in water; and the thickness is 6.35 to 6.45 mm. Use a coating solution of 250 mL. Optionally add coating solution gloss methocel, 90.00 mL. (See Appendix.)

Rifampicin Tablets (450 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
450.00	1	Rifampicin	450.00
58.00	2	Starch maize	58.00
9.00	3	Kollidon 90F	9.00
–	4	Isopropyl alcohol or alcohol, ca	50 mL
15.00	5	Kollidon CL	15.00
10.00	6	Stearic acid	10.00
2.00	7	Magnesium stearate	2.00
2.00	8	Aerosil 200	2.00

Manufacturing Directions

1. Granulate the mixture of items 1 and 2 with a solution of items 3 and 4. Dry, sieve, and mix with items 5 to 8, and press with low-compression force to tablets.
2. Compress into 550-mg tablets, using 12-mm biplanar punches.

Risedronate Sodium Tablets (5 mg/30 mg) Actonel

The inactive ingredients are crospovidone, ferric oxide yellow (5-mg tablets only), hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, and titanium dioxide.

Risedronate Sodium Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
30.00	1	Risedronate sodium[a]	30.00
156.00	2	Lactose anhydrous	156.00
60.50	3	Microcrystalline cellulose	60.50
7.40	4	Crospovidone	7.40
1.10	5	Magnesium stearate	1.10

[a]This quantity of risedronate sodium is determined by assay and then adjusted to provide the designed dosage level of risedronate sodium on an anhydrous basis.

Manufacturing Directions

1. Charge the risedronate active ingredient with the microcrystalline cellulose in a twin-shell blender. Blend for 20 minutes.
2. Pass the blend through an oscillator equipped with a 60-mesh screen.
3. Return the milled blend to the shell blender, along with the lactose and crospovidone, and mix until uniform.
4. Add the magnesium stearate, and mix until adequate lubrication is achieved.
5. Compress 250 mg.
6. Coat. (See Appendix.)

Risperidone Tablets (4 mg) Risperdal

Risperdal tablets are available in 0.25-mg (dark yellow), 0.5-mg (red-brown), 1-mg (white), 2-mg (orange), 3-mg (yellow), and 4-mg (green) strengths. The inactive ingredients are colloidal silicon dioxide, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, propylene glycol, sodium lauryl sulfate, and starch (corn). Tablets of 0.25, 0.5, 2, 3, and 4 mg also contain talc and titanium dioxide. The 0.25-mg tablets contain yellow iron oxide; the 0.5-mg tablets contain red iron oxide; the 2-mg tablets contain FD&C Yellow No. 6 Aluminum Lake; the 3-mg and 4-mg tablets contain D&C Yellow No. 10; and the 4-mg tablets contain FD&C Blue No. 2 Aluminum Lake.

Risperidone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4.00	1	Risperidone	4.00
140.00	2	Lactose monohydrate	140.00
105.00	3	Microcrystalline cellulose (Avicel PH 102)	105.00
81.00	4	Maize starch	81.00
18.00	5	Maize starch, dried	18.00
1.00	6	Colloidal silicone dioxide (Aerosil 200)	1.00
1.00	7	Magnesium stearate	1.00
QS	8	Purified water	QS

Manufacturing Directions

1. Sift risperidone, lactose monohydrate, Avicel PH 102, and a part of the maize starch through a stainless steel 500-μm sieve.
2. Load the sifted powder into a mixer, and mix for 5 minutes.
3. Make a paste with the remaining part of the maize starch in purified water (80–90°C).
4. Knead the powder mix with the starch paste to get the desired granules.
5. Dry the granules in an air-circulating oven to a targeted LOD of not more than 2.5%.
6. Pass the dried granules through a 250-μm sieve into a blending vessel.
7. Lubricate with Aerosil 200, maize starch dried, and magnesium stearate previously sieved through a stainless steel 250-μm sieve. Blend for 1 minute.
8. Compress into tablets to get the labeled amount of risperidone per tablet using specified tools.
9. Coat the tablets using a hypermellose coating. (See Appendix.)

Rofecoxib Tablets (12.5 mg/25 mg/50 mg) Vioxx

Each tablet of Vioxx for oral administration contains 12.5, 25, or 50 mg of rofecoxib and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide.

Rosiglitazone Maleate Tablets (2 mg/4 mg/8 mg) Avandia

Each pentagonal film-coated Tiltab" tablet contains rosiglitazone maleate equivalent to rosiglitazone, 2 mg, 4 mg, or 8 mg, for oral administration. Inactive ingredients are hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol 3000, sodium starch glycolate, titanium dioxide, triacetin, and one or more of the following: synthetic red and yellow iron oxides and talc.

Roxithromycin-Dispersible Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Roxithromycin base	150.00
22.50	2	Crospovidone	22.50
62.50	3	Croscarmellose sodium	62.50
3.80	4	Polysorbate	3.80
666.20	5	Microcrystalline cellulose	666.20
40.00	6	Aspartame	40.00
20.00	7	Saccharin sodium	20.00
20.00	8	Mint flavor	20.00
5.00	9	Colloidal silica	5.00
10.00	10	Magnesium stearate	10.00

Roxithromycin-Dispersible Tablets (200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Roxithromycin	200.00
30.00	2	Ethylcellulose	30.00
12.80	3	Sodium croscarmellose	12.80
0.27	4	Isopropyl alcohol	270.00 mL
130.00	5	Dicalcium phosphate	130.00
4.40	6	Sodium lauryl sulfate	4.40
320.00	7	Starch (maize)	320.00
4.00	8	Magnesium stearate	4.00
4.00	9	Talc	4.00
28.00	10	Sodium starch glycolate	28.00
8.00	11	Aerosil 200	8.00
24.00	12	Aspartame	24.00
24.00	13	Flavor	24.00
–	14	Water, purified	QS

Manufacturing Directions

1. Sift items 1, 3, and 5 through a 250-μm sieve into a suitable mixing vessel.
2. In a separate vessel, add and mix items 2 and 4.
3. Add the binding solution in step 2 to step 1, and mix until a suitable mass is formed.
4. Pass the wet mass through a 2.38-mm sieve, and dry the granules in a dehumidified room.
5. Pass the dried granules through a 595-μm sieve into a blending vessel.
6. Pass items 6 and 7 through a 250-μm sieve into a blender, and mix for 15 minutes.
7. Prepare the paste with a portion of item 7 in hot water, and add to step 6. Mix until a proper mass is formed.
8. Dry the granules at 50°C overnight, and pass the dried granules through 595-μm sieve.
9. Lubricate the two granules mixed together with items 8 to 13.
10. Compress into 150-mg tablets, using 8-mm punches.
11. Coat using HPMC coating. (See Appendix.)

Saccharin Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Saccharin sodium	15.00
10.00	2	Tartaric acid	10.00
14.00	3	Sodium bicarbonate	14.00
2.00	4	Kollidon® VA 64	2.00
2.00	5	PEG-6000 (powder)	2.00

Manufacturing Directions

1. Dry saccharin sodium and tartaric acid for 1 hour at 100°C.
2. Mix all components, pass through an 0.8-mm sieve, and press with low compressive force.
3. Compress into 42-mg tablets, using 5-mm biplanar punches.

Saccharin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
37.50	1	Sodium cyclamate	37.50
17.00	2	Mannitol	17.00
6.35	3	Soda ash (light-milled powder, 58% Na_2O)	6.35
3.75	4	Saccharin sodium (dihydrated powder)	3.75
1.40	5	Povidone (PVP K-29–32)	1.40
8.00	6	Purified water	8.00
11.00	7	Tartaric acid	11.00
0.80	8	Soda ash (light-milled powder, 58% Na_2O)	0.80
1.00	9	Anhydrous sodium citrate	1.00
1.00	10	Sodium benzoate	1.00
0.20	11	PEG-8000	0.20

Manufacturing Directions

1. This product is hygroscopic and should be processed in a low-humidity area not exceeding 50% relative humidity at 24°C.
2. Maintain at 35% to 40% relative humidity at 24°C if possible.
3. If necessary, pass sodium cyclamate and mannitol (if used) through a FitzMill or similar type using a 420-μm or similar screen, then charge into a suitable mixer.
4. To this mixture, add soda ash (item 3) and blend for 30 minutes or until uniform.
5. Dissolve Povidone in 4 mL of warm purified water.
6. Dissolve saccharin sodium in 3 mL of warm purified water.
7. Add solutions from previous steps together plus sufficient purified water.
8. Mass with blended powders.
9. Blend for 1 hour or until uniform.
10. Pass the wet mass through a 4.76-mm or similar screen in an oscillating granulator, and spread onto trays.
11. Oven dry at 50°C to 55°C for 16 to 24 hours using a full oven load of trays (LOD NMT 0.9%).
12. Pass dried granulation through a 1.19-mm or similar screen in an oscillating granulator or through a 1.68-mm or similar screen using a comminuting mill (knives forward, slow speed).
13. Lubricants must meet LOD/moisture content before proceeding.
14. If lubricants fail, dry them at 80°C for 8 hours.
15. Use 60°C for tartaric acid.
16. Mill lubricants (except tartaric acid and granulated lactose, if used) through a 600-μm or similar screen in a comminuting mill (hammers forward, medium speed).
17. Load dried granulation, coated tartaric acid, lactose (if used), and milled lubricants into a suitable mixer and blend for 30 to 40 minutes.
18. Compress into 80-mg tablets, using 7/32-in. punches.

Saccharin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Saccharin sodium	15.00
31.00	2	Ludipress®	31.00
2.00	3	Kollidon® CL	2.00
0.30	4	Magnesium stearate	0.30
2.00	5	PEG-6000 (powder)	2.00
2.00	6	Lutrol F 68	2.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium-compression force.
2. Compress into 51-mg tablets (or 50 mg if items 5 and 6 are omitted), using 5-mm punches.

Salbutamol Tablets (2 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.00	1	Salbutamol, use as salbutamol sulfate	2.40
80.00	2	Lactose monohydrate	80.00
33.60	3	Starch (maize)	33.60
3.30	4	Starch (maize)	3.30
0.10	5	FD&C Yellow No. 6	0.10
0.60	6	Magnesium stearate	0.60
–	7	Purified water	28.00

Manufacturing Directions

Note: The binding solution is susceptible to microbial growth, and so prepare the solution directly before use.

1. Sift item 4 through a 250-μm sieve using a sifter.
2. Manually make a homogeneous slurry of item 4 in 4 g of cold item 7 (25–30°C) in a stainless steel container. Check that it is free of lumps.
3. Add item 5 and the slurry of the starch paste (from step 2) into 24 g of item 7, heated to 85°C into a Giusti vessel. Stir until there is complete gelatinization. Cool to 50°C.
4. Sift items 1, 3, and 2 through a 630-μm sieve using a sifter. Collect in a stainless steel container.
5. Load sieved powders in the mixer. Mix for 15 minutes at high speed.
6. Add starch paste from step 4 to the mixer. Mix this for 10 minutes.
7. Pass the wet mass through a FitzMill using sieve no. 24205 at medium speed, knives forward.
8. Spread the wet granules onto the trays. Load the trolleys into the oven. Dry the granules at 55°C for 10 hours. Scoop the granules after 4 hours of drying, then put the upper trays to the down position and the down trays to the upper position for uniform drying. Check the moisture content—as a limit, there should not be more than 2.5%.
9. Grind the dried granules through a 1-mm sieve using a granulator. Collect in a stainless steel drum, and load to the blender. Sift item 6 through a 250-μm sieve using a sifter. Collect in a polythene bag. Mix 2 g of granules with this, and add to the blender. Mix this for 1 minute.
10. Compress the granules. The weight of 10 tablets is 1.20 g ± 3%; hardness is not less than 2 kPa.

Salbutamol Tablets (4 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4.00	1	Salbutamol, use as salbutamol sulfate	4.80
80.00	2	Lactose monohydrate	80.00
31.28	3	Starch (maize)	31.28
3.30	4	Starch (maize)	3.30
0.02	5	Red FD&C No. 3	0.02
0.60	6	Magnesium stearate	0.60
–	7	Purified water	28.00

Manufacturing Directions

See the manufacturing directions for the 2.0-mg strength.

Scopolamine Tablets

Manufacturing Directions

1. To 0.2 g of scopolamine hydrobromide, 29.4 g of calcium hydrogenphosphate (anhydrous) is added in small portions and well mixed in a mortar to form a triturate.
2. Triturate (29.6 g) is well mixed with fumaric acid (60 g) and calcium stearate (0.4 g) in a polyethylene bag to form a mixed powder A.
3. 25 g of fumaric acid, 9.8 g of potassium hydrogenphosphate (anhydrous), and 0.2 g of calcium stearate are intimately mixed in a polyethylene bag to make a mixed powder B.
4. To 0.1 g of scopolamine hydrobromide, 10 g of crystalline cellulose is added in small portions and mixed well in a mortar to make a triturate.
5. This triturate (10.1 g) is mixed well with 24.7 g of lactose and 0.2 g of calcium stearate in a polyethylene bag to make a mixed powder C.
6. Multilayer tabletting is performed on a single-punch machine equipped with a die (8 mm) and flat-faced punches: first, 90 mg of the mixed powder A is placed in the die and precompressed lightly; 35 mg of the mixed powder B is placed on the first fill and lightly precompressed; thereafter, 35 mg of the mixed powder C is placed on the second fill and compressed with a total pressure of about 1.2 tons.

Selegiline Tablets (5 mg)

Formulation: Selegiline HCI (BASF), 5 g; Ludipress, 94 g; Magnesium stearate, 1 g;

Manufacturing Directions

Mix all components intensively, pass through a 0.8-mm sieve and press with low-compression force at 99 mg.

Selegiline Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Selegiline	5.00
94.00	2	Ludipress®	94.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components intensively, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress into 99-mg tablets, using 6-mm biplanar punches.

Serratiopeptidase Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Serratiopeptidase	10.00
228.00	2	Ludipress	228.00
2.00	3	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix intensively, and press with low-compaction force (6 kN).
2. Compress into 238-mg tablets, using 8-mm biplanar punches.

Serratiopeptidase Tablets (10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Serratiopeptidase, 40% excess	14.00
70.00	2	Lactose monohydrate	70.00
50.00	3	Microcrystalline cellulose potassium	50.00
80.00	4	Starch (maize)	80.00
–	5	Isopropyl alcohol	100 mL
2.50	6	Magnesium stearate	2.50
5.00	7	Talc	5.00

Manufacturing Directions

1. Charge items 2 to 4 in a suitable vessel. Mix these items for 5 minutes.
2. Add item 5 and granulate the mass. Pass it through a 2.38-mm sieve onto paper-lined trays.
3. Dry the granules in a dehumidified area overnight.
4. Pass the granules through #18 mesh into a blending vessel.
5. Add item 1 to step 4, and mix well.
6. Sift items 6 and 7 through a 250-µm sieve, and add to step 5.
7. Compress into 225-mg tablets, using 7-mm punches.
8. Coat with HPMC organic coating. (See Appendix.)

Serratiopeptidase Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Serratio peptidase	10.00
228.00	2	Ludipress®	228.00
2.00	3	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix intensively, and press with low compressive force (6 kN).
2. Compress into 238-mg tablets, using 8-mm biplanar punches.

Sertraline Hydrochloride Tablets (25 mg/50 mg/ 100 mg) Zoloft

Zoloft is supplied for oral administration as scored tablets containing sertraline hydrochloride equivalent to 25, 50, and 100 mg and the following inactive ingredients: dibasic calcium phosphate dihydrate, D&C Yellow No. 10 Aluminum Lake (in the 25-mg tablet), FD&C Blue No. 1 Aluminum Lake (in the 25-mg tablet), FD&C Red No. 40 Aluminum Lake (in the 25-mg tablet), FD&C Blue No. 2 Aluminum Lake (in the 50-mg tablet), hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, synthetic Yellow iron oxide (in the 100-mg tablet), and titanium dioxide.

Sertraline L-Lactate Osmotic Tablet

Manufacturing Directions

1. Tablet cores comprising sertraline L-lactate (13.8 wt%), L-aspartic acid (11 wt%), calcium acetate (5 wt%), microcrystalline cellulose (29.5 wt%), and fructose (38.2 wt%) are blended, then run through a roller compactor and milled.
2. This milled material is then blended wish 2.5 wt% magnesium stearate to form the final blended material that is used to make tablets having a total weight of 470 mg on a conventional tablet press.
3. Semipermeable asymmetric membrane coatings comprised 10 wt% cellulose acetate 398-10, 2.5 wt% polyethylene glycol 3350, 15 wt% water, and 72.5 wt% acetone.
4. The coating solution is spray-coated onto the tablets at a rate of 20 g/min until a 10 wt% coating level on the tablets had been achieved.

Sertraline Hydrochloride Tablets (25 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
27.98	1	Sertraline hydrochloride equivalent to Sertraline 25.00 mg	27.98
52.52	2	Dibasic calcium phosphate dihydrate, DC Grade	52.52
15.00	3	Microcrystalline cellulose (Avicel PH102)	15.00
3.00	4	Sodium starch glycolate	3.00
0.50	5	Hydroxypropyl cellulose	0.50
1.00	6	Magnesium stearate	1.00
2.00	7	Hypromellose	2.00
0.40	8	Polyethylene glycol 4000	0.40
0.20	9	Polysorbate 80	0.20
0.60	10	Titanium dioxide	0.60
0.20	11	D & C Yellow #10 aluminum lake	0.20
0.30	12	FD & C Blue #1 aluminum lake	0.30
–	13	Water, purified	30.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and charge in a tumbler.
2. Pass items 1, 4, and 5 through 0.5-mm sieve and add to step 1.
3. Pass item 3 through 0.7-mm sieve and charge to step 1.
4. Mix step 1 for 20 minutes using tumbler.
5. Pass item 6 through 0.250-mm sieve and add to step 4.
6. Mix step 5 for 2 minutes.
7. Compress into 100-mg tablets, using a suitable punch (5.0 mm, round).
8. Charge item 13 in a stainless steel vessel. Add item 7 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hypromellose.
9. Add items 8 to 12 to step 8 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
10. Load core tablets from step 7 in coating pan and apply coating dispersion from step 9 to get 2.5% to 3.0% weight gain.

Sertraline Hydrochloride Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
55.96	1	Sertraline hydrochloride equivalent to Sertraline 50.00 mg	55.96
105.04	2	Dibasic calcium phosphate dihydrate, DC grade	105.04
30.00	3	Microcrystalline cellulose (Avicel PH102)	30.00
6.00	4	sodium starch glycolate	6.00
1.00	5	Hydroxypropyl cellulose	1.00
2.00	6	Magnesium stearate	2.00
4.00	7	Hypromellose	4.00
0.80	8	Polyethylene glycol 4000	0.80
0.30	9	Polysorbate 80	0.30
1.20	10	Titanium dioxide	1.20
0.40	11	FD & C Red #40 aluminum lake	0.40
0.60	12	FD & C Blue #2 aluminum lake	0.60
–	13	Water, purified	60.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and charge in a tumbler.
2. Pass items 1, 4, and 5 through 0.5-mm sieve and add to step 1.
3. Pass item 3 through 0.7-mm sieve and charge to step 1.
4. Mix step 1 for 20 minutes using tumbler.
5. Pass item 6 through 0.250-mm sieve and add to step 4.
6. Mix step 5 for 2 minutes.
7. Compress into 200-mg tablets, using a suitable punch (6.5 mm × 10 mm, oblong).
8. Charge item 13 in a stainless steel vessel. Add item 7 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hypromellose.
9. Add items 8 to 12 to step 8 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
10. Load core tablets from step 7 in coating pan and apply coating dispersion from step 9 to get 2.5% to 3.0% weight gain.

Sertraline Hydrochloride Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
111.92	1	Sertraline hydrochloride equivalent to Sertraline 100.00 mg	111.92
110.08	2	Dibasic calcium phosphate dihydrate, DC grade	110.08
60.00	3	Microcrystalline cellulose (Avicel PH102)	60.00
12.00	4	sodium starch glycolate	12.00
2.00	5	Hydroxypropyl cellulose	2.00
4.00	6	Magnesium stearate	4.00
6.00	7	Hypromellose	6.00
1.20	8	Polyethylene glycol 4000	1.20
0.40	9	Polysorbate 80	0.40
1.80	10	Titanium dioxide	1.80
0.20	11	Yellow iron oxide	0.20
–	12	Water, purified	90.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and charge in a tumbler.
2. Pass items 1, 4, and items 5 through 0.5-mm sieve and add to step 1.
3. Pass item 3 through 0.7-mm sieve and charge to step 1.
4. Mix step 1 for 20 minutes using tumbler.
5. Pass item 6 through 0.250-mm sieve and add to step 4.
6. Mix step 5 for 2 minutes.
7. Compress into 300-mg tablets, using a suitable punch (10 mm, round).
8. Charge item 12 in a stainless steel vessel. Add item 7 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3% to 4 hours for saturation of hypromellose.
9. Add items 8 to item 11 to step 8 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
10. Load core tablets from step 7 in coating pan and apply coating dispersion from step 9 to get 2.5% to 3.0% weight gain.

Sildenafil Tablets (25 mg/50 mg/100 mg), Viagra

Viagra is formulated as blue, film-coated, rounded-diamond-shaped tablets equivalent to 25, 50, and 100 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, lactose, triacetin, and FD&C Blue No. 2 Aluminum Lake.

Sildenafil Citrate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Sildenafil, use sildenafil citrate	70.50
100.00	2	Avicel PH 102	100.00
131.00	3	Dibasic calcium phosphate anhydrous	131.00
9.00	4	Ac-Di-Sol	9.00
1.00	5	Aerosil 200	1.00
1.50	6	Magnesium stearate	3.50

Manufacturing Directions

1. Charge items 1 and 2 in a suitable blender or plastic bag after sifting through a 500-μm sieve. Mix them for 5 minutes.
2. Add item 3 to step 1 after sifting through a 500-μm sieve. Mix for 5 minutes.
3. Add items 4 to 6 after sifting them through a 500-μm sieve (item 6 through a 250-μm sieve). Blend this for 1 minute.
4. Compress into 315-mg tablets, using diamond-shaped 13.2 × 8.2-mm punches.
5. Coat using an HPMC coating. (See Appendix). Use dispersed Blue E, 132 1.4 mg/tab, to match the color of Viagra. Following is a proposed formulation of coating solution:

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4.00	1	Hypermellose	4.00
0.80	2	Triacetin	0.80
1.22	3	Talc	1.22
2.60	4	Titanium dioxide	2.60
0.46	5	Lactose monohydrate	0.46
1.41	6	Dispersed blue E112	1.41
0.40	7	Opadry OY-LS 29019 clear	0.40
QS	8	Water, purified	QS

Silimarin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
35.50	1	Silimarin	35.50
410.50	2	Ludipress®	410.50
4.50	3	Magnesium stearate	4.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force (about 10 kN).
2. Compress into 458-mg tablets, using 12-mm biplanar punches.

Silimarin Tablets (35 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
35.00	1	Silimarin	35.50
410.50	2	Ludipress	410.50
4.50	3	Magnesium stearate	4.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low-compression force (about 10 kN).
2. Compress into 458-mg tablets, using 12-mm biplanar punches.

Simethicone and Magnesium Carbonate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
16.00	1	Dextrose Monohydrate, USP25.0 kg	16.00
0.16	2	Yellow #10 D&C Dye Lake 250 g	0.16
0.06	3	Blue #1 FD&C Dye Lake 90.0 g	0.06
80.00	4	Simethicone Pwd GS (30%) 417 kg	266.40
64.00, 266.4	5	Magnesium Carbonate 100 kg	64.00, 266.4
128.00	6	Microcryst Cellulose 200 kg	128.00
175.68	7	Dextrates 275 kg	175.68
5.00	8	Stearic Acid 8.00 kg	5.00

Manufacturing Directions

1. Simethicone mix is processed by preblending magnesium carbonate and simethicone powder GS 30% in a V-blender.
2. This preblended mix is then dry granulated and placed in a V-shell blender.
3. Dextrates and microcrystalline cellulose are then added to the preblended mix in the V-shell blender and the preblended mix, dextrates and microcrystalline cellulose are blended for approximately 10 minutes.
4. Blue #1 FD&C dye lake, yellow #10 D&C dye lake and dextrose are combined in a drum roller, dry granulated and then placed in the V-shell blender with the preblended mix, dextrates and microcrystalline cellulose.
5. An additional amount of dextrose is dry granulated in the same granulator that the colorants are granulated in, for the purpose of rinsing the granulator after the dry granulation of the colorants.
6. This amount of dextrose is also added to the V-shell blender.
7. An amount of stearic acid is then passed through a 30-mesh screen and added to the V-shell blender.
8. The preblended mix, dextrates, microcrystalline cellulose, colorants, dextrose and stearic acid are then blended in the V-shell blender for 3 minutes.
9. A sample of the V-shell blender mix is then measured to test blend uniformity.
10. Upon meeting satisfactory blend uniformity requirements, the simethicone layer mix is transferred to tote bins and then compressed into 650 mg tablets.

Simethicone Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
70.00	1	Simethicone dry powder 25%	280.00
158.00	2	Sucrose, powder	158.00
7.00	3	Kollidon® 90F	7.00
3.50	4	Kollidon® 90F	3.50
QS	5	Isopropanol	QS
2.80	6	Aerosil® 200	2.80

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with solution of items 4 and 5, dry, pass through a 0.8-mm sieve, add item 6, mix thoroughly, and press with high compressive force.
2. Compress into 442-mg tablets, using 12-mm biplanar punches.

Simethicone Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
80.00	1	Simethicone (Wacker silicon oil, S184)	80.00
400.00	2	Sorbitol, (crystalline)	400.00
20.00	3	Aerosil® 200	20.00
390.00	4	Ludipress®	390.00
2.00	5	Menthol (powder)	2.00
8.00	6	Magnesium stearate	8.00

Manufacturing Directions

1. Mix items 2 and 3 with item 1, pass through a 0.8-mm sieve, add mixture of items 4 to 6, mix thoroughly, pass again through a 0.8-mm sieve, and press with high compressive force.
2. Compress into 870-mg tablets, using 16-mm biplanar punches.

Simethicone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
70.00	1	Simethicone	70.00
71.40	2	Microcrystalline cellulose	71.40
71.40	3	Magnesium hydroxide	71.40
265.00	4	Mannitol	265.00
100.00	5	Lactose	100.00
395.10	6	Granular sugar	395.10
0.70	7	Menthol	0.70
10.00	8	Fumed silica	10.00
5.00	9	Fumed silica	5.00
10.00	10	Magnesium stearate	10.00

Manufacturing Directions

1. Blend item 2 and item 3 in a V-blender for 10 minutes.
2. Transfer to planetary mixer.
3. Slowly add weighted amount of item 1 to the mix, and mix slowly using a "B" flat beater blade; after thorough mixing, pass through a #20-mesh screen.
4. Add the balance of the ingredients, mix, and compress.

Simvastatin Fast-Melt Tablet

Manufacturing Directions

1. Mix simvastatin 15%, sodium bicarbonate 25%, citric acid anhydrous 25%, xylitol 12%, microcrystalline cellulose 15%, anhydrous lactose 6%, and crodesta F160 2%.
2. Dry the above ingredients at elevated temperature in the presence of a desiccant to significantly reduce the moisture content of each material.
3. Blend for 10 minutes and extrude in a hot melt extruder at 70°C to 100°C to soften and melt the thermal binders (sucrose stearate and xylitol) and to form granules containing the effervescent ingredients.
4. Mix SV-EGF (30–80 mesh), 45%; Avicel PH113, 31%; Mannogen 3215, 15%; L-HPC LH-11, 5%; aspartame, 3%; redberry flavor, 0.25%; natural orange powder, 0.15%; magnesium stearate, 0.5%; fumed silicon dioxide, 0.1%.
5. Blend for 5 minutes prior to compression.
6. Simvastatin tablets are then compressed to a hardness of approximately 1 to 5 kPa (depending upon the dose of the drug) and tablets disintegrate in water in approximately 15 to 35 seconds.

Simvastatin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Simvastatin	10.10
55.23	2	Lactose monohydrate	55.23
15.000	3	Pregelatinized starch (Starch 1500)	15.00
0.02	4	Butylated hydroxy anisole	0.02
2.50	5	Ascorbic acid	2.50
1.25	6	Citric acid	1.25
15.00	7	Microcrystalline cellulose (Avicel PH 102)	15.00
0.60	8	Magnesium stearate	0.60
0.30	9	Colloidal silicon dioxide (Aerosil 200)	0.30
–	10	Purified water	12.00
–	11	Absolute alcohol (ethanol, dehydrated alcohol)	5.00

Manufacturing Directions

Note: Avoid overmixing lubricants, or hardness may be reduced.

1. Preparation of granulating solution
   a. Make a clear solution of item 4 in item 11 by slow stirring.
   b. Dissolve items 5 and 6 in item 10 under slow stirring by a stirrer.
2. Dry powder mixing: Sift items 1, 2, and 3 through a stainless steel 500-μm sieve in a sifter. Load into the mixer, and mix for 3 minutes at low speed.
3. Kneading
   a. Add a binding solution, 25 to 31 g/min, to the dry powders while mixing at low speed. After the addition is over, scrape the sides and blades. Mix further for 2 minutes using a mixer and chopper at low speed. Scrape sides and blades. Check for the end point of granulation. (End point of the granulation is the point when the wet mass consists of little or no lumps of granule.)
   b. If required, add purified water. Record the extra quantity of purified water added. Unload the wet granules onto stainless steel trays for drying.
4. Drying
   a. Dry the wet granules in an oven at 55°C for 6 hours. After 3 hours of drying, scrape the semidried granules to break the lumps for uniform drying.
   b. Check the LOD, with a limit of 1.0% to 1.5%.
   c. If required, dry further at 55°C for 1 hour. Check the LOD. Transfer the dried granules in a stainless steel drum.
5. Grinding: Grind the dried granules through a 1.25-mm sieve. Collect in a polyethylene bag.
6. Lubrication
   a. Sift items 7 and 9 through a 500-μm sieve, and add this to the double polyethylene bag used in step 5a. Mix manually for 1 minute.
   b. Sift item 8 through a 500-μm sieve. Add 6 to 12 g granules from bulk (step 5). Mix in a polythene bag for 1 minute. Add this mixture to the polyethylene bag in step 5. Mix manually for 30 seconds. Add the two loads in the polyethylene bag, and mix manually for 15 seconds.
   c. Unload into stainless steel drums.
7. Compression: Compress the granules using a rotary tabletting machine. The dimension should be 8.5 mm × 5-mm oval punches; 100 mg per tablet should be compressed.
8. Coating: Coat the tablets using an HPMC coating. (See Appendix.)

Simvastatin Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Simvastatin	20.200
110.460	2	Lactose monohydrate	110.460
30.000	3	Pregelatinized starch (Starch 1500)	30.000
0.040	4	Butylated hydroxy anisol	0.040
5.000	5	Ascorbic acid	5.000
2.500	6	Citric acid	2.500
30.000	7	Microcrystalline cellulose (Avicel PH 102)	30.000
1.200	8	Magnesium stearate	1.200
0.600	9	Colloidal silicon dioxide (Aerosil 200)	0.600
–	10	Purified water	24.000
–	11	Absolute alcohol (ethanol, dehydrated alcohol)	10.000

Simvastatin Tablets (10 mg) Zocor

Zocor® tablets for oral administration contain 5, 10, 20, 40, or 80 mg of simvastatin and the following inactive ingredients: cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, lactose, magnesium stearate, starch, talc, titanium dioxide, and other ingredients. Butylated hydroxyanisole is added as a preservative.

Sodium Fluoride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.50	1	Sodium fluoride	0.55
56.25	2	Sorbitol, crystalline	56.25
56.25	3	Dicalcium phosphate	56.25
2.20	4	Kollidon® VA 64	2.20
0.50	5	Magnesium stearate	0.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with high compressive force.
2. Compress into 116-mg tablets, using 6-mm biplanar punches.
3. If the content uniformity is not sufficient, a premix of sodium fluoride and sorbitol or dicalcium phosphate should be prepared separately before mixing with the rest of the excipients.

Sodium Fluoride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.30	1	Sodium fluoride	1.30
76.70	2	Ludipress®	76.70
0.40	3	Magnesium stearate	0.40

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress into 78-mg tablets, using 5-mm biplanar punches.
3. If the content uniformity does not meet the requirements, prepare a premix of the active ingredient with a small part of Ludipress® or with lactose monohydrate before mixing with the other components of the formulation.

Sotalol Hydrochloride Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Sotalol hydrochloride	500.00
100.00	2	Microcrystalline cellulose or lactose anhydrous	100.00
80.00	3	Starch maize	80.00
30.00	4	Sodium starch glycolate	30.00
4.00	5	Magnesium stearate	4.00
4.00	6	Silicon dioxide colloidal	4.00
QS	7	Dyes	QS
—	8	Water, purified	QS

Manufacturing Directions

1. Charge items 1 to 3 in a granulating bowl, and mix for 20 minutes. (*Note:* For item 2, a choice of using cellulose or lactose, or a combination thereof, is available.)
2. Add a sufficient quantity of item 8 to form a wet mass.
3. Pass the wet mass in step 2 through #8 mesh onto paper-lined trays. Dry at 60°C for 12 hours to achieve an LOD of less than 5%.
4. Pass the dried granules through 16 or 20 mesh, and transfer to a blending vessel.
5. Add items 4 to 7, and blend for 5 minutes.
6. Compress an appropriate amount in a suitable punch.

Spiramycin-Dispersible Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
750.00	1	Spiramycin base	750.00
45.00	2	Crospovidone	45.00
85.00	3	Croscarmellose sodium	85.00
7.50	4	Polysorbate	7.50
762.50	5	Microcrystalline cellulose	762.50
160.00	6	Aspartame	160.00
80.00	7	Saccharin sodium	80.00
80.00	8	Mint flavor	80.00
10.00	9	Colloidal silica	10.00
20.00	10	Magnesium stearate	20.00

Spironolactone Tablets (25 mg/50 mg/100 mg) Aldactone

Aldactone oral tablets contain 25, 50, or 100 mg of spironolactone. Inactive ingredients include calcium sulfate, cornstarch, flavor, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, polyethylene glycol, povidone, and titanium dioxide.

Spironolactone Tablets

Bill of Materials			
Scale(mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Spironolactone	25.00
175.00	2	Ludipress	175.00
1.50	3	Magnesium stearate	1.50

Manufacturing Directions

1. Mix all components.
2. Pass the mixture through a sieve, and press with medium-compression force.
3. Compress into 197-mg tablets, using 8-mm biplanar punches.

Spirulina Extract Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Spirulina extract (powder)	250.00
245.00	2	Ludipress®	245.00
25.00	3	PEG-6000 (powder)	25.00
5.00	4	Aerosil® 200	5.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium compressive force.
2. Compress into 495-mg tablets, using 12-mm biplanar punches.

Sucralfate and Sodium Alginate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Sucralfate	500.00
20.00	2	Sodium alginate	20.00
70.00	3	Cornstarch	70.00
20.00	4	Kollidon® 30	20.00
–	5	Ethanol (95%)	80.00 mL
30.00	6	Kollidon® CL	30.00
3.00	7	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with solution of items 4 and 5, pass through a sieve, mix the dry granules with items 6 and 7, and press with low compressive force.
2. Compress into 660-mg tablets, using 12-mm biplanar punches.

Sulfadimidine Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Sulfadimidine	500.00
100.00	2	Lactose monohydrate	100.00
15.00	3	Kollidon 30	15.00
–	4	Water, purified, ca	200.00
25.00	5	Kollidon CL	25.00
2.40	6	Talc	2.40
0.30	7	Aerosil 200	0.30
0.30	8	Calcium arachinate	0.30

Manufacturing Directions

1. Granulate the mixture of items 1 and 2 with the solution of items 3 and 4. Dry, pass through a 0.8-mm sieve, mix with items 5 to 8, and press.
2. Compress into 610-mg tablets, using 12-mm biplanar punches.

Sulfamethoxazole and Trimethoprim Tablets (400 mg/80 mg; 800 mg/160 mg; 100 mg/20 mg)

Each DS tablet contains 160 mg of trimethoprim and 800 mg of sulfamethoxazole plus magnesium stearate, pregelatinized starch, and sodium starch glycolate. Each tablet contains 80 mg of trimethoprim and 400 mg of sulfamethoxazole, plus magnesium stearate, pregelatinized starch, sodium starch glycolate, FD&C Blue No. 1 Lake, FD&C Yellow No. 6 Lake, and D&C Yellow No. 10 Lake. Each teaspoonful (5 mL) of the pediatric suspension or suspension contains 40 mg of trimethoprim and 200 mg of sulfamethoxazole in a vehicle containing 0.3% alcohol, edetate disodium, glycerin, microcrystalline cellulose, parabens (methyl and propyl), polysorbate 80, saccharin sodium, simethicone, sorbitol, sucrose, FD&C Yellow No. 6, FD&C Red No. 40, flavors, and water.

Sulfamethoxazole and Trimethoprim Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
800.00	1	Sulfamethoxazole	800.00
160.00	2	Trimethoprim	160.00
70.00	3	Starch (corn)	70.00
5.00	4	Alginic acid	5.00
–	5	Water, purified, ca	320.00 mL
5.00	6	Magnesium stearate	5.00

Manufacturing Directions

1. Granulation
   a. Pass the following ingredients through a 595-µm aperture screen: sulfamethoxazole, trimethoprim, and starch (corn), and charge into a suitable blender. Blend for approximately 20 minutes.
   b. Add and dissolve alginic acid (60°C) and purified water. Cool the solution to 35°C.
   c. Add the solution from step 1b to blended powders, and blend until a suitable granulating mass is obtained. Add more purified water if needed.
   d. Pass the granulating mass through a 2.38-mm aperture screen.
   e. Oven dry the wet granules at 45°C for 16 hours until the LOD is not more than 0.9% (105°C for 1 hour).
2. Lubrication
   a. Pass the dried granulate through a 1.2-mm aperture screen on an oscillating granulator, and charge into a suitable blender.
   b. Add magnesium stearate, and mix well for approximately 10 minutes.
3. Compression
   a. Compress using a 19-mm caplet punch. The weight of 10 tablets is 10.4 g; the thickness is 7.4 to 8.2 mm; and the hardness is 14 to 22 kPa units.
   b. For 400/80 tablets, use an 11.5-mm diameter flat, beveled edge punch. The weight of 10 tablets is 5.20 g; the thickness is 4.2 to 4.6 mm; and the hardness is 13 to 24 kPa.
   c. For 100/20 tablets, use 7.5-mm diameter beveled edge punch. The weight of 10 tablets is 1.2 g; the thickness is 2.4 to 2.7 mm; and the hardness is 6 to 12 kPa.

Sulfamethoxazole and Trimethoprim Tablets (400 mg/80 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Sulfamethoxazole	400.00
80.00	2	Trimethoprim	80.00
15.00	3	Kollidon 30	15.00
–	4	Isopropyl alcohol	QS
24.00	5	Kollidon CL	24.00
2.00	6	Talc	2.00
8.00	7	Magnesium stearate	8.00

Manufacturing Directions

1. Granulate a mixture of items 1 and 2 with a solution of items 3 and 4. Pass this through a 0.8-mm sieve, dry, add items 5 to 7, and press with low-compression force.
2. Compress into 546-mg tablets, using 12-mm biplanar punches.

Sulfamethoxazole and Trimethoprim Tablets (800 mg/160 mg; 400 mg/80 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/500000 Tablets (kg)
800.00	1	Sulfamethoxazole	800.00
160.00	2	Trimethoprim	160.00
20.00	3	Povidone K30	20.00
24.20	4	Primojel (sodium carboxymethyl starch)	24.20
5.00	5	Magnesium stearate	5.00
0.20	6	Dioctyl sodium sulfosuccinate	0.20

Manufacturing Directions

1. First prepare the PVP solution sufficient for the above batch divided into four lots.
2. In a suitable stainless steel container, take 30 kg of deionized water, heat it to 70°C, and add to it while stirring item 4 gradually.
3. After complete dissolution, continue to stir, and add 140 kg of deionized water, item 3. Stir until completely dissolved.
4. Let stand overnight.
5. In a separate container, take one-fourth of items 1 and 2, and mix. Then add, in small portions, the PVP solution made in step 1, 45.1 kg each, until a moist mass with granular lumps is obtained. Pass the granules through a centrifugal granulator using a 10-mm sieve.
6. Spread the granules on trays, and dry at 60°C for 28 hours. The relative humidity should be 15% to 20%.
7. Pass the granules through an oscillating granulator with 2-mm perforations at a rate of 2 to 2.5 kg/min.
8. Charge the granules in a V-type blender from each of the four lots, mix for 5 minutes, and transfer to a drum. Then add item 5 and the balance of Primojel (12.1 kg). Mix in a tumble mixer for 10 minutes.
9. Charge the mixture in a V-blender, and mix for 1 hour. The relative humidity should be 20% to 25%.
10. Compress at 4- to 5-ton pressure. The weight of one tablet is 1.010 mg. This is the formula for a double-strength tablet. Adjust quantities and fill the weight for 400/80 strength.

Sulfamethoxazole and Trimethoprim Tablets, Dispersible (800 mg/160 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
800.00	1	Sulfamethoxazole powder	800.00
160.00	2	Trimethoprim micronized	160.00
80.00	3	Starch (maize)	90.00
3.00	4	Sodium lauryl sulfate	3.00
15.00	5	Gelatin	15.00
25.00	6	Starch (maize)	25.00
8.00	7	Magnesium stearate	8.00
9.00	8	Guar gum	9.00
–	9	Purified water	300.00

Manufacturing Directions

Note: The binding solution is liable to microbiological growth, so prepare the solution fresh, before the granulation process.

1. Preparation of starch paste: Manually make a slurry of item 6 in 40 g of item 9 (40°C). Then add 110 g of item 9 into the vessel, and heat to 80°C. Add the slurry of item 6 to it, and mix until it swells and is translucent.
2. Add item 5 slowly to 150 g of item 9 (70°C) using a stirrer. Avoid lumps and excessive foam formation. Add the gelatin solution to the starch paste in step 1, and mix for 10 minutes.
3. Dry powder mixing: Load items 1, 2, 3, and 4 in the mixer. Mix and chop at high speed for 6 minutes.
4. Wet massing: Add starch paste from step 2 to the dry powders in the mixer, while mixing and chopping at low speed. When the addition is over, mix further for 5 minutes or until a satisfactory mass is obtained. *Note:* Avoid lumps or a ball formation that is too big.
5. Drying
   a. Dry the granules in a fluid-bed dryer at 55°C for 1 hour.
   b. Check the moisture content. The limit is 1% to 1.5%. *Note:* Moisture control is a very important step. It affects the microbial quality of this product.
6. Grinding: Grind the dried granules through a 1.5-mm sieve first, and then through a 1.25-mm sieve fitted on a dry granulator. Collect the granules in a stainless steel drum. Load the granules to the blender.

7. Lubrication
   a. Mix items 7 and 8 in a polythene bag. Pass the mix through a 250-μm sieve using a sifter. Collect in a polythene bag. Add 10 g granules from step 6. Mix for 1 to 2 minutes, add to the blender, and mix for 2 minutes.
   b. Unload into stainless steel drums.
8. Compression: Compress the granules using a rotary tabletting machine with 19 × 8.8-mm oblong punches. Each tablet will be 1100 mg.

Sulfathiazole Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Sulfathiazole	250.00
237.00	2	Lactose monohydrate or dicalcium phosphate	237.00
12.00	3	Kollidon 30	12.00
–	4	Water, purified	QS
12.00	5	Kollidon CL	12.00
2.00	6	Magnesium stearate	2.00

Manufacturing Directions

1. Granulate a mixture of items 1 to 3 with item 4, pass through a 0.8-mm sieve, dry, add items 5 and 6, and press with low-compression force.
2. Compress into 504-mg tablets (512 mg if using dicalcium phosphate), using 12-mm biplanar punches.

Sumatriptan Succinate Fast-Melt Tablets

Manufacturing Directions

1. Mix sumatriptan succinate 15%, sodium bicarbonate 27%, citric acid anhydrous 26%, microcrystalline cellulose 11%, anhydrous lactose 9%, xylitol 10%, and sucrose stearate 2%.
2. The above ingredients are dried at elevated temperatures to significantly reduce the moisture content of the materials.
3. Blend for approximately 10 minutes and extruded in a hot melt extruder at 70°C to 100°C to soften and melt the thermal binders (sucrose stearate and xylitol) and to form granules containing the effervescent ingredients.
4. Mix SS-EGF (30–60 mesh) 50%, microcrystalline cellulose 31%, Mannitol 10%, L-HPC LH-11 5%, aspartame 3%, redberry flavor 0.3%, natural orange powder 0.1%, magnesium stearate 0.5%, and fumed silicon dioxide 0.1%.
5. Screen and blend for 5 minutes prior to compression.
6. Surnatriptan succinate tablets are then compressed to a hardness of approximately 1 to 5 kPa (depending upon the dose of the active) and tablets disintegrate in water in approximately 15 to 35 seconds.

Sumatriptan Succinate Tablets (25 mg/50 mg) Imitrex

Each Imitrex tablet for oral administration contains 35 or 70 mg of sumatriptan succinate equivalent to 25 or 50 mg of sumatriptan, respectively. Each tablet also contains the inactive ingredients croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, and titanium dioxide dye.

Sumatriptan Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
140.00	1	Sumatriptan, use*	140.00
154.00	2	Lactose monohydrate	154.00
17.00	3	Microcrystalline cellulose	17.00
3.30	4	Sodium croscarmellose	3.30
1.70	5	Magnesium stearate	1.70
–	6	Water, purified, ca	12.50 mL

*For 25 mg strength, use 35 mg of sumatriptan succinate.

Manufacturing Directions

1. Sift items 1 and 2 through a 0.6-mm mesh sieve screen into a fluid-bed granulator.
2. Granulate by spraying item 6 with an inlet temperature of 75°C; allow granules to dry.
3. Pass granules through a granulator fitted with a 0.8-mm mesh screen.
4. Transfer granules to a blender, add item 5, and mix for 5 minutes.
5. Compress about 320 mg in a suitable punch.

Tamoxifen Tablets (10 mg/20 mg), Nolvadex

Nolvadex tablets are available as follows. *10-mg tablets:* each 10-mg tablet contains 15.2 mg of tamoxifen citrate, which is equivalent to 10 mg of tamoxifen; *20-mg tablets:* each 20-mg tablet contains 30.4 mg of tamoxifen citrate, which is equivalent to 20 mg of tamoxifen. The inactive ingredients are carboxymethyl-cellulose calcium, magnesium stearate, mannitol, and starch.

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Tamoxifen, use tamoxifen citrate	15.30
114.50	2	Lactose monohydrate	114.50
38.00	3	Starch (maize)	38.00
3.50	4	PVP K30	3.50
0.75	5	Magnesium stearate	0.75
3.00	6	Ac-Di-Sol	3.00
–	7	Water, purified, ca	30 mL

Manufacturing Directions

1. Charge items 1 to 3 after sifting them through a 500-μm sieve in a suitable mixer. Mix this for 5 minutes at low speed.
2. In a separate vessel, add and dissolve item 4 in item 7 at a slow speed.
3. Add step 2 into step 1, and knead and mix for 5 minutes, and then again, long enough to achieve a suitable wet mass.
4. Dry the wet mass on trays at 55°C for 5 hours to an LOD of not more than 1 to 1.5%. If required, dry for another hour.
5. Pass the dried granules through a 1.25-mm sieve, and transfer to a blender.
6. Add items 5 and 6 (sifted through a 500-μm sieve) to step 5, and blend for 1 minute.
7. Compress into 175-mg tablets, using 8-mm round, plain concave punches. For 20-mg tablet, use appropriate fill weight in 10-mm punches.

Tamsulosin Hydrochloride Buccal Tablets

Directions

1. 80 g of tamsulosin hydrochloride and 80 g of hydroxypropylmethyl cellulose (TC5E) are dissolved in a mixture of 304 g purified water and 2736 g methanol.
2. 4000 g of Celphere 102 (mean particle diameter of approximately 127 μm, particle diameter of approximately 50 to approximately 150 μm) is introduced to a fluidized bed granulator and coated with this solution by the side spraying method (spraying liquid volume 100 g/min, spraying air pressure 4 kg/cm^2, product temperature 40°C, inlet temperature 80°C) to obtain tamsulosin hydrochloride particles.
3. Separately, 533 g of ethyl cellulose and 187 g of hydroxypropylmethyl cellulose (TC5E) are dissolved in a mixture of 698 g purified water and 22582 g methanol.
4. Tamsulosin hydrochloride (4000 g) particles are introduced to a fluidized bed granulator and coated with this solution by side spraying (spraying liquid volume of 40 g/min, spraying air pressure of 4 kg/cm^2, product temperature of 50°C, inlet temperature of 60°C) to obtain sustained-release fine particles.
5. These sustained-release fine particles (4000 g) are introduced to a fluidized bed granulator and coated with a mixture of 2000 g of Aquacoat, 4000 g of Eudragit L30D55, 667 g of Eudragit NE30D, and 6667 g of purified water (spraying liquid volume of 40 g/min, spraying air pressure of 4 kg/cm^2, product temperature of 40°C, inlet temperature of 60°C) to obtain enteric sustained-release fine particles.
6. Then 368 g of these enteric sustained-release fine particles, 2560 g mannitol, and 640 g lactose are granulated (spraying liquid volume 200 g/min, spraying air pressure of 1.5 kg/cm^2, product temperature of 29°C, inlet temperature of 80°C, spraying cycle of 10 seconds spraying to 30 seconds drying) with an aqueous 40% w/w solution containing 400 g maltose in a fluidized bed granulator to obtain the final composition.
7. After further mixing 32 g calcium stearate with the composition that is obtained, 200 mg tablets containing 0.2 mg tamsulosin hydrochloride per tablet are made under a tabletting pressure of 100 kg/punch and an initial hardness of 1.0 kPa using a rotary tabletting machine.
8. Next, these tablets are kept for 18 hours while heating and humidifying at 25°C/75% RH using a thermostatic chamber at constant humidity.
9. Then they are dried for 3 hours at 30°C and 40% RH. The tablets that are obtained showed a hardness of 5.9 kPa ($n = 5$), friability of 0.8% (100 rounds) and disintegration time in the buccal cavity of 20 seconds.

Tannin–Crospovidone Complex Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
55.00	1	Tannic acid	55.00
230.00	2	Water	230.00
230.00	3	Kollidon® CL	230.00
33.00	4	Avicel™ PH101	33.00
2.60	5	Talc	2.60
0.30	6	Aerosil® 200	0.30
0.30	7	Calcium arachinate	0.30

Manufacturing Directions

1. Prepare solution of items 1 and 2, suspend item 3, and filter the formed insoluble tannin–crospovidone complex.
2. Wash with water until the water is clear, pass the solids through a 0.8-mm sieve, and dry.
3. Add items 4 to 7, and press with low compressive force.
4. Compress into 323-mg tablets, using 12-mm biplanar punches.

Tegaserod Maleate Tablets 2 mg

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.77	1	Tegaserod maleate equivalent to Tegaserod 2 mg	2.77
87.73	2	Lactose Spray Dried	87.73
3.00	3	Crospovidone	3.00
5.00	4	Poloxamer	5.00
0.50	5	Hypromellose	0.50
1.00	6	Glyceryl behenate	1.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass item 1, item 4 and item 5 through 0.5-mm sieve and collect in a stainless steel container and mix well.
4. Add 5% (=2.2 g) powder from step 1 to step 3 and mix well.
5. Add 15% (=6.6 g) powder from step 1 to step 4 and mix well.
6. Transfer step 5 into step 2.
7. Pass item 3 through 0.5-mm sieve and add to step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 6 through 0.250-mm sieve and charge in step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 100-mg tablets, using a suitable punch (5.5 mm, round).

Tegaserod Maleate Tablets 6 mg

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
8.31	1	Tegaserod maleate equivalent to Tegaserod 2 mg	8.31
127.44	2	Lactose spray dried	127.44
4.50	3	Crospovidone	4.50
7.50	4	Poloxamer 188	7.50
0.75	5	Hypromellose	0.75
1.50	6	Glyceryl behenate	1.50

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 4, and 5 through 0.5-mm sieve and collect in a stainless steel container and mix well.
4. Add 10% (=6.3 g) powder from step 1 to step 3 and mix well.
5. Transfer step 4 into step 2.
6. Pass item 3 through 0.5-mm sieve and add to step 2.
7. Transfer balance quantity of step 1 into step 2.
8. Mix step 2 for 20 minutes using tumbler.
9. Pass item 6 through 0.250-mm sieve and add to step 8.
10. Mix step 9 for 2 minutes.
11. Compress into 150-mg tablets, using a suitable punch (5.5 mm × 7.0 mm, modified oval).

Temafloxacin Hydrochloride Tablets (200 mg/300 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Temafloxacin hydrochloride, excess 10%	220.00
112.50	2	Lactose monohydrate	112.50
40.00	3	Sodium starch glycolate	40.00
12.50	4	Hydroxypropyl cellulose	12.50
100.00	5	Cellulose microcrystalline	100.00
5.00	6	Magnesium stearate	5.00
10.00	7	Talc	10.00
QS	8	Water, purified, ca	186.00 mL

Manufacturing Directions

1. Granulation
   a. Dissolve hydroxypropyl cellulose in two-thirds volume of purified water (item 8).
   b. Pass lactose, temafloxacin hydrochloride, and the sodium starch glycolate through an approximately 765-μm aperture screen, if necessary, and charge into a mixer and mix. Add hydroxypropyl cellulose solution from step 1a, mix, and granulate. Add more water, if needed, until a granule mass is formed.
   c. Pass the wet mass through an approximate 4.8-mm aperture screen, and dry in a dryer at 45°C to 52°C to an LOD of not more than 1.5%. Pass the dried granules through an approximately 1.18-mm screen. If necessary, screen the microcrystalline cellulose (and crospovidone for 400- and 600-mg tablets) through an approximate 500-μm aperture screen. Add to the dried granules, and blend for 10 minutes.
   d. Pass magnesium stearate and talc through a 500-μm aperture screen. Add to the bulk from step 1c, and blend for 5 to 10 minutes.
   e. Compress as follows: 200 mg, 7.32 × 15.19 mm; 500 mg and 300 mg, 8.5 × 17.5 mm; 750 mg.
   f. Coat the compressed tablets by spraying with a color coat and then apply gloss. (See Appendix.)

Tenoxicam Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
20.00	1	Tenoxicam	20.00
90.00	2	Lactose monohydrate	90.00
84.00	3	Maize starch	84.00
4.00	4	Talc	4.00
2.00	5	Magnesium stearate	2.00
–	6	Water, purified, ca	50.00 mL

Manufacturing Directions

1. Charge item 6 and item 3 (20%) in a mixer heated to 40°C, and mix for 10 minutes. Heat at 70°C to 80°C until a homogenous paste is formed. Cool to 50°C.
2. In a separate vessel, charge item 2, the balance of item 3, and item 1. Mix well.
3. Add the paste from step 1 into step 2, and mix for 15 minutes until a loose, moist mass is obtained.
4. Granulate the moist mass using a centrifugal granulator with a 7-mm sieve.
5. Spread over paper-lined trays, and dry at 45°C overnight (the relative humidity over the granules should be 20–35%).
6. Pass the dried granules through a 1.5-mm sieve granulator.
7. Transfer the granules to a tumbler, add item 4 and then item 5, and mix for 20 minutes.
8. Compress into 200-mg tablets, using a suitable punch (11.5 × 6.0 mm).

Terazosin Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.00	1	Terazosin hydrochloride	1.10
98.00	2	Ludipress	98.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix intensively, and press with low-compression force (10 kN).
2. Compress 98.1 mg for 1-mg and 97.6 mg for 5-mg strength, using 6-mm biplanar punches.
3. If the content uniformity does not meet the requirements, prepare a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation.
4. For 5-mg strength, adjust with item 2.

Terazosin Tablets (1 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
128.560	1	Lactose	128.530
1.000	2	Terazosin, use terazosin monohydrate	1.187
7.500	3	Starch (maize)	7.500
6.000	4	Starch (maize)	6.000
–	5	Water, purified, ca	25 mL
6.000	6	Talc	6.000
1.123	7	Magnesium stearate	1.120

Manufacturing Directions

1. Granulation
   a. Mix the terazosin and a portion of lactose. Mill the mixture through a 425-μm (or similar) aperture screen using a comminuting mill, with impact forward, at high speed.
   b. If necessary, mill the remainder of lactose.
   c. Add the powders (step 1a and 1b) and starch (item 3) to the mixer. and blend for 20 minutes.
   d. Disperse starch (item 4) in purified water, and heat to make a paste.
   e. Add starch paste to powder blend, and blend for 5 to 7 minutes, adding extra purified water. Record any additional volume.
   f. If necessary, pass the granule through a 4.76mm aperture on an oscillating granulator or a 12.7-mm aperture screen on a comminuting mill, with knives forward, at slow speed.
   g. Dry at 49°C to an LOD of not more than 2% (105°C for 1 hour).
   h. Pass granules through a 1.18-mm aperture screen on an oscillating granulator.
   i. Add one-half of the granules to a suitable blender.
   j. Blend the magnesium stearate and talc with a portion of the granules. Pass through a 1.18-mm aperture screen, and add to the bulk.
   k. Add the remainder of granule, and blend for 10 minutes. 2. Compression: Use 7.14-mm or other similar size punches. For 2-mg, 5-mg, and 10-mg strengths, adjust with item 1 and any dye added to differentiate tablets.

Terbinafine Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Terbinafine (used as terbinafine hydrochloride)	250.00
10.00	2	Hypromellose (hydroxy propyl methyl cellulose)	10.00
105.00	3	Avicel PH 102 (microcrystalline cellulose)	105.00
2.50	4	Ac-Di-Sol (croscarmellose sodium)	2.50
1.50	5	Magnesium stearate	1.50
QS	6	Purified water	QS

Manufacturing Directions

1. Sift terbinafine hydrochloride and Avicel through a 250-μm sieve.
2. Dissolve hydroxy propyl methyl cellulose in purified water to make a granulating solution.
3. Knead the powder mix in step 1 with the granulation solution to get the desired wet mass. Pass the mass through a #8 sieve onto drying trays.
4. Dry granules at 60°C for 12 hours to an LOD of not more than 2%.
5. Pass the granules through #16 mesh into the blending vessel.
6. Pass croscarmellose sodium and magnesium stearate through a 250-μm sieve, and add to step 5. Blend for 3 minutes.
7. Compress into 400-mg tablets, using a suitable punch.

Terfenadine Chewable Tablets

Manufacturing Directions

1. Terfenadine, 10.00% (micronizer or powdered); PVP K-90, 3.00%; block co-polymer poloxomer 188, 1.00%; Maltodextrin QD M500 fine, 10.00%; Sorbitol INSTANT, 30.00%; aspartame, 0.50%; Mannitol or xylitol, 44.50%; magnesium stearate, 0.50%; spray-dried flavor, 0.50%.
2. Terfenadine, block-copolymer, aspartame, spray-dried flavor, and PVP are premixed in a cube blender for a time period of 10 minutes.
3. The sorbitol INSTANT is added, and the resulting admixture is mixed for another 10-minute time period.
4. The maltodextrin and mannitol or xylitol are added, and the resulting composition is mixed for a further 10 minutes. The magnesium stearate lubricant is then added and mixed into the composition for a further 3 minutes.
5. The lubricated admixture is then made into tablets by compression to a hardness of 9 to 12 kPa (12–18 Strong Cobb units) using 3/8-in. standard concave punches or an appropriate punch/die set.

Terfenadine Tablets (60 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Terfenadine	60.00
235.00	2	Ludipress	235.00
6.00	3	Kollidon CL	6.00
1.00	4	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with very low-compressive force.
2. Compress into 301-mg tablets, using 8-mm biplanar punches.

Testosterone and Norethindrone Buccal Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Testosterone	50.00
35.00	2	Norethindrone	35.00
14.80	3	Polyethylene oxide	14.80
0.20	4	Magnesium stearate	0.20

Manufacturing Directions

1. All components (i.e., testosterone, norethindrone, polyethylene oxide and magnesium stearate, as set forth in the above table) are thoroughly mixed prior to tablet formation using aqueous fluid-bed granulation to provide a homogeneous mixture of active agents and excipients.
2. The individual dosage units are then made by applying approximately 10 to 15 mg of the mixture into the punch die of a tablet press, and compressing the mixed components using a pressure in the range of approximately 500 to 2000 psi. Tablets having a diameter of approximately 4 mm and a height of 1 mm are prepared. The tablet is removed from the punch die and the weight and dimensions of the tablet are measured.

Testosterone, Estradiol, and Progesterone Buccal Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.50	1	Testosterone	1.50
0.30	2	Estradiol	0.30
4.70	3	Progesterone	4.70
2.48	4	Polyethylene oxide (Polyox WSR-303)	2.48
1.00	5	Carbopol	1.00
0.02	6	Magnesium Stearate	0.02

Manufacturing Directions

1. All components (i.e., testosterone, estradiol, polyethylene oxide, carbomer, and magnesium stearate) are thoroughly mixed prior to tablet formation using aqueous fluid-bed granulation to provide a homogeneous mixture of active agents and excipients.
2. The individual dosage units are then made by applying 10 mg of the mixture into the punch die of the tablet press, and compressing the mixed components using a pressure in the range of approximately 500 to 2000 psi. Tablets having a diameter of approximately 4 mm and a height of 1 mm are prepared.

Tetracycline Tablets (125 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
125.00	1	Tetracycline hydrochloride	125.00
100.00	2	Ludipress	100.00
42.00	3	Microcrystalline cellulose (Avicel PH 101)	42.00
3.00	4	Magnesium stearate	3.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press to tablets with very low-compression force.
2. Compress into 278-mg tablets, using 8-mm biplanar punches.

Tetracycline Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Tetracycline hydrochloride	250.00
175.00	2	Lactose monohydrate	175.00
15.00	3	Kollidon 30	15.00
25.00	4	Kollidon CL	25.00
28.00	5	Talc	28.00
3.50	6	Aerosil 200	3.50
3.50	7	Calcium arachinate	3.50

Manufacturing Directions

1. Pass items 1 to 4 through a 0.5-mm sieve, add the mixture of items 6 and 7, and press with low-compression force.
2. Compress into 505-mg tablets, using 12-mm biplanar punches.

Tetrazepam Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Tetrazepam	50.00
113.00	2	Microcrystalline cellulose (Avicel PH 101)	113.00
30.00	3	Starch 1500 (Colorcon)	30.00
5.00	4	Kollidon VA 64	5.00
2.00	5	Magnesium stearate	2.00

Manufacturing Directions

1. Pass the components through a 0.5-mm sieve, and press with low-compression force.
2. Compress into 208-mg tablets, using 8-mm biplanar punches.

Theophylline and Ephedrine Tablets (130 mg/15 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
130.00	1	Theophylline (0.1–0.4 mm)	130.00
15.00	2	Ephedrine hydrochloride	15.00
150.00	3	Ludipress	150.00
2.00	4	Aerosil 200	2.00
2.00	5	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all components, pass through a sieve, and press with very low-compression force.
2. Compress into 302-mg tablets, using 8-mm biplanar punches.

Theophylline Sustained-Release Tablets (500 mg) DC

Formulation: Theophylline, granular type (BASF), 500 g; Kollidon SR, 125 g; Ludipress LCE, 225 g; magnesium stearate, 3 g.

Manufacturing Directions

Mix all components, pass through a sieve of 0.8 mm, and press with medium-compression force at 853 mg.

Theophylline Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Theophylline (0.1–0.4 mm)	100.00
147.00	2	Ludipress	147.00
3.00	3	Magnesium stearate	3.00

Manufacturing Directions

1. Mix all components, pass through a sieve, and press with low-compression force.
2. Compress into 247-mg tablets, using 8-mm biplanar punches.

Theophylline Tablets

Manufacturing Directions

1. Theophylline, 200 mg; crystalline PVA homopolymer, 200 mg; magnesium stearate, 5 mg. Total = 405 mg.
2. Mix in a geometric dilution.

Compress on 2.7×10^6 kg/m^2 pressure with 3/8-in. (9.53 mm) diameter standard concave tooling to form tablets with average hardness of 12SCU.

Theophylline Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Theophylline	100.00
70.62	2	Starch 1500	70.62
72.50	3	Microcrystalline Cellulose (50 μm)	72.50
5.00	4	Stearic Acid	5.00
1.25	5	Fumed Silica	1.25
0.63	6	Magnesium Stearate	0.63

Manufacturing Directions

1. All ingredients except magnesium stearate are blended for 10 minutes in a twin-shell blender.
2. Magnesium stearate is added and blended for an additional 5 minutes.
3. Tablets are compressed at 250 mg.

Theophylline Tablets (100 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Theophylline	100.00
137.10	2	Lactose anhydrous	137.10
60.00	3	Carbopol® 971P	60.00
1.50	4	Cab-o-Sil®	1.50
1.50	5	Magnesium stearate	1.50

Manufacturing Directions

1. Pass all items through a 250-μm mesh, and charge items 1 to 3 in a suitable blender. (item 3 can be used granulated in a fluid-bed.)
2. Add items 4 and 5, and blend for 3 minutes.
3. Compress into 300-mg tablets, using a suitable punch.

Theophylline Tablets CR (200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Theophylline powder	200.00
2.00	2	Sodium lauryl sulfate	2.00
2.00	3	Calcium stearate	2.00
35.00	4	Ethyl cellulose	35.00
3.60	5	Cetanol	3.60
1.60	6	Sodium lauryl sulfate	1.60
148.00	7	Triethyl citrate	148.00
–	8	Water, purified	QS

Manufacturing Directions

1. Charge items 1 to 3 in a suitable mixer, and mix for 10 minutes.
2. Granulate step 1 by passing the items through a compactor or dry granulator.
3. Pass the compact material from step 2 through #16 to #32 mesh.
4. In a separate vessel, add items 4 to 7, and make a solution with item 8 to 200 g.
5. Transfer step 3 into a fluid-bed granulator, and apply the solution in step 4 to coat the granules.
6. Compress.

Theophylline Tablets (100 mg)

Formulation: Theophylline granules 0.1/0.4 mm (BASF), 100 g; Ludipress, 147 g; magnesium stearate, 3 g.

Manufacturing Directions

Mix all components, pass through a sieve, and press with low-compression force at 247 mg.

Thiamine and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Thiamine hydrochloride	500.00
100.00	2	Caffeine	100.00
30.00	3	Cornstarch	30.00
20.00	4	Kollidon® VA 64	20.00
15.00	5	Kollidon® VA 64	15.00
QS	6	Ethanol (96%)	QS
35.00	7	PEG-6000 (powder)	35.00

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with solution of item 5 and 6, dry, sieve, mix with item 7, and press with low compressive force.
2. Compress into 698-mg tablets, using 16-mm biplanar punches.

Thiamine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine HCl with excess	110.00
43.50	2	Lactose monohydrate	43.50
4.00	3	Crospovidone (Kollidon® CL)	4.00
5.50	4	Povidone (PVP K-90)	5.50
5.50	5	Crospovidone (Kollidon® CL)	5.50
32.00	6	Microcrystalline cellulose (Avicel™ PH112)	32.00
5.60	7	Talc (fine powder)	5.60
3.70	8	Glyceryl behenate (glyceryl monostearate)	3.70
0.20	9	Magnesium stearate	0.20
–	10	Alcohol (ethanol, 95%)	50.67

Manufacturing Directions

1. Sift items 1, 2, and 3 through a stainless steel 630-μm sieve.
2. Load into mixer.
3. Mix for 5 minutes at high speed.
4. Dissolve item 4 in item 10 under slow stirring by stirrer.
5. Add the binding solution while mixing at high speed over a period of 2 minutes. Scrape sides and blades.
6. Mix and chop at high speed for 2 minutes.
7. Check the end point of granulation.
8. If required, add additional item 10 to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Dry wet granules in oven at 55°C for 8 hours.
9. After 2 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying.
10. Check the LOD (limit: 1.0–1.5%).
11. If required, dry at 55°C for an additional hour.
12. Check the LOD again.
13. Grind the dried granules through a 1.25-mm sieve with the granulator set at medium speed.
14. Collect in stainless steel drums.
15. Load the granules into blender.
16. Sift items 5 and 6 through a 500-μm sieve, and add to blender.
17. Mix for 2 minutes (do not overmix).
18. Sift items 8 and 9 through a 500-μm sieve.
19. Add 1.33 to 2.67 g of granules.
20. Mix in a polyethylene bag for 1 minute.
21. Add to blender.
22. Blend for 1 minute.
23. Check temperature and humidity before start of compression (limit: temperature should not exceed 25°C; relative humidity, 45–50%).
24. Compress using 8-mm, round, beveled, concave punches.

Thiamine Hydrochloride Tablets, Sugar-Coated

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine hydrochloride monohydrate (with excess)	110.00
110.00	2	Lactose	110.00
5.00	3	Luviskol® K-98	5.00
1.00	4	Magnesium stearate	1.00
40.00	5	Ethyl alcohol (denatured)	40.00
251.44	6	Sugar (crystalline)	251.44
1.40	7	Sugar powder	1.40
14.50	8	Maize starch	14.50
14.81	9	Talcum	14.81
21.00	10	Copolymer lacquer	21.00
0.40	11	Paraffin (solid)	0.40
0.16	12	Gum acacia	0.16
0.228	13	Ethyl alcohol (denatured)	0.228
0.01	14	Paraffin (liquid)	0.01
QS	15	Purified water	QS

Manufacturing Directions

1. In a suitable stainless steel vessel, add denatured ethyl alcohol and Luviskol; mix until homogeneous mixture is obtained. Set aside.
2. Pass lactose through a #2-mesh sieve, add thiamine, and mix for 10 minutes in an appropriate mixer.
3. Slowly add to this mixture the solution made earlier, and stir until slightly lumpy mass is obtained.
4. If required, add ethyl alcohol to the mixture.
5. Pass the wet mass through an oscillating granulator with a 7.00-mm perforated sieve.
6. Spread the granules over paper-lined trays, and dry at 40°C for 5 hours in a drying oven.
7. The relative humidity of the granules should be 15% to 25%.
8. Pass magnesium stearate and talcum through a 1-mm hand sieve.
9. Compress on a rotary tablet machine at about 4 to 5 tons of pressure; the weight of each tablet should be about 230 mg.
10. In a suitable container, add purified water and acacia gum; pass the resulting solution through a 0.8-mm sieve.
11. Charge the compressed tablets into a coating pan and apply the copolymer lacquer in ten portions; after the last application, apply neutral spray (crystalline sugar in demineralized water).
12. Dry the insulated tablets in a drying oven overnight at 45°C (minimum 14 hours); the tablet weight should be around 236 mg each.
13. In an electric, jacketed kettle, put demineralized water, crystalline sugar, maize starch, and talcum; mix by stirring until homogeneous.
14. Pass through a sieve of mesh size 0.8 mm (pH, 6.0–8.0; density, 1.335–1.356).
15. Coat the tablets to 400 mg weight using the coating solution and a sugar-coating pan; set pans at slow speed, open air inlets, and set air inflow at 80°C and maximum contact temperature set at 42°C.
16. Roll tablets to reach this temperature.
17. Turn pan to fast speed, close the inlet air flap, and make first application of syrup.
18. When all tablets are wet and distribution of syrup is uniform, open the air inlet flap and allow 80°C air to blow (tablet temperature falls 1–2°C for a short time and then slowly rises to 42°C).
19. The next application of the syrup cycle begins.
20. Coat the tablets with color solution as described above to 495-mg weight.
21. Set the air inflow temperature at 25°C, and reduce the size of application with the falling temperature, whereby tablets are evenly and lightly moistened after each application; the temperature drops from 42°C to 32°C.
22. Turn the coating pans slowly during the drying phase; for the last three applications, keep the pan lids closed, as well as the air intake and outflow during this phase.
23. Drying only with outlet air may be extended for the last three applications up to 10 to 15 minutes.
24. Immediately after the last application of syrup has dried slightly, begin the polishing step.
25. The polishing paste is prepared in a suitable boiling vessel by adding stock gum solution, crystalline sugar, and demineralized water.
26. Boil until temperature reaches 106°C with stirring.
27. In a steam kettle, melt solid and liquid paraffin, and pour melted paraffins into the mixture of gum; make up the weight with demineralized water.
28. Polishing paste ready for use contains 0.75 kg of paste and 0.113 kg of ethyl alcohol.
29. Tablet temperature is 28°C to 32°C.
30. Shut off the inlet flaps and outlet flaps, set the pans at the fast speed, and add polishing paste (about 0.3% of tablet weight).
31. Close the pans with inner lids and allow them to rotate at fast speed for 90 seconds for even distribution.
32. Remove the inner lid of the pan, and set it on slow speed.
33. Open the outlet air for 3 minutes, blow the inlet air at 40°C for 6 to 8 minutes until a good sheen appears.
34. Set the pans on automatic system for overnight, with intermission time of 5 minutes off and 10 seconds on.

Thiamine, Pyridoxine, and Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
110.00	1	Thiamine mononitrate	110.00
210.00	2	Pyridoxine hydrochloride	210.00
76.82	3	Lactose monohydrate	76.82
10.00	4	Crospovidone (Kollidon® CL)	10.00
18.50	5	Povidone (PVP K-90)	18.50
0.30	6	Cyanocobalamin	0.30
85.00	7	Microcrystalline cellulose (Avicel™ PH102)	85.00
14.00	8	Crospovidone (Kollidon® CL)	14.00
10.00	9	Glyceryl behenate (glyceryl monostearate)	10.00
0.49	10	Magnesium stearate	0.49
15.00	11	Talc (fine powder)	15.00
–	12	Alcohol (ethanol, 95%)	88.90

Manufacturing Directions

1. Dissolve item 5 in item 12 by using a stirrer to make a clear solution.
2. Dissolve item 6 carefully in the solution.
3. Sift items 1 to 4 through a 630-μm sieve.
4. Load the material into a mixer.
5. Mix and chop at high speed for 5 minutes.
6. Add binding solution from previous step to the dry powder in the mixer while mixing and chopping at high speed for 2 minutes.
7. Check for satisfactory wet mass.
8. Add additional item 12, if required, to obtain a satisfactory wet mass.
9. Do not allow big lumps.
10. Record the additional quantity of ethanol 95%.
11. Spread the granules onto stainless steel trays to a thickness of 1/4th of the tray thickness, and load the trays onto a trolley.
12. Load the trolley into an oven.
13. Keep the door open, switch on the oven with air circulation, heater turned off for 2 hours.
14. Dry the granules at 55°C for 12 hours.
15. Check the LOD of dried granules (limit: NMT 0.7%).
16. Grind the dried granules through a 1.25-mm sieve using a granulator.
17. Collect in a stainless steel drum.
18. Load into the blender.
19. Sift items 7, 8, and 9 through a 500-μm sieve.
20. Collect in stainless steel container.
21. Load the sieved powder into the blender.
22. Blend for 3 minutes.
23. Sift items 11 and 10 through a 500-μm sieve.
24. Collect in a polyethylene bag.
25. Add 4.44 to 6.67 g of granules from earlier step, and mix manually for 1 minute.
26. Add this mixture to the blender, and mix for 1 minute.
27. Compress the granules using a rotary tabletting machine.
28. Compress into 550-mg tablets, using round, binconvex punches at 9 to 16 kp.
29. Coat tablets using an HPMC coating (see Appendix).

Thiamine, Pyridoxine, and Cyanocobalamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine mononitrate (powder)	115.00
50.00	2	Pyridoxine hydrochloride	50.00
9.75	3	Anhydrous Citric Acid (powder)	9.75
20.10	4	Monohydrate lactose (powder, regular)	20.10
1.67	5	Saccharin sodium	1.67
0.24	6	Dye	0.24
0.009	7	Dye	0.009
0.02	8	Dye	0.02
2.00	9	Cornstarch	2.00
QS	10	Purified water	18.00 mL
50.00 μg	11	Vitamin B12; use vitamin B12 oral powder cobalamin conc	62.50
12.50	13	Monohydrate lactose (powder, regular)	12.50
1.50	14	Oil orange terpeneless	1.50
3.50	15	Magnesium stearate	3.50
1.50	16	Talc (powder)	1.50
17.70	17	Corn starch, Light Coral Red 6 LA	17.70

Manufacturing Directions

1. Pass thiamine mononitrate, pyridoxine HCl, citric acid, lactose (item 4), and saccharin sodium through a #30-mesh (595-μm or similar) screen.
2. Charge into mixer, and dry mix.
3. Dissolve the dyes in purified water.
4. Add the starch (item 9) to this dye solution with stirring.
5. Heat and continue stirring until a thick paste is formed.
6. Cool to room temperature before using.
7. (*Note*: Use 7.5 g of colored starch paste for the vitamin B1 and B6 blend and 12.5 g of colored starch paste for the vitamin B12 blend.) Add 7.5 g of colored starch paste to powder blend, and mix until mass is formed.
8. Pass through a #6-mesh (3.36-mm or similar) screen, and air dry for 3 to 4 hours.
9. Screen vitamin B12 oral powder and lactose (item 12) through a #30-mesh (595-μm or similar) screen.
10. Charge into mixer, and dry mix.
11. Add 12.5 g colored starch paste to powder blend, and mix until mass is formed.
12. Pass through #6-mesh (3.36-mm or similar) screen, and air dry for 3 to 4 hours.
13. Dry granulations from the two steps separately at 49°C overnight or until LOD is less than 1%.
14. Mill the two dried granulations through a #16-mesh (1.2-mm or similar) screen (knives forward, medium speed), and combine.
15. Sift a small quantity of granulation from the steps above over a #30-mesh (595-μm or similar) screen, and add the orange oil to the fines.
16. Add magnesium stearate, talc powder, and Light Coral Red starch to mixture, and pass through a #30-mesh (595-μm or similar) screen.
17. Charge base granulation and lubricants into a blender, and blend thoroughly.
18. Compress using 11/32-in. concave punches.

Thiamine, Pyridoxine, and Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine hydrochloride	100.00
10.00	2	Pyridoxine hydrochloride	10.00
0.10	3	Cyanocobalamin (gelatin coated, 1%)	10.00
277.00	4	Ludipress®	277.00
3.00	5	Magnesium stearate	3.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with low compressive force.
2. Compress into 394-mg tablets, using 12-mm biplanar punches.

Thiamine, Pyridoxine, and Cyanocobalamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine mononitrate	100.00
200.00	2	Pyridoxine hydrochloride	200.00
0.10	3	Cyanocobalamin (gelatin coated, 1%)	10.00
250.00	4	Ludipress®	250.00
45.00	5	PEG-6000 (powder)	45.00
5.00	6	Aerosil® 200	5.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress into 609-mg tablets, using 12-mm biplanar punches.

Thiamine, Pyridoxine, and Cyanocobalamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.00	1	Thiamine mononitrate	250.00
250.00	2	Pyridoxine hydrochloride	250.00
75.00	3	Lactose monohydrate	75.00
25.00	4	Kollidon® 30	25.00
QS	5	Isopropanol	QS
1.00	6	Cyanocobalamin (gelatin coated, 1%)	100.00
25.00	7	Kollidon® CL	25.00
2.00	8	Magnesium stearate	2.00
2.00	9	Talc	5.00

Manufacturing Directions

1. Granulate mixture items 1 to 3 with solution of items 4 and 5, dry, pass through a 0.8-mm sieve, mix with items 6 to 9, and press with low compressive force, applying a vibrating hopper.
2. Compress into 730-mg tablets, using 12-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Thiamine hydrochloride or thiamine mononitrate	50.00
293.00	2	Ludipress®	293.00
5.00	3	Magnesium stearate	5.00
2.00	4	Aerosil® 200	2.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with medium compressive force.
2. Compress 357 mg, if hydrochloride salt is used, or 347 mg, if mononitrate salt is used, with 12-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Thiamine hydrochloride or thiamine mononitrate	50.00
150.00	2	Lactose monohydrate	150.00
150.00	3	Avicel™ PH101	150.00
15.00	4	Kollidon® CL	15.00
2.00	5	Aerosil® 200	2.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with high compressive force.
2. Compress 344 mg, if hydrochloride salt is used, or 373 mg, if mononitrate salt is used, with 12-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine hydrochloride or thiamine mononitrate	110.00 (or 100.00)
190.00	2	Ludipress®	190.00
100.00	3	Lactose monohydrate	100.00
100.00	4	Avicel™ PH 101	100.00
9.00	5	Kollidon® CL	9.00
3.00	6	Aerosil® 200	3.00
2.00	7	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with medium compressive force.
2. Compress 302 mg, if hydrochloride salt is used, or 320 mg, if mononitrate salt is used, with 8-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Thiamine hydrochloride	100.00
200.00	2	Lactose monohydrate	200.00
10.00	3	Kollidon® 30	10.00
60.00	4	Isopropanol	60.00
10.00	5	Kollidon® CL	10.00
2.00	6	Magnesium stearate	2.00
1.00	7	Aerosil® 200	1.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 3 and 4, dry, and sieve through a 0.8-mm screen, mix with items 5 to 7, and press to tablets.
2. Compress into 330-mg tablets, using 8-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Thiamine mononitrate	300.00
100.00	2	Dicalcium phosphate (Di-Tab)	100.00
15.00	3	Kollidon® 30	15.00
QS	4	Isopropanol	~50.00
10.00	5	Kollidon® CL	10.00
4.00	6	Magnesium stearate	4.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 2 and 3, dry, and sieve through a 0.8-mm screen.
2. Mix with items 5 and 6, and compress into 430-mg tablets, using 12-mm biplanar punches.

Tibolone Tablets (0.3 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
0.30	1	Tibolone (Org GD 14)	0.30
1.95	2	Hydroxypropyl cellulose	1.95
32.50	3	Starch (maize)	32.50
0.32	4	Magnesium stearate	0.32
29.93	5	Lactose anhydrous	29.33
–	6	Water, purified	QS

Manufacturing Directions

1. Charge items 3 and 5 in a suitable blender, and mix for 1 minute after passing them through a 250-μm sieve.
2. In a separate vessel, charge items 1 and 2; add a sufficient amount of item 6 to make a uniform solution.
3. Add step 2 into step 1 gradually, and granulate for 2 minutes.
4. Pass the wet mass through #8 mesh, and dry at 40°C for 4 hours.
5. Screen the granules through a 710-μm sieve into a blender.
6. Add item 4, and blend for 1 minute.
7. Compress into 65-mg tablets, using a suitable punch.

Ticlopidine Hydrochloride Tablets (250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
250.0	1	Ticlopidine HCl	250.0
72.0	2	Starch, maize	72.0
68.8	3	Microcrystalline cellulose (Avicel)	68.8
6.0	4	Polyvinylpyrrolidone (PVP K30)	6.0
1.2	5	Colloidal silicon dioxide (Aerosil 200)	1.2
2.0	6	Magnesium stearate	2.0
–	7	Water, purified	QS

Manufacturing Directions

1. Blend ticlopidine HCl, maize starch, Avicel, and PVP K-30 after passing through a 350-μm sieve.
2. Charge item 3 in a separate vessel, and prepare a paste using item 7.
3. Add step 2 into step 1. Knead to make a suitable wet mass.
4. Pass the wet mass through #8 mesh onto drying trays. Dry at 60°C for 12 hours. The LOD should not be more than 2.5%.
5. Pass the dried granules through #16 mesh into a blending vessel.
6. Blend with Avicel, Aerosil, and magnesium stearate previously sieved through a 500-μm sieve.
7. Compress into 400-mg tablets, using 15-mm punches.
8. Coat the tablets with hypermellose solution. (See Appendix.)

Tinidazole Controlled Release Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1000.00	1	Tinidazole	1000.00
17.50	2	Methocel K15 MCR	17.50
10.00	3	Methocel K4 MCR	10.00
50.00	4	Lactose	50.00
25.00	5	Polyvinylpyrrolidone K30	25.00
10.00	6	Talc	10.00
5.00	7	Colloidal silicon dioxide	5.00
31.50	8	Sodium stearyl fumarate	31.50
1.00	9	Magnesium stearate	1.00

Manufacturing Directions

1. The drug is blended with the two polymers and lactose and granulated with a solution of polyvinylpyrrolidone in water.
2. The granules are dried, sized lubricated, and compressed to tablets at 1148 mg.

Tolterodine Tablets (1 mg/2 mg) Detrol

Detrol® tablets contain tolterodine tartrate. Detrol tablets for oral administration contain 1 or 2 mg of tolterodine tartrate. The inactive ingredients are colloidal anhydrous silica, calcium hydrogen phosphate dihydrate, cellulose microcrystalline, hydroxypropyl methylcellulose, magnesium stearate, sodium starch glycolate (pH 3.0–5.0), stearic acid, and titanium dioxide.

Topiramate Tablets (100 mg/200 mg), Topamax

Topamax (topiramate) tablets contain the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide (100- and 200-mg tablets), and polysorbate 80.

Tosufloxacin Tosylate Tablets (75 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Tosufloxacin tosylate monohydrate	75.00
37.40	2	L-Aspartic acid	37.50
21.45	3	Cellulose, crystalline	21.45
34.50	4	Starch (maize)	34.50
7.50	5	Silicon dioxide, hydrated	7.50
2.25	6	Hydroxypropyl cellulose	2.25
1.80	7	Magnesium stearate	1.80

Manufacturing Directions

1. Pass items 1 and 2 through a 790-μm sieve into a suitable blender.
2. Blend for 2 minutes.
3. Add items 3 to 6, passing each item through a 500-μm sieve.
4. Blend for 5 minutes.
5. Pass item 7 through #100 mesh into step 4.
6. Blend for 1 minute.
7. Compress into 180-mg tablets, using 8-mm punches.

Tramadol Sustained-Release Tablets (100 mg)

Formulation: Tramadol-HCI (Chemagis), 100.0 g; Kollidon SR, 150.0 g; silicon dioxide, colloidal, 2.5 g; magnesium stearate, 1.5 g.

Manufacturing Directions

All ingredients are passed through a 0.8-mm sieve, blended for 10 minutes in a mixer, and then compressed with medium-compression force at 254 mg.

Tramodol Hydrochloride Matrix Tablets

Manufacturing Directions

1. Tramadolhydrochloride (100 mg), methylhydroxypropylcellulose type 2208, 100000 mPas (85 mg), calcium hydrogen phosphate (62 mg), colloidal silicon dioxide (5 mg), and magnesium stearate (3 mg).
2. Sieve all components through a 0.63-mm sieve, mixing in a cube blender for 10 minutes and pressing into tablets having a diameter of 9 mm, a radius of curvature of 8.5 mm and a mean weight of 255 mg.

Trazodone Hydrochloride Tablets (100 mg)

Trazodone HCl is supplied for oral administration in 50-mg, 100-mg, 150-mg, and 300-mg tablets. Trazodone HCl tablets, 50 mg, contain the following inactive ingredients: dibasic calcium phosphate, castor oil, microcrystalline cellulose, ethylcellulose, FD&C Yellow No. 6 Aluminum Lake, lactose, magnesium stearate, povidone, sodium starch glycolate, and starch (corn).

Trazodone HCl tablets, 100 mg, contain the following inactive ingredients: dibasic calcium phosphate, castor oil, microcrystalline cellulose, ethylcellulose, lactose, magnesium stearate, povidone, sodium starch glycolate, and starch (corn).

Trazodone HCl tablets, 150 mg, contain the following in active ingredients: microcrystalline cellulose, FD&C Yellow No. 6 Aluminum Lake, magnesium stearate, pregelatinized starch, and stearic acid.

Trazodone HCl tablets, 300 mg, contain the following inactive ingredients: microcrystalline cellulose, yellow ferric oxide, magnesium stearate, sodium starch glycolate, pregelatinized starch, and stearic acid.

Triamcinolone Tablets (4 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4.00	1	Triamcinolone	4.00
191.00	2	Ludipress	191.00
2.00	3	Kollidon CL	2.00
2.00	4	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all components, pass through a sieve, and press with low-compression force.
2. Compress into 206-mg tablets, using 8-mm biplanar punches.
3. If the content uniformity does not meet the requirements, prepare a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation.

Triametrene and Hydrochlorothiazide Tablets

Manufacturing Directions

1. First mixture—triamterene, 75 mg; Avicel, PH-102, 125 mg, Rexcel, 38 mg; Ac-Di-Sol, 10 mg; magnesium stearate/sodium lauryl sulfate (94/6), 6 mg; sodium lauryl sulfate, 4 mg; Cab-O-Sil, M-5, 2 mg.
2. Second mixture—hydrochlorothiazide, 50 mg; Avicel, PH-102, 80 mg; Ac-Di-Sol, 5 mg; magnesium stearate/sodium lauryl sulfate (94/6), 1 mg; Cab-O-Sil, M-5, 1 mg; D & C Yellow #10 Lake, 1 mg.
3. After the separate granules are prepared, 250 g of magnesium stearate/sodium lauryl sulfate (94/6) are added and the final mixture thoroughly blended and then formed into tablets (or capsules) by customary methods.

Trifluoperazine Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Trifluoperazine hydrochloride	5.00
194.00	2	Ludipress	194.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, pass through a sieve, and press with very low-compression force.
2. Compress into 204-mg tablets, using 8-mm biplanar punches.
3. If the content uniformity does not meet the requirements, prepare a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation.

Trimebutine and Ranitidine Hydrocloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Trimebutine	200.00
150.00	2	Ranitidine hydrochloride	150.00
122.00	3	Microcrystalline cellulose PH102	122.00
20.00	4	Lactose monohydrate	20.00
1.65	5	Magnesium stearate	1.65

Manufacturing Directions

1. In a suitable vessel, the trimebutine, ranitidine HCL, microcrystalline cellulose, and lactose monohydrate are milled to a suitable size and mixed until homogeneous.
2. The magnesium stearate is added and the mixture is mixed until homogeneous.
3. The mixture is then discharged and compressed using conventional tablet tooling to a suitable hardness (e.g., 10–12 kPa) to target a net tablet weight of 500 mg.

Triprolidine and Pseudoephedrine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.60	1	Triprolidine HCl (4% excess)	2.70
60.00	2	Pseudoephedrine HCl (5% excess)	63.00
122.40	3	Lactose monohydrate	122.40
25.50	4	Maize starch	28.00
1.00	5	Povidone (PVP K-30)	1.00
4.00	6	Povidone (PVP K-30)	4.00
–	7	Alcohol (ethanol, 95%)	28.00
1.50	8	Magnesium stearate	1.50

Manufacturing Directions

1. Dissolve item 6 in item 7 using a stirrer.
2. Avoid loss of ethanol by evaporation.
3. Pass items 1 to 5 through a 630-μm sieve using sifter.
4. Collect in a stainless steel drum.
5. Load the sieved powders into a mixer.
6. Mix and chop for 5 minutes at low speed.
7. Add PVP solution to the mixer at medium rate while mixing.
8. Start the chopper at low speed when half of the solution is added.
9. Mix and chop at low speed until the satisfactory mass is obtained.
10. Spread the wet granules onto the trays.
11. Keep the trolleys in the open air for about 1 hour.
12. Load the trolleys into the oven, and start the air circulation at room temperature for 2 hours.
13. Dry the granules at 55°C with air circulation for 5 hours.
14. Scoop the granules after 2 hours of drying; move the upper trays down and the lower trays up for uniform drying.
15. Check the moisture content (limit: NMT 1.5%).
16. Pass the dried granules through a 1-mm sieve using a granulator.
17. Collect in a stainless steel drum and load into the blender.
18. Pass item 8 through a 250-μm sieve using a sifter.
19. Collect in a polyethylene bag.
20. Mix 2 g of granules with this mixture, and add to the blender.
21. Mix for 1 minute.
22. Unload the lubricated granules in a stainless steel drum.
23. Compress into 220-mg tablets, using 8.5-mm, round, concave punches.

Tulobuterol Hydrochloride Tablets (1 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.00	1	Tulobuterol hydrochloride	1.00
44.96	2	Lactose monohydrate	44.96
40.00	3	Blue dye	40.00
28.00	4	Starch (maize)	28.00
2.00	5	Acacia	2.00
3.00	6	Calcium carboxymethyl cellulose	3.00
–	7	Water, purified, ca	20 mL
1.00	8	Magnesium stearate	1.00

Manufacturing Directions

Caution: Tulobuterol is a low-dose bronchodilator. Operators should wear a mask and gloves during all stages of manufacture.

1. Blending
   a. Cross feed tulobuterol, blue dye, and lactose through a comminuting mill fitted with a 790-μm screen, with high speed knives.
   b. Blend the maize starch, acacia, and calcium carboxymethyl cellulose. Put the tulobuterol blend in a suitable mixer/blender for 20 minutes, and disintegrate.
2. Granulation: Load the blended ingredients from Blend A or B into a suitable planetary mixer. While mixing, add water in a slow steady stream. Continue massing for 5 minutes after all the water is added. Proceed to the drying step.
3. Drying
   a. Pass the wet mass through a 4-mm aperture screen onto paper-lined trays. Dry at 50°C to 55°C. The final LOD should be between 1.5% and 5% (105°C for 1 hour).
   b. Pass the dried granule through an oscillating granulator fitted with a 720-μm aperture screen.
4. Lubrication: Load the dried granules into a suitable blender. Pass the magnesium stearate and an equal portion of dried granule through a 600-μm aperture screen. Add to a blender, and blend for 5 minutes.
5. Compression
   a. Compress using a rotary machine fitted with 7/32-in. flat bevel-edged punches. The weight should be 80 mg ± 3%.
   b. For a 2-mg dose, adjust with lactose.

Valacyclovir Hydrochloride Tablets (500 mg/1 g), Valtrex

Each caplet contains valacyclovir hydrochloride equivalent to 500 mg or 1 g of valacyclovir and the inactive ingredients carnauba wax, colloidal silicon dioxide, crospovidone, FD&C Blue No. 2 Lake, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, povidone, and titanium dioxide. The blue, film-coated caplets are printed with edible white ink.

Valdecoxib Tablets (10 mg/20 mg) Bextra

Bextra tablets for oral administration contain 10 or 20 mg of valdecoxib. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, polysorbate 80, and titanium dioxide.

Valeriana and Passiflora Extract Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
44.00	1	Valeriana extract, powder	44.00
33.00	2	Passiflora extract, powder (with excess)	36.00
120.00	3	Avicel™ PH101	120.00
11.00	4	Kollidon® CL	11.00
3.60	5	Aerosil® 200	3.60
7.30	6	Magnesium stearate	7.30

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with low compressive force.
2. Compress into 231-mg tablets, using 9-mm biconvex punches.

Valproate Sodium Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
576.00	1	Sodium Valproate	576.00
20.00	2	Cab-o-Sil	20.00
266.00	3	A-tab	266.00
154.00	4	Carbomer 971P	154.00
10.00	5	Magnesium stearate	10.00

Manufacturing Directions

1. Sodium valproate, CARBOPOL 971 carbomer, and nonhygroscopic additives are admixed and blended in V-blender for about 5 minutes.
2. The blend from step 1 is comminuted through a 0.250-in. screen.
3. The mixture from step 2 is passed through 20 mesh vibrating sieve.
4. The sifted material from step 3 is blended in a V-blender for an additional 15 minutes.
5. Magnesium stearate is passed through a 50-mesh sieve.
6. The sieved magnesium stearate from step 5 is added to the resulting granulate from step 4 and blended for 5 minutes.
7. The blend from step 6 is compressed into caplets.

Valproate Sodium Tablets (500 mg), Depakote

Depakote tablets are supplied in three dosage strengths containing divalproex sodium equivalent to 125, 250, or 500 mg of valproic acid. The inactive ingredients are cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains cornstarch), silica gel, talc, titanium dioxide, and vanillin. In addition, individual tablets contain the following. *125-mg tablets:* FD&C Blue No. 1 and FD&C Red No. 40; *250-mg tablets:* FD&C Yellow No. 6 and iron oxide; *500-mg tablets:* D&C Red No. 30, FD&C Blue No. 2, and iron oxide.

Valproate Sodium Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Valproate sodium	500.00
80.00	2	Starch (maize)	80.00
20.00	3	Kollidon 30	20.00
—	4	Isopropyl alcohol, ca	60 mL
5.00	5	Kollidon CL	5.00
5.00	6	Magnesium stearate	5.00

Manufacturing Directions

1. Granulate the mixture of items 1 and 2 with a solution of items 3 and 4. Pass through a sieve, mix the dry granules with items 5 and 6, and press with low-compression force.
2. Compress into 607-mg tablets, using 12-mm biplanar punches. *Note:* The powder mixture easily develops electric charge.

Valsartan and Hydrochlorothiazide Tablets (80 mg/12.5 mg; 160 mg/25 mg), Diovan HCT

Diovan HCT tablets are formulated for oral administration to contain valsartan and hydrochlorothiazide, USP 80/12.5 mg, 160/12.5 mg, and 160/25 mg. The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.

Valsartan and Hydrochlorothiazide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
80.00	1	Valsartan	80.00
12.50	2	Hydrochlorothiazide	12.50
1.50	3	Colloidal silica anhydrous (Aerosil 200)	1.50
31.50	4	Microcrystalline cellulose (Avicel PH 102)	31.50
20.00	5	Polyvinyl pyrrolidone crospovidone	20.00
4.50	6	Magnesium stearate	4.50

Manufacturing Directions

1. Blend all components (use only 50% of magnesium stearate) in a container mixer.
2. Sieve the blended material, and mix again.
3. Compact using a roller compactor such as Bepex Pharmapaktor L 200/50 P, Hosokawa Micron Group by applying a compaction force of 25 to 65 kN and a roller speed of 1.3 to 7.5 rpm.
4. Sieve the compacted material and the remaining portion of the magnesium stearate, and blend again for 2 minutes.
5. Compress into 150-mg tablets.

Venlafaxine Hydrochloride Tablets (25 mg/37.5 mg/50 mg) Effexor

Compressed tablets of Effexor® contain venlafaxine hydrochloride equivalent to 25, 37.5, 50, 75, or 100 mg of venlafaxine. Inactive ingredients consist of cellulose, iron oxides, lactose, magnesium stearate, and sodium starch glycolate.

Effexor XR is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5, 75, or 150 mg of venlafaxine. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, hydroxypropyl methylcellulose, iron oxide, and titanium dioxide.

Venlafaxine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Venlafaxine	25.00
90.00	2	Microcrystalline cellulose	90.00
100.30	3	Pregelatinized starch	100.30
7.00	4	Croscarmellose	7.00
0.20	5	Magnesium stearate	0.20

Manufacturing Directions

1. Sieve the active ingredient through a suitable sieve, and blend with the excipients until a uniform blend is formed.
2. Screen the dry blend, and blend with the magnesium stearate.
3. Compress and adjust weight for different strengths.

Verapamil Sustained-Release Tablets (220 mg)

Formulation: Verapamil hydrochloride, 240.0 g; Ludipress LCE, 230.0 g; Methocel K15M (Dow), 75.0 g; Talc, 75.0 g; magnesium stearate, 5.0 g; Aerosil 200, 2.5 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press with low-compression force using a vibrating hopper at 628 mg.

Verapamil Tablets

Manufacturing Directions

1. Verapamil hydrochloride 240 mg, Sodium alginate (300 cps) 135 mg, hydroxypropylmethyl cellulose (methocel E4M viscosity of 4000 cps) 45 mg, Avicel pH 101 33.2 mg, lactose 8.3 mg, hydroxypropylmethyl E5 9.0 mg, magnesium stearate 4.5 mg, purified water q.s.
2. Verapamil hydrochloride, hydroxypropylmethyl cellulose, sodium alginate, microcrystalline cellulose and lactose are dry blended for 5 minutes in a suitable blender. The powders are then wet massed using binder in aqueous solution and the mix passed through a 10# screen. The granules are dried and the magnesium stearate added thereto.
3. The so-formed mixture is then thoroughly mixed and compressed into tablets each weighing 475 mg.

Verapamil Tablets (120 mg), Calan

Calan is available for oral administration in film-coated tablets containing 40, 80, or 120 mg of verapamil HCl. The inactive ingredients are microcrystalline cellulose, cornstarch, gelatin, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide colorant, lactose, magnesium stearate, polyethylene glycol, talc, and titanium dioxide. Sustained-release/extended-release tablets are designed for sustained release of the drug in the gastrointestinal tract. Sustained-release characteristics are not altered when the tablet is divided in half.

Verpamil Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
120.00	1	Verapamil hydrochloride	120.00
270.00	2	Ludipress	270.00
3.00	3	Magnesium stearate	3.00
3.00	4	Aerosil 200	3.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium-compression force.
2. Compress into 400-mg tablets, using 12-mm biplanar punches.

VESIcare Tablet 5 mg Film-Coated Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Solifenacin succinate	5.00
74.30	2	Lactose spray dried	74.30
5.00	3	Cornstarch	5.00
5.00	4	Starch 1500	5.00
0.70	5	Magnesium stearate	0.70
2.00	6	Hydroxylpropylmethyl cellulose	2.00
0.40	7	Polyethylene glycol 8000	0.40
0.30	8	Talc	0.30
0.60	9	Titanium dioxide	0.60
0.20	10	Yellow ferric oxide	0.20
–	11	Water, purified	30.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 3, and item 4 through 0.5-mm sieve and collect in a stainless steel container and mix well.
4. Add 5% (=1.9 g) powder from step 1 to step 3 and mix well.

5. Add 15% (=5.7 g) powder from step 1 to step 3 and mix well.
6. Transfer step 5 into step 2.
7. Transfer balance quantity of step 1 into step 2.
8. Mix step 2 for 20 minutes using tumbler.
9. Pass item 5 through 0.250-mm sieve and add to step 8.
10. Mix step 9 for 2 minutes.
11. Compress into 90-mg tablets, using a suitable punch (5.5 mm, round).
12. Charge item 11 in a stainless steel vessel. Add item 6 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of Hydroxylpropylmethyl cellulose.
13. Add items 7 to 10 one by one to step 12 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
14. Load core tablets from step 11 in coating pan and apply coating dispersion from step 13 to get 2.5% to 3.0% weight gain.

VESIcare Tablet (10 mg) Film-Coated

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Solifenacin succinate	10.00
122.20	2	Lactose Spray Dried	122.20
8.33	3	Cornstarch	8.33
8.33	4	Starch 1500	8.33
1.20	5	Magnesium stearate	1.20
3.00	6	Hydroxylpropylmethyl cellulose	3.00
0.75	7	Polyethylene glycol 8000	0.75
0.50	8	Talc	0.50
1.00	9	Titanium dioxide	1.00
0.30	10	Red ferric oxide	0.30
–	11	Water, purified	45.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 3, and 4 through 0.5-mm sieve and collect in a stainless steel container and mix well.
4. Add 5% (=3 g) powder from step 1 to step 3 and mix well.
5. Add 15% (=9.1 g) powder from step 1 to step 3 and mix well.
6. Transfer step 5 into step 2.
7. Transfer balance quantity of step 1 into step 2.
8. Mix step 2 for 20 minutes using tumbler.
9. Pass item 5 through 0.250-mm sieve and add to step 8.
10. Mix step 9 for 2 minutes.
11. Compress into 150-mg tablets, using a suitable punch (7.5 mm × 6.0 mm, oval).
12. Charge item 11 in a stainless steel vessel. Add item 6 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of Hydroxylpropylmethyl cellulose.
13. Add items 7 to 10 one by one to step 13 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
14. Load core tablets from step 11 in coating pan and apply coating dispersion from step 13 to get 2.5% to 3.0% weight gain.

VIRACEPT 250-mg Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
292.00	1	Nelfinavir mesylate equivalent to Nelfinavir 250 mg	292.00
158.00	2	Lactose Monohydrate	158.00
25.00	3	Povidone	25.00
–	4	Water, purified	50.00
20.00	5	Crospovidone	20.00
5.00	6	Magnesium stearate	5.00
10.00	7	Hypromellose	10.00
2.00	8	Triacetin	2.00
0.30	9	FD& C blue #2	0.30
–	10	Water, purified	100.00

Manufacturing Directions

1. Dissolve item 3 in item 4 in a stainless steel container.
2. Pass items 2 and 1 and 20% of item 5 (4 g) through 0.7-mm sieve and mix well.
3. Charge step 2 in a granulator.
4. Knead step 3 with solution of step 1 for 5 to 10 minutes until a loose, moist mass is obtained.
5. Granulate the moist mass using a centrifugal granulator with a 7-mm sieve.
6. Spread step over paper-lined trays and dry at 50°C to 55°C for 8 hours (the relative humidity over the granules should be 20–35%).
7. Pass the dried granules through a 1.25-mm sieve granulator.
8. Transfer the granules to a tumbler.
9. Pass the remaining quantity of item 5 through 0.5-mm sieve and add to step 8 and mix for 15 minutes.
10. Pass item 6 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 500-mg tablets, using a suitable punch (14.5 mm, round).
13. Charge item 10 in a stainless steel vessel. Add item 7 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hydroxylpropylmethyl cellulose.
14. Add item 8 and item 9 one by one to step 12 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
15. Load core tablets from step 12 in coating pan and apply coating dispersion from step 14 to get 1.5% to 2.0% weight gain.

VIRACEPT 625-mg Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
730.00	1	Nelfinavir mesylate equivalent to Nelfinavir 650 mg	730.00
62.00	2	Lactose Monohydrate	62.00
45.00	3	Povidone	45.00
–	4	Water, purified	100.00
45.00	5	Crospovidone	45.00
9.00	6	Colloidal Silicon Dioxide	9.00
9.00	7	Magnesium stearate	9.00
15.00	8	Hypromellose	15.00
3.00	9	Triacetin	3.00
0.50	10	FD& C blue #2	0.50
–	11	Water, purified	150.00

Manufacturing Directions

1. Dissolve item 3 in item 4 in a stainless steel container.
2. Pass item 2, item 1, and 20% of item 5 (9 g) through 0.7-mm sieve and mix well.
3. Charge step 2 in a granulator.
4. Knead step 3 with solution of step 1 for 5 to 10 minutes until a loose, moist mass is obtained.
5. Granulate the moist mass using a centrifugal granulator with a 7-mm sieve.

6. Spread step over paper-lined trays and dry at 50°C to 55°C for 8 hours (the relative humidity over the granules should be 20–35%).
7. Pass the dried granules through a 1.25-mm sieve granulator.
8. Transfer the granules to a tumbler.
9. Pass the remaining quantity of item 5 and the item 6 through 0.5-mm sieve and add to step 8 and mix for 15 minutes.
10. Pass item 7 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 900-mg tablets, using a suitable punch (16.5 mm, round).
13. Charge item 11 in a stainless steel vessel. Add item 8 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hydroxylpropylmethyl cellulose.
14. Add item 9 and item 109 one by one to step 13 with stirring. Stir for 10 minutes. Homogenize for
15. minutes. Pass the coating dispersion through 180-mm sieve (if required).
16. Load core tablets from step 12 in coating pan and apply coating dispersion from step 14 to get 1.5 % to 2.0% weight gain.

Vitamin A and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
33000 IU	1	Vitamin A acetate (dry powder, 500,000 IU/g)	69.00
70.00	2	Vitamin E acetate (dry powder)	70.00
146.00	3	Mannitol (granulated) with 10% of Kollidon® 30	146.00
17.00	4	Kollidon® CL	17.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with high compressive force.
2. Compress into 300-mg tablets, using 12-mm biplanar punches.

Vitamin A Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100000 IU	1	Vitamin A acetate (dry powder, 325000 IU/g)	350.00
350.00	2	Mannitol	350.00
25.00	3	Kollidon® VA 64	25.00
5.00	4	Magnesium stearate	5.00
3.00	5	Aerosil® 200	3.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium compressive force.
2. Compress into 750-mg tablets, using 12-mm biplanar punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50000 IU	1	Vitamin A acetate (dry powder, 500000 IU/g)	110.00
100.00	2	Avicel™ PH102	100.00
10.00	3	Kollidon® VA 64	10.00
5.00	4	Kollidon® CL	5.00
1.00	5	Aerosil® 200	1.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with low compressive force.
2. Compress into 231-mg tablets, using 9-mm binconvex punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5000	1	Vitamin A acetate (dry powder, 500,000 IU/g)	110.00
189.00	2	Ludipress®	189.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress into 306-mg tablets, using 8-mm punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50,000	1	Vitamin A acetate (dry powder, 500000 IU/g)	120.00
120.00	2	Ludipress®	120.00
10.00	3	Avicel™ PH101	10.00
1.00	4	Magnesium stearate	1.00
1.00	5	Aerosil® 200	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress into 277-mg tablets, using 8-mm punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50,000	1	Vitamin A acetate (dry powder, 500000 IU/g)	110.00
154.00	2	Avicel™ PH101	154.00
10.00	3	Kollidon® VA 64	10.00
4.00	4	Kollidon® CL	4.00
1.00	5	Aerosil® 200	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress into 250-mg tablets, using 8-mm punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25000 IU	1	Vitamin A acetate (dry powder, 500000 IU/g)	55.00
572.00	2	Dicalcium phosphate (granulated) (Di-Tab) with 3% of Kollidon® 30	572.00
28.00	3	Polyethylene glycol, powder	28.00
19.40	4	Kollidon® CL	19.40
5.60	5	Aerosil® 200	5.60

Manufacturing Directions

1. Granulate the dicalcium phosphate with Kollidon 30, dissolved in isopropanol or water, and pass through a 0.5- to 12-mm screen sieve using a vibrating hopper.
2. Mix the obtained dried granules with the other components, sieve, and press with high compressive force.
3. Compress into 680-mg tablets, using biplanar punches.

Vitamin A, Vitamin B6, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
40000 IU	1	Vitamin A acetate (dry powder, 500000 IU/g)	80.00
40.00	2	Pyridoxine hydrochloride	40.00
35.00	3	Vitamin E acetate (dry powder, SD 50)	75.00
395.00	4	Ludipress®	395.00
4.00	5	Magnesium stearate	4.00
5.00	6	Aerosil® 200	5.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high compressive force.
2. Compress into 583-mg tablets, using 12-mm biplanar punches.

Vitamin A, Vitamin C, and Vitamin D3 Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2000/200 IU	1	Vitamin A and vitamin D3 (dry powder, 500000 and 50,000 IU/g, respectively)	4.00
30.00	2	Ascorbic acid (powder)	33.00
300.00	3	Sucrose (crystalline)	300.00
300.00	4	Sorbitol (crystalline)	300.00
300.00	5	Mannitol	300.00
300.00	6	Ludipress®	300.00
5.00	7	Stearic acid	5.00
0.10	8	Saccharin sodium	0.10
30.00	9	Cyclamate sodium	30.00
30.00	10	Flavor mixture (Firmenich)	30.00
20.00	11	PEG-6000, powder	20.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high compressive force.
2. Compress into 1290-mg tablets, using 16-mm biplanar punches.

Vitamin A, Vitamin C, and Vitamin E Tablets (1200 IU/60 mg/30 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets
1200 IU	1	Vitamin A acetate (dry powder, 500000 IU/g)	2.40
60.00	2	Ascorbic acid (powder)	60.00
30.00	3	Vitamin E acetate (dry powder, 50%)	60.00
105.00	4	Lactose monohydrate	105.00
30.00	5	Avicel™ PH101	30.00
20.00	6	Kollidon® 25	20.00
5.00	7	Talc	5.00
1.00	8	Aerosil® 200	1.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium-compression force.
2. Compress into 285-mg tablets, using 8-mm biplanar punches.

Vitamin B-Complex and Carnitine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
95.00	1	Thiamine mononitrate	95.00
20.00	2	Riboflavin	20.00
100.00	3	Nicotinamide	100.00
50.00	4	Calcium D-pantothenate	50.00
2.00	5	Folic acid	2.00
0.20	6	Biotin	0.20
0.005	7	Cyanocobalamin (gelatin coated, 1%)	0.50
50.00	8	Carnitine hydrochloride	50.00
100.00	9	Inositol	100.00
2.00	10	Adenosine phosphate	2.00
15.70	11	Kollidon® 30	15.70
70.00	12	Isopropanol	70.00
26.00	13	Kollidon® CL	26.00
122.00	14	Lactose monohydrate	122.00
14.00	15	PEG-6000, powder	14.00

Manufacturing Directions

1. Granulate mixture of items 1 to 10 with solution of items 11 and 12.
2. Dry, pass through a 0.8-mm sieve, mix with items 13 and 15, and press with low compressive force.
3. Compress into 708-mg tablets, using 13-mm biplanar punches.

Vitamin B-Complex and Folic Acid Dragees

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
4.35	1	Calcium D-pantothenate (granulate, 67%)	6.50
2.60	2	Thiamine mononitrate (10.4%)	25.00
20.00	3	Magnesium oxide (light)	20.00
45.75	4	D-mannitol (powder)	45.75
100.00	5	DL-methionine	100.00
2.30	6	Riboflavin	2.30
6.30	7	Nicotinamide	6.30
2.40	8	Pyridoxine HCl	2.40
4.00	9	Magnesium stearate	4.00
0.1150	10	D-biotin	0.1150
0.46	11	Folic acid	0.46
100.00	12	Choline tartarate	100.00
28.00	13	Silicic acid (precipitated)	28.00
0.87 mcg	14	Vitamin B12 (as 0.1% water soluble form)	0.871
3.15	15	Vitamin E (50%)	6.30
30.00	16	Sodium carboxymethyl starch	30.00
116.66	17	Isopropyl alcohol	116.66
22.00	18	Povidone (PVK K-90) (Luviskol®)	22.00

Manufacturing Directions

1. Incorporate in mixer PVP K-90 and isopropyl alcohol, and make a solution with continuous stirring.
2. Place in mixer choline tartarate, DL-methionine, D-mannitol powder, magnesium oxide (previously sieved), silicic acid, and sodium carboxymethyl starch, and mix for 15 minutes.
3. Add the solution of isopropyl alcohol and alcohol in first step for 10 minutes until moist mass is obtained.
4. Granulate the moist mass through a centrifugal granulator with a 10-mm screen.
5. Spread the granules on paper-lined trays, and dry overnight in a drying oven at 50°C.
6. Crush the granules through a 1.5-mm sieve.
7. Vitamin granulate: Tumble D-biotin, vitamin B12, folic acid, riboflavin, and pyridoxine hydrochloride in mixer for 5 minutes.
8. Combine in the mixer nicotinamide, vitamin E, thiamine mononitrate/gelatin/mannitol granulate, D-mannitol powder, and sodium carboxymethyl starch, then add the vitamin mixture, and mix for 10 minutes.
9. Pass through a 1-mm sieve if lumpy.
10. In a mixer, make a separate solution of PVP K-90 and isopropyl alcohol.
11. Place in the mixer the solution of isopropyl alcohol and PVP, then knead until an evenly moist homogeneous mass is obtained.
12. Add calcium-D-pantothenate granules, and mix for 3 to 5 minutes.
13. Pass the granules through a centrifugal granulator with a 10-mm screen, and spread on paper-lined trays.
14. Keep overnight in a drying oven at 50°C; the relative humidity of the granules should be 10% to 20%.
15. Crush the dried granules through an oscillator with a 1.5-mm sieve.
16. Put the granulate mixture in the mixing drum—the choline tartarate and the two lots of vitamin granules.
17. Mix, and then add the magnesium stearate.
18. Check to be sure that the relative humidity of the mixture is 10% to 20%.
19. Compress, and apply a sealer coat (lacquer), sugar coat, and finishing coating.

Vitamin B-Complex and Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
33.00	1	Thiamine mononitrate	33.00
4.00	2	Riboflavin	4.00
10.00	3	Pyridoxine hydrochloride	10.00
66.00	4	Nicotinamide	66.00
17.00	5	Calcium D-pantothenate	17.00
350.00	6	Tartaric acid (powder)	350.00
450.00	7	Sodium bicarbonate	450.00
750.00	8	Sucrose, crystalline	750.00
30.00	9	Kollidon® 30	30.00
QS	10	Isopropanol	QS
500.00	11	Ascorbic acid (crystalline)	500.00
3.00 g	12	Riboflavin	3.00
10.00	13	Cyanocobalamin (gelatin coated, 0.1%)	10.00
10.00	14	Orange flavor	10.00
2.00	15	Saccharin sodium	2.00
5.00	16	Cyclamate sodium	5.00
50.00	17	PEG-6000 (powder)	50.00

Manufacturing Directions

1. Granulate mixture of items 1 to 9 with solvent item 10, dry, pass through a 0.8-mm sieve, mix with items 13 to 17, and press with high compressive force at a maximum of relative atmospheric humidity of 30%.
2. Compress into 2315-mg tablets, using 20-mm biplanar punches.

Vitamin B-Complex and Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Thiamine mononitrate	5.00
5.00 g	2	Riboflavin	5.00
5.00	3	Pyridoxine hydrochloride	5.00
0.50	4	Folic acid	0.50
30.00	5	Niacin	30.00
0.10	6	Biotin	0.10
10.00	7	Calcium D-pantothenate	10.00
150.00	8	Ascorbic acid (crystalline/powder)	150.00
172.40	9	Ludipress®	172.40
20.00	10	Kollidon® VA 64	20.00
2.00	11	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all ingredients and pass through a 0.8-mm sieve, and then mix.
2. Use medium to low compressive force to compress 400 mg in 10-mm biplanar punches.

Vitamin B-Complex and Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Thiamine hydrochloride	15.00
2.00	2	Riboflavin	2.00
5.00	3	Pyridoxine hydrochloride	5.00
25.00	4	Choline bitartrate	25.00
10.00	5	Nicotinamide	10.00
100.00	6	Ascorbic acid (crystalline/powder)	100.00
220.00	7	Ludipress®	220.00
8.00	8	Stearic acid	8.00

Manufacturing Directions

1. Mix all ingredients and pass through a 0.8-mm sieve, and mix.
2. Use medium to low compressive force to compress 411 mg in 12-mm biplanar punches.
3. The thiamine mononitrate formulation is more stable compared with the thiamine hydrochloride formulation (above).

Vitamin B-Complex Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Thiamine mononitrate or hydrochloride	25.00
25.00	2	Riboflavin	25.00
80.00	3	Nicotinamide	80.00
40.00	4	Calcium D-pantothenate	40.00
16.00	5	Pyridoxine hydrochloride	16.00
0.16	6	Cyanocobalamin (gelatin coated, 0.1%)	16.00
282.00	7	Avicel™ PH101	282.00
16.00	8	Kollidon® 30	16.00
3.00	9	Aerosil® 200	3.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix.
2. Compress using 12-mm biplanar punches with medium- to high-compression force.
3. The mononitrate formulation is preferred for stability reasons.

Vitamin B-Complex Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.30	1	Thiamine mononitrate	2.30
2.60	2	Riboflavin	2.60
2.30	3	Nicotinamide	2.30
2.20	4	Calcium D-pantothenate	2.20
2.70	5	Pyridoxine hydrochloride	2.70
0.024	6	Cyanocobalamin (gelatin coated, 0.1%)	2.40
280.00	7	Ludipress®	280.00
14.00	8	Flavor (Firmenich)	14.00
0.050	9	Saccharin sodium	0.05
4.00	10	Cyclamate sodium	4.00
5.00	11	Magnesium stearate	5.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and 8-mm biplanar punches.
2. Compress into 314-mg tablets, using low-compression force.
3. According to European Commission, this formulation is classified as dietary food.

Vitamin B-Complex Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Microcrystalline cellulose (Avicel™ PH102)	15.00
0.20	2	Colloidal silicon dioxide (Aerosil® 200)	0.20
3.00	3	Calcium pantothenate	3.00
9.33	4	Powdered cellulose	9.33
35.60	5	Lactose (spray-dried)	35.60
0.91	6	Magnesium stearate	0.91
20.00	7	Nicotinamide	20.00
2.10	8	Pyridoxine hydrochloride	2.10
2.00	9	Riboflavin base	2.00
0.80	10	Talc (fine powder)	0.80
2.10	11	Thiamine mononitrate	2.10

Manufacturing Directions

1. Riboflavin base is a fine powder that tends to form globules while mixing.
2. Disperse the base with Aerosil and lactose carefully.
3. Mix items 9 and 2 and 6.67 g of item 5 in the drum of a drum mixer for 10 minutes.
4. Pass the mix two times through a 500-μm sieve using a sifter.
5. Pass items 11, 8, and 3 and 6.67 g of item 5 through a granulator fitted with a 1.0-mm sieve.
6. Pass items 7, 1, and 4 and 22.27 g of item 5 through a granulator fitted with a 1.0-mm sieve.
7. Pass items 10 and 6 through a sifter fitted with a 500-μm sieve.
8. Load sieved material from previous step to the blender.
9. Load sieved material to the blender.
10. Blend the powders for 15 minutes.
11. Load lubricant powders into the blender, and mix for an additional 5 minutes.
12. Compress into 91-mg tablets at low relative humidity (55–60%).
13. Coat tablets with a sealing coat, color coat, and polishing coat.

Vitamin B-Complex, Choline, and Bile Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
60.00	1	Acid dehydrochloric (powder)	60.00
100.00	2	Choline dihydrogen citrate	100.00
20.00	3	Niacinamide (white powder)	20.00
100.00	4	Inositol	100.00
2.50	5	Riboflavin (2% excess)	2.55
0.50	6	Pyridoxine hydrochloride	0.50
30.00	7	Povidone (*K* value, 29– 32)	30.00
100.00	8	Racemethionine (crystals)	100.00
60.00	9	Ox bile extract (powder, #30-mesh) (Bilein)	60.00
–	10	Alcohol dehydrated (200 proof)	26.00
3.0 μg	11	Cyanocobalamin (oral powder in gelatin, 1000 μg/g)	3.30
3.00	12	Thiamine hydrochloride (powder, regular)	3.60
8.40	13	Magnesium stearate (impalpable powder)	8.40
8.40	14	Stearic acid (fine powder)	8.40

Manufacturing Directions

1. Mill dehydrochloric acid, choline dihydrogen citrate, nicotinamide, inositol, and methionine through a 600-μm screen.
2. Charge milled mixture from first step with riboflavin, pyridoxine hydrochloride, Povidone, and ox bile extract in mass mixer.
3. Add alcohol QS (approximately 26 g or 32.7 mL) very slowly to the mass.
4. Mass for approximately 45 minutes in mixer.
5. Scrape all material from the mass mixer as much as possible.
6. Rinse mass mixer between runs.
7. Granulate through a comminuting or similar mill or a 4.76-mm screen.
8. Dry at 49°C to less than 1% LOD.
9. Sift through an 840-μm screen in a shaker and grind coarsely through a comminuting mill (knives forward, medium speed).
10. Charge one half of the base granulation through a 1.68-mm screen into a blender, if necessary.
11. Mix cyanocobalamine oral powder with an equal volume of base granulation, and charge into a blender through a 1.68-mm screen.
12. Blend thiamine hydrochloride, magnesium stearate, and stearic acid.
13. Then hand-screen mixture through a 600-μm screen.
14. Load into a blender through a 1.68-mm screen with the remainder of the base granulation, and blend for 20 minutes.
15. Compress and coat tablets using an appropriate formulation to render required color and sealing of tablet.

Vitamin B-Complex, Vitamin A, Vitamin C, and Vitamin D Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.00	1	Thiamine mononitrate (20% excess)	2.40
1.00	2	Riboflavin (10% excess)	1.10
74.50	3	Lactose (spray-dried)	74.50
15.00	4	Nicotinamide	15.00
300 IU	5	Vitamin D3 (dry powder, 100000 IU/g)	3.60
3000 IU	6	Vitamin A palmitate (250000 IU/g)	18.00
36.00	7	Cellulose (microcrystalline) (Avicel™ PH102)	36.00
20.00	8	Ascorbic acid (90%) (33% excess)	26.60
1.00	9	Silicon dioxide (colloidal) (Aerosil® 200)	1.00
1.80	10	Magnesium stearate	1.80

Manufacturing Directions

1. Mix items 1 and 2 and 13.33 g of item 3 in a drum using a drum mixer for 10 minutes.
2. Pass the mix through a 250-μm sieve using a sifter.
3. Collect in a stainless steel drum, and load into the blender.
4. Pass items 4 to 7 and 61.17 g of item 3 through a granulator fitted with a 1.0-mm sieve.
5. Collect in a stainless steel drum, and load into the blender.
6. Pass item 8 through a FitzMill fitted with sieve number 24230.
7. Collect in a stainless steel drum, and load into the blender.
8. Mix for 10 minutes.
9. Pass item 9 through a 500-μm sieve using a sifter.
10. Collect in a polyethylene bag.
11. Pass item 10 through a 250-μm sieve using a sifter.
12. Collect in the same polyethylene bag.
13. Mix and add 0.53 to 1.33 g powder from the step above.
14. Mix gently.
15. Add to the blender.
16. Mix for 3 minutes.
17. Unload lubricated granules in stainless steel drums.
18. Compress into 180-mg tablets, using 7-mm round concave punches.
19. Apply a sealing coat, a color coat, and finishing coat (see Appendix).

Vitamin B-Complex, Vitamin A, Vitamin C, Vitamin D, and Mineral Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
61.00	1	Ascorbic acid (coated), EC	61.00
5.50	2	Calcium pantothenate	5.50
8.00 mcg	3	Cyanocobalamin	0.008
4.00	4	Copper sulfate, $5H_2O$	4.00
1.70	5	Magnesium oxide (heavy)	1.70
10.00	6	Nicotinamide	10.00
0.575	7	Pyridoxin hydrochloride	0.575
0.16	8	Potassium iodide	0.16
2.30	9	Riboflavin	2.30
3.25	10	Thiamine mononitrate	3.25
24.00	11	Vitamin A palmitate (250000 IU/g)	24.00
4.80	12	Vitamin D3 powder (100000 IU/g)	4.80
2.20	13	Zinc sulfate, $7H_2O$	2.20
19.265	14	Lactose monohydrate	19.265
25.00	15	Cellulose (microcrystalline) (Avicel™ PH102)	25.00
3.00	16	Povidone (PVP K-90)	3.00
6.50	17	Cellulose (microcrystalline) (Avicel™ PH102)	6.50
7.00	18	Crospovidone (Kollidon® CL)	7.00
1.00	19	Colloidal silicon dioxide (Aerosil® 200)	1.00
0.75	20	Magnesium stearate	0.75
3.00	21	Microcrystalline cellulose (powder)	3.00
–	22	Alcohol (absolute)	18.46

Manufacturing Directions

1. Dissolve item 16 in item 22 using a stirrer.
2. Dissolve item 3 while stirring to obtain a clear solution.
3. Press items 10, 9, 7, 6, 2, 14, and 15 through a 500-μm stainless steel sieve in a sifter.
4. Load into mixer, and mix for 5 minutes at high speed.
5. Knead the dry powder with binding solution while mixing at high speed for 3 minutes.
6. After the addition is complete, scrape the sides and blades.
7. Mix for an additional 2 minutes using a mixer and chopper at high speed. Check the end point of granulation.
8. (The end point occurs when the granulation consists of few or no lumps.) If required, add an additional quantity of item 22, and record this extra quantity of item 22.
9. Unload the wet granules in stainless steel trays for drying.
10. Transfer the trays to an oven.
11. Keep the door partially open.
12. Switch on the oven, with air circulation, heater switched off, for 2 hours to evaporate alcohol.
13. Close the door of the oven.
14. Dry the granules at 55°C for 12 hours.
15. After 4 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying.
16. Check the LOD (limit: 0.8–1.2%).
17. If required, dry further at 55°C for 2 hours.
18. Check the LOD.
19. Grind the dried granules through a 1.25 mm sieve using a granulator set at medium speed.
20. Load granules into the blender.
21. Mix items 4 and 13 and 3.08 g of item 17 in a polyethylene bag.
22. Mill through a FitzMill using sieve number 1530-0030 (knives forward, medium speed).
23. Collect in stainless steel drum.
24. Add to blender.
25. Sift items 11, 12, and 1 through a 630-μm sieve.
26. Add to blender.
27. Sift items 5, 8, 18, 19, and 21 and 3.42 g of item 17 through a 500-μm sieve.
28. Add to blender.
29. Mix for 5 minutes.
30. Sift item 20 through a 250-μm sieve.
31. Mix a portion of the powder mix (~3.85 g) with sieved item 20.
32. Add to the blender.
33. Mix for 1 minute.
34. Compress into 185-mg tablets, using 7-mm, round, concave punches.
35. Coat using a subcoat, a color coat, and a finishing coat (see Appendix).

Vitamin B-Complex, Vitamin C, and Calcium Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
7.00	1	Thiamine mononitrate	7.00
5.00	2	Riboflavin	5.00
25.00	3	Nicotinamide	25.00
20.00	4	Pyridoxine hydrochloride	20.00
12.00	5	Calcium D-pantothenate	12.00
75.00	6	Calcium carbonate	75.00
164.00	7	Calcium glycerophosphate	164.00
400.00	8	Sodium bicarbonate	400.00
300.00	9	Tartaric acid (powder)	300.00
400.00	10	Sucrose (crystalline)	400.00
350.00	11	Sucrose (powder)	350.00
50.00	12	Kollidon® 30	50.00
10.00	13	Kollidon® 30	10.00
QS	14	Isopropanol	QS
550.00	15	Ascorbic acid (powder)	550.00
2.00	16	Riboflavin	2.00
5.00	17	Cyanocobalamin (gelatin coated, 0.1%)	5.00
40.00	18	PEG-6000 (powder)	40.00
50.00	19	Kollidon® CL	50.00

Manufacturing Directions

1. Granulate mixture of items 1 to 12 with solution of item 19.
2. Granulate items 13 to 18 separately, dry at 60°C with vacuum, mix with item 1, blend.
3. Compress into 2.5-g tablets, using 20-mm planar punches at medium- to high-compression force.

Vitamin B-Complex, Vitamin C, and Ferrous Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Ferrous sulfate	300.00
15.00	2	Kollidon® 30	15.00
6.00	3	Kollidon® 30	6.00
QS	4	2-Propanol	QS
45.00	5	Thiamine mononitrate	45.00
10.00	6	Riboflavin	10.00
82.00	7	Pyridoxine hydrochloride	82.00
69.00	8	Nicotinamide	69.00
470.00	9	Ascorbic acid (powder)	470.00
690.00	10	Ludipress®	690.00
50.00	11	PEG-6000 (powder)	50.00
9.00	12	Aerosil® 200	9.00

Manufacturing Directions

1. Granulate the mixture of items 1 to 2 with solution of items 5 to 12.
2. Pass through a 0.8-mm sieve.
3. Mix with items 3 and 4.
4. Compress with high compressive force 25 to 30 kN. Compress into 1750-mg tablets, using 20-mm biplanar punches.

Vitamin B-Complex, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Niacinamide, (white powder), USP	100.00
750.00	2	Ascorbic acid; use sodium ascorbate (microcrystalline), USP	843.65
20.00	3	Calcium pantothenate, USP	30.00
10.00	4	Riboflavin, USP	10.00
5.00	5	Pyridoxine hydrochloride, USP	5.25
40.00	6	Povidone, USP	40.00
68.00	7	Anhydrous isopropyl alcohol	68.00
15.00	8	Thiamine mononitrate (powder), USP	15.75
24.79	9	Vitamin E, USP, d,l-α-tocopoheryl acid succinate	33.71
150.00 mcg	10	Folic acid (powder), USP	0.18
5.00	11	Magnesium stearate	5.00
40.00	12	Cellulose (microcrystalline), NF	40.00
4.00 mcg	13	Vitamin B12; use cyanocobalamine powder in gelatin (1000 μg/g)	4.20

Manufacturing Directions

1. Av oid unnecessary exposure to light and moisture.
2. Mill the nicotinamide and the sodium ascorbate through a 600-μm screen fitted to a FitzMill, or similar (impact forward, high speed).
3. Load into a suitable mass mixer.
4. Load calcium pantothenate, riboflavin, and pyridoxine hydrochloride into the mass mixer.
5. Dry blend for 5 minutes.
6. Dissolve Povidone in alcohol (~84 mL) in a separate container.
7. While mixing the blended powders add the Povidone solution.
8. Continue to mix until a satisfactory granule mass is obtained.
9. If required, use additional alcohol.
10. Granulate through a FitzMill, or similar, using a 5/8-in. band (15.88-mm aperture or similar) or a 4.76-mm screen with knives forward at slow speed.

11. Dry the granulation at 49°C to less than 1.5% LOD.
12. Sift the dry granulation through a 1.19-mm screen.
13. Pass remaining coarse granules through a #2 band (1.59-mm aperture or similar) using a FitzMill, or similar (knives forward, medium speed).
14. Blend together the thiamine mononitrate, vitamin E, folic acid, magnesium stearate, and a portion of the microcrystalline cellulose.
15. Mill blended powders through a 600-μm screen (impact forward, high speed).
16. Care must be taken to prevent losses.
17. Load half of the base granulation, the balance of the microcrystalline cellulose, and the powder blend into a suitable blender.
18. Blend for 5 minutes.
19. Add balance of base granulation, and blend for 15 minutes.
20. Do not mill cyanocobalamine.
21. Blend together by hand the cyanocobalamine with a portion of the blended powders.
22. Return to the blender, and blend for 15 minutes.
23. Compress using ovaloid-shaped punches.
24. Seal tablets with a subcoat, and then apply color coat and finishing coating.

Vitamin C and Calcium Carbonate Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
300.00	1	Calcium; use calcium carbonate	315.00
450.00	2	Sodium bicarbonate/tartaric acid (powder)	450.00
600.00	3	Kollidon® 30	600.00
35.00	4	Kollidon® 30	35.00
200.00	5	Isopropanol	200.00
400.00	6	Sucrose (crystalline)	400.00
500.00	7	Ascorbic acid (crystalline, with excess)	550.00
120.00	8	Kollidon® CL	120.00
60.00	9	PEG-6000 (powder)	60.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with a solution of items 4 and 5, mix with item 6, and dry.
2. Add items 7 to 9, and press with high compressive force at a maximum atmospheric relative humidity of 30%.
3. Compress into 2500-mg tablets, using 20-mm biplanar punches.

Vitamin C and Vitamin E Lozenges

Bill of Materials			
Scale (mg/lozenge)	Item	Material Name	Quantity/1000 Lozenges (g)
100.00	1	Ascorbic acid (crystalline)	100.00
50.00	2	Vitamin E acetate (dry powder, SD 50)	100.00
400.00 g	3	Dextrose	400.00
4.00 g	4	Kollidon® 90F	4.00
25.00 g	5	Isopropanol	25.00
6.00 g	6	PEG-6000 (powder)	6.00

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with isopropanol, dry, pass through a 0.8-mm sieve, mix with item 6, and press with high-compression force.
2. Compress into 600-mg tablets, using 12-mm biplanar punches.

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Ascorbic acid: 222.20 mg ascorbic acid and 312.50 mg sodium ascorbate microcrystalline	500.00
850.00	2	Sorbitol (granular)	850.00
100.00	3	Lactose (120 mesh)	100.00
3.30	4	FD&C Yellow Dye No. 5 lake	3.30
82.90	5	Cellulose (microcrystalline), NF (Avicel™ PH101)	82.90
11.60	6	Silica gel	11.60
8.29	7	Flavor	8.29
0.50	8	Flavor	0.50
8.29	9	Sodium cyclamate	8.29
33.20	10	Magnesium stearate	33.20

Manufacturing Directions

1. Pass ascorbic acid, sodium ascorbate, sorbitol, lactose, FD&C Yellow Dye, microcrystalline cellulose, silica gel, flavors, and sodium cyclamate through a 420-μm screen.
2. Using a comminuting mill, pass the coarse granules through a 420-μm screen (knives forward, medium speed).
3. Transfer milled materials to a suitable blender, and blend for 5 minutes.
4. Screen the magnesium stearate by hand through an 840-μm screen, and transfer to blender.
5. Mix for 1 minute.
6. Compress using 18-mm standard concave punches.

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
422.00	1	Ascorbic acid (powder)	422.00
283.00	2	Microcrystalline cellulose	283.00
130.00	3	Sucrose (powder)	130.00
80.00	4	Sucrose (crystalline)	80.00
24.00	5	Kollidon® VA 64	24.00
24.00	6	Cyclamate sodium	24.00
20.00	7	PEG-6000 (powder)	20.00
12.00	8	Orange flavor and strawberry flavor	12.00
2.00	9	Aerosil® 200	2.00
1.00	10	Saccharin sodium	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press into tablets with medium- to high-compression force.
2. Compress 250 mg (for 100 mg strength), 1250 mg (for 500 mg strength), or 2500 mg (for 500 mg strength).

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Ascorbic acid (crystalline)	500.00
1100.00	2	Sorbitol (crystalline)	1100.00
200.00	3	Sucrose (crystalline)	200.00
200.00	4	Sucrose (powder)	200.00
300.00	5	Dextrose	30.00
100.00	6	PEG-6000 (powder)	100.00
10.00	7	Magnesium stearate	10.00
10.00	8	Aerosil® 200	10.00
1.00	9	Saccharin sodium	1.00
10.00	10	Cyclamate sodium	10.00
30.00	11	Orange flavor	30.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium- to high-compression force.
2. Compress into 2080-mg tablets, using 20-mm biplanar punches.

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Ascorbic acid (crystalline)	100.00
450.00	2	Sodium ascorbate (crystalline)	450.00
264.00	3	Sorbitol (crystalline)	264.00
200.00	4	Sucrose (crystalline)	200.00
200.00	5	Sucrose (powder)	200.00
300.00	6	Dextrose	300.00
60.00	7	PEG-6000 (powder)	60.00
3.00	8	Magnesium stearate	3.00
4.00	9	Aerosil® 200	4.00
1.00	10	Saccharin sodium	1.00
10.00	11	Cyclamate sodium	10.00
20.00	12	Orange flavor	20.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium- to high-compression force.
2. Compress into 1295-mg tablets, using 16-mm biplanar punches.

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
6.70	1	Anhydrous silica (colloidal) (Aerosil® 200)	6.70
40.00	2	Cellulose (microcrystalline) (Avicel™ PH101)	40.00
6.50	3	Aspartame	6.50
170.00	4	Ascorbic acid (coated), EC	170.00
10.50	5	Orange flavor (dry)	10.50
13.00	6	Carmellose sodium (sodium CMC 7 MFD)	13.00
2.80	7	Orange dye	2.80
470.00	8	Dextrates, NF	470.00
19.50	9	Magnesium stearate	19.50
13.00	10	Stearic acid (fine powder)	13.00
160.00	11	Sorbitol (powder)	160.00
388.00	12	Sodium ascorbate (granular)	388.00

Manufacturing Directions

1. Processing should be done in a controlled temperature and humidity area (limit: relative humidity, 40–50%; temperature, 20–25°C).
2. Mix items 2 and 7 in a polyethylene bag for 1 to 2 minutes.
3. Sift twice through a 250-μm sieve.
4. Collect in a polyethylene bag, and check the uniformity of dispersion.
5. If required, sift again.
6. Mix items 3, 5, and 6 in a polyethylene bag for 1 to 2 minutes.
7. Sift once through a 250-μm sieve.
8. Add to the first step, and mix for 1 to 2 minutes.
9. Sift items 8, 11, 4, and 12 once through a 1000-μm sieve, and collect in a stainless steel drum.
10. Add the sieved materials from the above steps to the stainless steel drum.
11. Mix in a drum blender for 2 to 3 minutes.
12. Mix items 10, 9, and 1 in a polyethylene bag for 1 to 2 minutes.
13. Sift twice through a 500-μm sieve.
14. Add 25.0 to 30.0 g of granules to the lubricant mixture.
15. Mix for 1 to 2 minutes.
16. Add this mixture to the granules.
17. Mix in a drum blender for 1 minute.
18. Check the moisture content (limit: moisture content NMT 3.5%).
19. Check temperature and humidity before beginning compression (limit: relative humidity, 40–50%; temperature, 20–25°C).
20. Compress into 1300-mg tablets, using 16-mm punches.
21. Fill appropriate amounts for lower strength (e.g., 100 mg tablets in 10-mm punches).

Vitamin C Chewable Tablets with Dextrose

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Ascorbic acid (crystalline); use ascorbic acid (coated, 97.5%), EC	110.00
500.00	2	Dextrose	500.00
4.00	3	Kollidon® 90F	4.00
30.00–50.00	4	Water and/or isopropanol	30.00–50.00
6.00	5	PEG-6000 (powder)	6.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 4 and 5 (in a fluidized bed), sieve, add item 6, and press with high-compression force.
2. Compress into 620-mg tablets, using 12-mm biplanar punches.
3. If no fluidized bed is available, use of water as a granulation solvent should be avoided.
4. The use of coated ascorbic acid does not increase the stability.

Vitamin C Chewable Tablets with Fructose

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
120.00	1	Ascorbic acid (powder)	120.00
500.00	2	Fructose	500.00
200.00	3	Ludipress®	200.00
100.00	4	Avicel™ PH101	100.00
15.00	5	Kollidon® VA 64	15.00
4.00	6	Aerosil® 200	4.00
35.00	7	PEG-6000 (powder)	35.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high-compression force.
2. Compress into 970-mg tablets, using 12-mm biplanar punches.

Vitamin C Chewable Tablets with Sucrose

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Ascorbic acid	500.00
850.00	2	Sucrose, crystalline	850.00
575.00	3	Avicel™ PH 101	575.00
60.00	4	Kollidon® VA 64	60.00
15.00	5	Magnesium stearate	15.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium-compression force.
2. Compress into 2000-mg tablets, using 20-mm biplanar punches.

Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1000.00	1	Vitamin C (as ascorbic acid)	1000.00
800.00	2	Tartaric acid (fine crystals)	800.00
1000.00	3	Sodium bicarbonate	1000.00
0.50	4	Riboflavin	0.50
20.00	5	Saccharin sodium	20.00
20.00	6	Sodium chloride (milled)	20.00
50.00	7	Lime flavor	50.00
1709.50	8	Sugar (fine crystals)	1709.50
QS	9	Alcohol	QS

Manufacturing Directions

1. All operations must be carried out at a relative humidity of less than 40% at 25°C.
2. Active substance granulate: If saccharin sodium is lumpy, sieve it by means of a centrifugal granulator (1 mm) or a 3-mm band sieve.
3. Suck into the mixer the entire amount of sugar, ascorbic acid, tartaric acid, and saccharin sodium (previously sieved, if required), together with 1st part sieved sodium bicarbonate (open filter, closed bypass; jacket temperature of 40°C); backflash filter twice, evacuate to ~800 mbar, and close filter.
4. Mix with mixer for approximately 10 minutes (jacket temperature 40°C) at a speed of 50 rpm.
5. Turn off the mixer, and evacuate to 10 mbar (open filter, closed bypass; jacket temperature of 40°C).
6. Separately dissolve or suspend riboflavin in alcohol.
7. Suck this granulating liquid into the evacuated vessel at a mixer speed of 30 rpm (closed filter, closed bypass; jacket temperature of 40°C).
8. With jacket heating turned off, granulate up to a product temperature of 60°C at a mixer speed of 110 rpm (time required is approximately 20–25 minutes).
9. At a jacket temperature of 56°C and a mixer rotation speed of approximately 15 rpm, dry for 2 to 5 minutes (closed filter, open bypass).
10. When dust develops in the course of further drying, close the bypass and open the filter.
11. At a mixer speed of 20 rpm and interval setting (2 minutes/15 seconds), continue the drying at a jacket temperature of approximately 58°C and vacuum of 10 mbar until a total drying time of 10 to 20 minutes is reached.
12. Sieve the active substance granulate by sucking it by means of vacuum at a jacket temperature of approximately 59°C and a mixer speed of 20 rpm through a Buehler universal mill (1.5-mm screen) directly into a suitable container.
13. Preferable relative humidity of the active substance is less than 10%.
14. Sieve milled sodium chloride and lime flavor through a round hand sieve (1 mm) with a diameter of approximately 38 cm; add to sieved sodium carbonate (2nd part) in a mixing drum, and mix (e.g., tumble mix, 19 rpm for 10 minutes).
15. Combine this dry mix (sucked by vacuum) with the active substance granulate.
16. Finally, add the remaining sieved and lump-free sodium bicarbonate (3rd part).
17. Mix the mixture that is ready for compression for 45 minutes.
18. The preferable relative humidity of the mixture is less than 20%.
19. In a suitable rotary tablet press, compress effervescent tablets with a weight of 4600 mg and a hardness of 8 kpi.

Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Ascorbic acid, (powder)	112.00
200.00	2	Sorbitol (instant)	200.00
1000.00	3	Anhydrous citric acid	1000.00
587.00	4	Sodium bicarbonate	587.00
65.00	5	PEG-6000 (powder)	65.00
10.00	6	Lemon flavor	10.00
25.00	7	Cyclamate sodium	25.00
1.00	8	Saccharin sodium	1.00

Manufacturing Directions

1. Dry the sodium bicarbonate for 1 hour at 100°C, mix with the other components, pass all through a 0.8-mm sieve, and press with high-compression force at a maximum atmospheric relative humidity of 30%.
2. Compress into 2050-mg tablets, using 20-mm biplanar punches.

Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1000.00	1	Ascorbic acid (crystalline)	1000.00
800.00	2	Sorbitol (crystalline)	800.00
150.00	3	Anhydrous citric acid	150.00
660.00	4	Sodium bicarbonate	660.00
80.00	5	PEG-6000 (powder)	80.00
QS	6	Lemon flavor	QS
QS	7	Cyclamate sodium	QS
QS	8	Saccharin sodium	QS

Manufacturing Directions

1. Dry the sodium bicarbonate for 1 hour at 100°C, mix with the other components, pass all through a 0.8-mm sieve, and press with high-compression force at a maximum atmospheric relative humidity of 30%.
2. Compress into 2690-mg tablets, using 20-mm biplanar punches.

Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
500.00	1	Sodium hydrogen carbonate	500.00
430.00	2	Tartaric acid	430.00
8.00	3	Kollidon® 25	8.00
0.20	4	2-Propanol	200.00 mg
550.00	5	Ascorbic acid (crystalline)	550.00
660.00	6	Sucrose	660.00
67.00	7	PEG-6000 (powder)	67.00
67.00	8	Dextrose (powder)	67.00
10.00	9	Orange flavor	10.00
1.00	10	Saccharin sodium	1.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 2 and 3, pass through a 0.5-mm sieve, and dry at 60°C.
2. Dry mixture of items 5 and 6 at 60°C.
3. Mix together with the previous granules and with items 7 to 10.
4. At a maximum atmospheric relative humidity of 30%, press to effervescent tablets.
5. Compress into 2300-mg tablets, using 20-mm biplanar punches.

Vitamin C Tablets

Manufacturing Directions

1. A 5% by weight vitamin C containing tablet is produced in the following manner for a batch size of 100000 tablets (100 kg).
2. The following components are fine screened (Frewitt screening machine) to a 1.0-mm mesh size and mixed for 10 minutes in a tumbling drum mixer in a V2A high-grade steel container (200 L): Ascorbic acid 5000 g; Glucose 1H.sub.2O 89000 g Cellulose powder (tabletting aid K) 4000 g Poly(1-vinyl-2-pyrrolidone 1000 g 25000 (Kollidone 25).
3. Thereafter, 1000 g of magnesium stearate are then screened in by hand and mixed for 2 minutes in the tumbling drum mixer and compressed.

Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Ascorbic acid (coated)	104.00
2.40	2	Anhydrous colloidal silica (Aerosil® 200)	2.40
60.00	3	Cellulose (microcrystalline) (Avicel™ PH102)	60.00
0.13	4	FD&C Yellow Dye No.10 lake	0.13
37.00	5	Lactose (spray-dried)	37.00
3.20	6	Glyceryl behenate (glyceryl monostearate)	3.20
2.40	7	Stearic acid (fine powder)	2.40
1.00	8	Magnesium stearate	1.00

Manufacturing Directions

1. Processing should be done under controlled temperature and humidity (limit: relative humidity, 40–50%; temperature, 20–25°C).
2. Mix items 5 and 4 in a polyethylene bag for 1 to 2 minutes.
3. Sift twice through a 630-μm sieve.
4. Collect in a polyethylene bag.
5. Check the uniformity of dispersion.
6. If required, sift again.
7. Sift item 3.
8. Sift mixture from first step and item 2 through a 630-μm sieve.
9. Load into a drum blender.
10. Sift item 4 through a 630-μm sieve.
11. Load into the mix in the drum blender.
12. Mix items 6, 7, and 8 in a polyethylene bag for 1 to 2 minutes.

14. Sift through a 250-μm sieve.
15. Collect in a polyethylene bag.
16. Add 13.33 to 20.00 g of granules to the lubricant mixture.
17. Mix for 1 to 2 minutes.
18. Add this to the mix in a stainless steel drum blender.
19. Mix in a drum blender for 2 minutes.
20. Check the temperature and humidity before beginning compression (limit: relative humidity, 40–45%; temperature, 20–25°C).
21. Compress into 210-mg tablets, using 8-mm round concave punches.

Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Ascorbic acid (powder)	100.00
232.00	2	Ludipress®	232.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, sieve, and press into 335-mg tablets.
2. Compression force affects disintegration time.

Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Ascorbic acid (powder)	200.00
231.00–256.00	2	Ludipress®	231.00–256.00
25.00	3	Kollidon® VA 64	25.00
15.00	4	Kollidon® CL	15.00
1.20	5	Aerosil® 200	1.20
2.50	6	Magnesium stearate	2.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm screen, and press with medium-compression force (18 kN).
2. Compress into 499-mg tablets, using 12-mm biplanar punches.

Vitamin E Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Vitamin E acetate (SD 50)	200.00
493.00	2	Ludipress®	493.00
390.00	3	Sorbitol (crystalline)	390.00
100.00	4	Mannitol	100.00
400.00	5	Dicalcium phosphate (granulated with 5% Kollidon® 30)	400.00
7.00	6	Aerosil® 200	7.00
3.00	7	Magnesium stearate	3.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm screen, and press with high-compression force.
2. Compress into 711-mg tablets, using 12-mm biplanar punches.

Vitamin E Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
150.00	1	Vitamin E acetate (dry powder, 50%)	300.00
300.00	2	Sorbitol	300.00
6.00	3	Aerosil® 200	6.00
0.20	4	Saccharin sodium	0.20
6.00	5	Magnesium stearate	6.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high-compression force.
2. Compress into 620-mg tablets, using 12-mm biplanar punches.

Vitamin E Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
400.00	1	Vitamin E acetate (dry powder, SD 50)	800.00
790.00	2	Ludipress®	790.00
20.00	3	Aerosil® 200	20.00
QS	4	Flavors	QS

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with high-compression force.
2. Compress into 1665-mg tablets, using 20-mm biplanar punches.

Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Vitamin E acetate (dry powder, SD 50)	100.00
140.00	2	Mannitol	140.00
140.00	3	Tablettose®	140.00
15.00	4	Kollidon® VA 64	15.00
2.00	5	Magnesium stearate	2.00
10.00	6	Aerosil® 200	10.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high-compression force.
2. Compress into 410-mg tablets, using 12-mm biplanar punches.

Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Vitamin E acetate (dry powder, SD 50)	100.00
300.00	2	Sorbitol (crystalline)	300.00
3.00	3	Magnesium stearate	3.00
3.00	4	Aerosil® 200	3.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high-compression force.
2. Compress into 413-mg tablets, using 12-mm biplanar punches.

Voltaren Enteric-Coated Tablets (25 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
25.00	1	Diclofenac sodium	25.00
44.20	2	Lactose Spray Dried	44.20
25.00	3	Microcrystalline cellulose (Avicel PH102)	25.00
2.00	4	Povidone K30	2.00
3.00	5	Sodium starch glycolate	3.00
0.80	6	Magnesium stearate	0.80
18.60	7	Eudragit L30 D, 30% dispersion (Methacrylic acid copolymer)	18.60
0.50	8	Triethyl Citrate (Eudraflex)	0.50
1.00	9	Talc	1.00
–	10	Water, purified	15.00
2.00	11	Hydroxylpropylmethyl cellulose	2.00
0.40	12	Polyethylene glycol 6000	0.40
0.30	13	Talc	0.30
0.70	14	Titanium dioxide	0.70
0.25	15	D&C Yellow No. 10 Aluminum Lake	0.25
–	16	Water, purified	35.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and charge in a tumbler.
2. Pass item 1, item 4 and item 5 through 0.5-mm sieve and charge in step 1.
3. Pass item 3 through 0.7-mm sieve and charge to step 1.
4. Mix step 1 for 20 minutes using tumbler.
5. Pass item 6 through 0.250-mm sieve and add to step 4.
6. Mix step 5 for 2 minutes.
7. Compress into 100-mg tablets, using a suitable punch (5.5 mm, round).
8. Charge item 10 in a stainless steel vessel. Add item 7 slowly to the vortex while stirring.
9. Add item 8 and item 9 one by one to step 8 with stirring. Stir for 5 minutes.
10. Load core tablets from step 7 in coating pan and apply coating dispersion from step 9 to get 6.0% to 6.5% weight gain.
11. 11 Charge item 16 in a stainless steel vessel. Add item 11 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of Hydroxylpropylmethyl cellulose.
12. Add item 12, Item13, item 14 and item 15 one by one to step 11 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Check that coating dispersion is clear and lump free. Pass the coating dispersion through 180-mm sieve (if required).
13. Apply coating dispersion from step 12 to step 10.

Voltaren Enteric-Coated Tablets (50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
50.00	1	Diclofenac sodium	50.00
68.25	2	Lactose Spray Dried	68.25
45.00	3	Microcrystalline cellulose (Avicel PH102)	45.00
5.00	4	Povidone K30	5.00
5.25	5	Sodium starch glycolate	5.25
1.50	6	Magnesium stearate	1.50
32.38	7	Eudragit L30 D, 30% dispersion (Methacrylic acid copolymer)	32.38
0.875	8	Triethyl Citrate (Eudraflex)	0.875
2.00	9	Talc	2.00
–	10	Water, purified	25.00
3.50	11	Hydroxylpropylmethyl cellulose	3.50
0.70	12	Polyethylene glycol 6000	0.70
0.50	13	Talc	0.50
1.20	14	Titanium dioxide	1.20
0.20	15	FD&C Blue No. 1 Aluminum Lake	0.20
–	16	Water, purified	55.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and charge in a tumbler.
2. Pass items 1, 4, and 5 through 0.5-mm sieve and charge in step 1.
3. Pass item 3 through 0.7-mm sieve and charge to step 1.
4. Mix step 1 for 20 minutes using tumbler.
5. Pass item 6 through 0.250-mm sieve and add to step 4.
6. Mix step 5 for 2 minutes.
7. Compress into 175-mg tablets, using a suitable punch (8.0 mm, round).
8. Charge item 10 in a stainless steel vessel. Add item 7 slowly to the vortex while stirring.
9. Add item 8 and item 9 one by one to step 8 with stirring. Stir for 5 minutes.
10. Load core tablets from step 7 in coating pan and apply coating dispersion from step 9 to get 6.0% to 6.5% weight gain.
11. 11 Charge item 16 in a stainless steel vessel. Add item 11 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hydroxylpropylmethyl cellulose.
12. Add item 12, Item13, item 14 and item 15 one by one to step 11 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Check that coating dispersion is clear and lump free. Pass the coating dispersion through 180-mm sieve (if required).
13. Apply coating dispersion from step 12 to step 10.

Voltaren Enteric-Coated Tablet (75 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
75.00	1	Diclofenac sodium	75.00
124.50	2	Lactose Monohydrate	124.50
75.00	3	Microcrystalline cellulose (Avicel PH102)	75.00
12.00	4	Povidone K30	12.00
10.50	5	Sodium starch glycolate	10.50
3.00	6	Magnesium stearate	3.00
–	7	Ethanol 95%	45.00
55.50	8	Eudragit L30 D, 30% dispersion (Methacrylic acid copolymer)	55.50
1.50	9	Triethyl Citrate (Eudraflex)	1.50
3.00	10	Talc	3.00
–	11	Water, purified	45.00
4.50	12	Hydroxylpropylmethyl cellulose	4.50
0.90	13	Polyethylene glycol 6000	0.90
0.90	14	Talc	0.90
2.00	15	Titanium dioxide	2.00
0.20	16	Red Ferric Oxide	0.20
–	17	Water, purified	60.00

Manufacturing Directions

1. Dissolve item 4 in item 7 in a stainless steel container.
2. Pass item 2, item 1 and half quantity of item 3 (37.5 g) through 0.5-mm sieve and mix well.
3. Charge step 2 in a granulator.
4. Knead step 3 with solution of step 1 for 5 to 10 minutes until a loose, moist mass is obtained.
5. Granulate the moist mass using a centrifugal granulator with a 7-mm sieve.
6. Spread step over paper-lined trays, and dry at 45°C to 50°C for 8 hours (the relative humidity over the granules should be 20–35%).
7. Pass the dried granules through a 1.25-mm sieve granulator.
8. Transfer the granules to a tumbler.
9. Pass item 5 and the remaining half quantity of item 9 through 0.5-mm sieve and add to step 8 and mix for 15 minutes.
10. Pass item 6 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 300-mg tablets, using a suitable punch (10.5 mm, round).
13. Charge item 11 in a stainless steel vessel. Add item 8 slowly to the vortex while stirring.
14. Add item 9 and item 10 one by one to step 13 with stirring. Stir for 5 minutes.
15. Load core tablets from step 12 in coating pan and apply coating dispersion from step 14 to get 6.0% to 6.5% weight gain.
16. Charge item 17 in a stainless steel vessel. Add item 12 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hydroxylpropylmethyl cellulose.
17. Add item 13, Item14, item 15 and item 16 one by one to step 11 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Check that coating dispersion is clear and lump free. Pass the coating dispersion through 180-mm sieve (if required).
18. Apply coating dispersion from step 17 to step 15.

VYTORIN Tablets (10 mg/10 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Ezetimibe	10.00
10.00	2	Simvastatin	10.00
50.16	3	Lactose Monohydrate	50.16
25.00	4	Microcrystalline cellulose (Avicel PH102)	25.00
0.02	5	Butylated hydroxyanisole	0.02
1.50	6	Citric acid monohydrate	1.50
0.02	7	Propyl gallate	0.02
2.50	8	Croscarmellose sodium	2.50
0.80	9	Magnesium stearate	0.80
–	10	Water, purified	10.00
–	11	Ethanol 95%	5.00
2.20	12	Hydroxylpropylmethyl cellulose	2.20
–	13	Water, purified	20.00

Manufacturing Directions

1. Dissolve item 6 in item 10 in a stainless steel container.
2. Dissolve item 5 and item 7 one by one in item 11 in another stainless steel container.
3. Mix step 2 with step 1.
4. Pass items 3, 1, and 2 through 0.5-mm sieve and mix well.
5. Charge step 4 in a granulator.
6. Knead step 5 with solution of step 3 for 5 to 10 minutes until a loose, moist mass is obtained.
7. Granulate the moist mass using a centrifugal granulator with a 7-mm sieve.
8. Spread step over paper-lined trays, and dry at 45°C to 50°C for 8 hours (the relative humidity over the granules should be 20–35%).
9. Pass the dried granules through a 1.25-mm sieve granulator.
10. Transfer the granules to a tumbler.
11. Pass items 4 and 8 through 0.5-mm sieve and add to step 10 and mix for 15 minutes.
12. Pass item 9 through 0.250-mm sieve and add to step 11.
13. Mix step 12 for 2 minutes.
14. Compress into 100-mg tablets, using a suitable punch (6.0 mm, round).
15. Charge item 13 in a stainless steel vessel. Add item 12 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hydroxylpropylmethyl cellulose.
16. Load core tablets from step 14 in coating pan and apply coating dispersion from step 15 to get 1.5% to 1.8% weight gain.

VYTORIN Tablets (10 mg/20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Ezetimibe	10.00
20.00	2	Simvastatin	20.00
75.24	3	Lactose monohydrate	75.24
37.50	4	Microcrystalline cellulose (Avicel PH102)	37.50
0.03	5	Butylated hydroxyanisole	0.03
2.25	6	Citric acid monohydrate	2.25
0.03	7	Propyl gallate	0.03
3.75	8	Croscarmellose sodium	3.75
1.20	9	Magnesium stearate	1.20
–	10	Water, purified	15.00
–	11	Ethanol 95%	7.50
3.3	12	Hydroxylpropylmethyl cellulose	3.3
–	13	Water, purified	30.00

Manufacturing Directions

1. Dissolve item 6 in item 10 in a stainless steel container.
2. Dissolve item 5 and item 7 one by one in item 11 in another stainless steel container.
3. Mix step 2 with step 1.
4. Pass items 3, 1, and 2 through 0.5-mm sieve and mix well.
5. Charge step 4 in a granulator.
6. Knead step 5 with solution of step 3 for 5 to 10 minutes until a loose, moist mass is obtained.
7. Granulate the moist mass using a centrifugal granulator with a 7-mm sieve.
8. Spread step over paper-lined trays, and dry at 45°C to 50°C for 8 hours (the relative humidity over the granules should be 20–35%).
9. Pass the dried granules through a 1.25-mm sieve granulator.
10. Transfer the granules to a tumbler.
11. Pass items 4 and 8 through 0.5-mm sieve and add to step 10 and mix for 15 minutes.
12. Pass item 9 through 0.250-mm sieve and add to step 11.
13. Mix step 12 for 2 minutes.
14. Compress into 150-mg tablets, using a suitable punch (7.5 mm × 6.0 mm, oval).
15. Charge item 13 in a stainless steel vessel. Add item 12 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hydroxylpropylmethyl cellulose.
16. Load core tablets from step 14 in coating pan and apply coating dispersion from step 15 to get 1.5% to 1.8% weight gain.

Warfarin Tablets (1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg), Coumadin

Warfarin Sodium Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
11.470	1	Starch (maize)	11.470
0.215	2	Dye	0.215
0.119	3	Dye	0.119
3.020	4	Starch (maize)	3.020
–	5	Water, purified, ca	9.000
37.000	6	Cellulose microcrystalline	37.000
126.310	7	Lactose monohydrate	126.310
1.000	8	Warfarin sodium anhydrous[a]	1.000
0.930	9	Magnesium stearate	0.930
0.930	10	Amberlite (RP-88) ion exchange resin	0.930

[a]Factored quantity; adjust with lactose. Dyes are selected to color-code different strengths for safety.

Manufacturing Directions

Caution: Warfarin is poisonous. Wear a dust mask when handling. Send a 5-g sample to redetermine factor before granulating.

1. Granulation
   a. Roughly blend cornstarch (item 1) with dyes, and mill through a #80-mesh (117-μm aperture or similar) screen.
   b. Rough blend 200 mg of colored starch mixture from step A with cornstarch (item 4).
   c. Make a starch paste using the colored starch mixture from step 1b and approximately 18 mL purified water. *Note:* Starch paste should be smooth and thin. A thick starch paste will cause dye spots.
   d. Rough blend the remaining colored starch mixture from step 1a with the following items: cellulose microcrystalline, lactose, and warfarin sodium, and mill through a 30-mesh (600-μm aperture or similar) screen.
   e. Charge the milled material into a day mixer (or similar) and blend for 10 minutes. Mass with hot starch paste. The addition of starch paste should be finished in 2 minutes. Mass for another 15 minutes using additional purified water, if necessary. Record the amount of purified water added. (*Note:* Do not over wet or mass for too long.)
   f. Granulate through a 5/8-in. (15.88-mm aperture or similar) band.
   g. Dry overnight at 49°C to not more than a 1.5% LOD at 105°C.
      Note: Protect the granules from moisture from this step on. Make sure that the relative humidity is not greater than 40% at 24°C (54 grains).
   h. Sift and grind through a #30-mesh (600-μm aperture or similar) screen.
   i. Or, sift the dried granulation through a #20-mesh (840-μm aperture or similar) screen, and mill the coarse material through a #20-mesh (840-μm aperture or similar) screen using FitzMill (or similar), with knives forward, at medium speed.
2. Lubrication
   a. Charge the granulation into the blender.
   b. Sift magnesium stearate and Amberlite through a #30-mesh (600-μm aperture, or similar) screen into a partial drum of granulation. Mix by hand, and charge into a blender.
   c. Add the remaining granulation to a blender, and blend for 10 minutes.
   d. Discharge the blender into polyethylene-lined drums.
3. Compression: Compress using an 8-mm round flat, beveledged punch. The weight of 10 tablets is 1.85 g; thickness is 2.7 to 2.9 mm. Different dyes and different strengths of warfarin sodium can be adjusted with lactose.

YASMIN Tablet (3 mg/0.03 mg)—Active Film-Coated Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
3.00	1	Drospirenone	3.00
0.03	2	Ethinyl estradiol	0.03
74.47	3	Lactose Spray Dried	74.47
5.00	4	Cornstarch	5.00
1.80	5	Povidone K25	1.80
5.00	6	Starch 1500	5.00
0.70	7	Magnesium stearate	0.70
2.00	8	Hydroxylpropylmethyl cellulose	2.00
0.40	9	Polyethylene glycol 6000	0.40
0.30	10	Talc	0.30
0.60	11	Titanium dioxide	0.60
0.20	12	Yellow ferric oxide	0.20
–	13	Water, purified	30.00

Manufacturing Directions

1. Pass item 3 through 0.7-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 2, 4, 5, and 6 through 0.5-mm sieve and collect in a stainless steel container and mix well.
4. Add 5% (=1.9 g) powder from step 1 to step 3 and mix well.
5. Add 10% (=3.8 g) powder from step 1 to step 4 and mix well.
6. Add 15% (=5.7 g) powder from step 1 to step 5 and mix well.
7. Transfer step 6 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 7 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 90-mg tablets, using a suitable punch (5.5 mm, round).
13. Charge item 13 in a stainless steel vessel. Add item 8 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of Hydroxylpropylmethyl cellulose.
14. Add items 9 to 12 one by one to step 13 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
15. Load core tablets from step 12 in coating pan and apply coating dispersion from step 14 to get 2.5% to 3.0% weight gain.

YASMIN Tablet—Inert Film-Coated Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
92.20	1	Lactose Spray Dried	92.20
5.00	2	Cornstarch	5.00
2.00	3	Povidone K25	2.00
0.80	4	Magnesium stearate	0.80
2.00	5	Hydroxylpropylmethyl cellulose	2.00
0.30	6	Talc	0.30
0.60	7	Titanium dioxide	0.60
–	8	Water, purified	30.00

Manufacturing Directions

1. Pass items 1 to 3 through 0.7-mm sieve and collect in a tumbler.
2. Mix step 1 for 5 minutes using tumbler.
3. Pass item 4 through 0.250-mm sieve and add to step 2.
4. Mix step 3 for 1 minute.
5. Compress into 100-mg tablets, using a suitable punch (4.5 mm × 4.5 mm square).
6. Charge item 8 in a stainless steel vessel. Add item 5 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of Hydroxylpropylmethyl cellulose.
7. Add items 6 and 7 to step 6 with stirring. Stir for 10 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
8. Load core tablets from step 5 in coating pan and apply coating dispersion from step 7 to get 2.0% to 2.5% weight gain.

Zolmitriptan Orally Disintegrating Tablets (2.5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.50	1	Zolmitriptan	2.50
64.80	2	Mannitol DC Grade	64.80
10.00	3	Microcrystalline cellulose	10.00
2.50	4	Crospovidone	2.50
1.00	5	Aspartame	1.00
8.00	6	Sodium bicarbonate	8.00
8.00	7	Citric acid anhydrous	8.00
2.00	8	Orange flavor	2.00
0.70	9	Colloidal silicon dioxide (Aeosil-200)	0.70
0.50	10	Magnesium stearate	0.50

Manufacturing Directions

1. Pass items 2 and 7 through 1-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 4, 5, and 8 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 15% (=5.5 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity from step 4 into step 2.
6. Pass items 3, 6, and 9 through 0.5-mm sieve and add to step 2.
7. Transfer the remaining half quantity of step 4 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 10 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 100-mg tablets, using a suitable punch (5.5 mm, round).

Zolmitriptan Orally Disintegrating Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Zolmitriptan	5.00
62.30	2	Mannitol DC grade	62.30
10.00	3	Microcrystalline cellulose	10.00
2.50	4	Crospovidone	2.50
1.00	5	Aspartame	1.00
8.00	6	Sodium bicarbonate	8.00
8.00	7	Citric acid anhydrous	8.00
2.00	8	Orange flavor	2.00
0.70	9	Colloidal silicon dioxide (Aeosil-200)	0.70
0.50	10	Magnesium stearate	0.50

Manufacturing Directions

1. Pass items 2 and 7 through 1-mm sieve and collect in a stainless steel container.
2. Charge half quantity of step 1 in a tumbler.
3. Pass items 1, 4, 5, and 8 through 0.5-mm sieve and collect in a stainless steel container.
4. Add 15% (=5.2 g) powder from step 1 to step 3 and mix well.
5. Transfer half quantity from step 4 into step 2.
6. Pass items 3, 6, and 9 through 0.5-mm sieve and add to step 2.
7. Transfer the remaining half quantity of step 4 into step 2.
8. Transfer balance quantity of step 1 into step 2.
9. Mix step 2 for 20 minutes using tumbler.
10. Pass item 10 through 0.250-mm sieve and add to step 9.
11. Mix step 10 for 2 minutes.
12. Compress into 100-mg tablets, using a suitable punch (5.0 mm × 5.5 mm, oval).

Zolmitriptan Tablets (2.5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
2.50	1	Zolmitriptan	2.50
58.70	2	Lactose Spray Dried	58.70
35.00	3	Microcrystalline cellulose (Avicel PH102)	35.00
3.00	4	Sodium starch glycolate	3.00
0.80	5	Magnesium stearate	0.80
2.20	6	Hydroxypropyl methylcellulose	2.20
0.40	7	Polyethylene glycol 4000	0.40
0.70	8	Titanium dioxide	0.70
0.20	9	Yellow Iron Oxide	0.20
–	10	Water, purified	30.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and charge in a tumbler.
2. Pass item 1 and item 4 through 0.5-mm sieve and collect in a stainless steel container.
3. Add 5% (=3.0 g) Lactose from step 1 to step 2 and mix well.
4. Add 10% (=5.8 g) Lactose from step 1 to step 3 and mix well.
5. Transfer step 4 into step 1.
6. Pass item 3 through 0.7-mm sieve and charge to step 1.
7. Mix step 1 for 20 minutes using tumbler.
8. Pass item 5 through 0.250-mm sieve and add to step 7.
9. Mix step 8 for 2 minutes.
10. Compress into 100-mg tablets, using a suitable punch (5.5 mm, round).
11. Charge item 10 in a stainless steel vessel. Add item 6 slowly to the vortex while stirring. Stir till lumps dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of Hydroxypropyl methylcellulose.
12. Add items 7 to 9 one by one to step 10 with stirring. Stir for 5 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
13. Load core tablets from step 10 in coating pan and apply coating dispersion from step 12 to get 2.5% to 3.0% weight gain.

Zolmitriptan Tablets (5 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
5.00	1	Zolmitriptan	5.00
56.20	2	Lactose Spray Dried	56.20
35.00	3	Microcrystalline cellulose (Avicel PH102)	35.00
3.00	4	Sodium starch glycolate	3.00
0.80	5	Magnesium stearate	0.80
2.20	6	Hydroxypropyl methylcellulose	2.20
0.40	7	Polyethylene glycol 4000	0.40
0.70	8	Titanium dioxide	0.70
0.20	9	Red Iron Oxide	0.20
–	10	Water, purified	30.00

Manufacturing Directions

1. Pass item 2 through 0.7-mm sieve and charge in a tumbler.
2. Pass items 1 and 4 through 0.5-mm sieve and collect in a stainless steel container.
3. Add 10% (=5.6 g) Lactose from step 1 to step 2 and mix well.
4. Transfer step 3 into step 1.
5. Pass item 3 through 0.7-mm sieve and charge to step 1.
6. Mix step 1 for 20 minutes using tumbler.
7. Pass item 5 through 0.250-mm sieve and add to step 6.
8. Mix step 7 for 2 minutes.
9. Compress into 100-mg tablets, using a suitable punch (5.0 mm × 5.5 mm, oval).
10. Charge item 10 in a stainless steel vessel. Add item 6 slowly to the vortex while stirring. Stir till lumps

dissolved. Homogenize for 5 minutes. Keep for 3 to 4 hours for saturation of hydroxypropyl methylcellulose.
11. Add item 7, item 8 and item 9 one by one to step 10 with stirring. Stir for 5 minutes. Homogenize for 5 minutes. Pass the coating dispersion through 180-mm sieve (if required).
12. Load core tablets from step 9 in coating pan and apply coating dispersion from step 11.

Zolmitriptan Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
1.25	1	Zolmitriptan	1.25
0.12	2	Talc	0.12
0.15	3	Polyvinylpyrrolidone	0.15
Qs	4	Water	Qs
Qs	5	Ethanol	Qs
60.00	6	Sugar spheres	60.00
6.00	7	Eudragit S	6.00
3.00	8	Triethyl citrate	3.00
1.50	9	Talc	1.50
0.105	10	Ammonium hydroxide 1N solution	0.105
3.10	11	Hydroxypropyl methyl cellulose	3.10
0.40	12	Polyethylene glycol	0.40
0.50	13	Flavor optional	0.50
0.50	14	Color optional	0.50
Qs	15	Water	Qs
qs	16	Ethanol	qs

Manufacturing Directions

1. Prepare a dispersion containing Zolmitriptan and talc in polyvinylpyrrolidone solution prepared in water and/or ethanol or a mixture thereof.
2. Apply or spray solution (1) onto the sugar spheres using a coating pan or a fluid-bed coater until a desired amount of solution (1) is applied.
3. The coated spheres may be further seal-coated with a solution containing polyvinylpyrrolidone prepared in water and/or ethanol or a mixture thereof.
4. Prepare the coating solution by mixing water, Eudragit S100, ammonium hydroxide solution, triethyl citrate and talc to form a uniform dispersion.
5. Coat Zolmitriptan beads (from (3)) with Eudragit S coating solution using a coating pan or a fluid-bed coater until a desired coat weight is achieved.
6. Seal Coat of the Enteric-Coated Zolmitriptan Beads: Prepare a coating solution of Hydroxypropyl methylcellulose and polyethylene glycol in water or ethanol or combination thereof.
7. Coat zolmitriptan enteric-coated beads (step (5)) with the above coating solution in a coating pan or a fluid-bed coater until a desired coating weight is obtained for tablets containing 1.25 or 2.50 mg zolmitriptan.

Zolpidem Hemitartarate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Zolpidem hemitartrate	10.00
91.00	2	Lactose monohydrate	91.00
12.00	3	Microcrystalline cellulose	12.00
2.52	4	Hydroxypropyl methyl cellulose	2.52
3.84	5	Sodium carboxymethyl cellulose	3.84
0.72	6	Magnesium stearate	0.72
–	7	Water, purified	QS

Manufacturing Directions

1. Mix items 1 to 4, and blend for 10 minutes.
2. Add item 7 to granulate, dry, and sieve granules.
3. Mix granules with items 5 and 6.
4. Compress into 120-mg tablets.

Zolpidem Tartrate Tablets (5 mg/10 mg), Ambien

Each Ambien® tablet includes the following inactive ingredients: hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. The 5-mg tablet also contains FD&C Red No. 40, iron oxide colorant, and polysorbate 80.

Part III

Tablet Coating Formulations

Tablet Coating Formulations

INTRODUCTION

Solid dosage forms are frequently coated for varied purposes, including the following:

- Mask taste and smell.
- Offer protection from the environment.
- Provide protection from gastric acid (enteric coating).
- Make dose easy to swallow.
- Provide identification.
- Add esthetic appeal.
- Hide surface defects.

Many types of coatings are available.

I. Sugar coating: Compressed tablets are coated with colored or uncolored sugar layer that is water-soluble and quickly dissolves after swallowing. The sugar-coat protects the enclosed drug from the environment and provides a barrier to objectionable taste or order. The sugar coat also enhances the appearance of the compressed tablet and permit imprinting manufacturing's information. Sugar coating provides a combination of insulation, taste masking, smoothing the tablet core, and coloring and modified release. The disadvantages of sugar coating are the time and expertise required in the coating process and thus increases size, weight, and shipping costs. Sugar coating process involves five separate operations:

   a. Sealing/water proofing: Prior to applying any sugar/water syrup, the tablet cores must be sealed, thoroughly dried, and free of all residual solvents. The seal coat provides a moisture barrier and hardness to the surface of the tablet in order to minimize attritional effects. Core tablets having very rapid disintegration rates conceivably could start the disintegration process during the initial phase of sugar coating. The sealants are generally water-insoluble polymers/film formers applied from an organic solvent solution. The quantities of material applied as a sealing coat will depend primarily on the tablet porosity, since highly porous tablets will tend to soak up the first application of solution, thus preventing it from spreading uniformly across the surface of every tablet in the batch. Hence, one or more further application of resin solution may be required to ensure that the tablet cores are sealed effectively. Common materials used as a sealant include shellac, zinc sulfate, cellulose acetate phthalate (CAP), polyvinylacetate phthalate, hyroxypropyl cellulose, hydroxypropyl methylcellulose, etc.

   b. Subcoating: Subcoating is the actual start of the sugar coating process and provides the rapid buildup necessary to round up the tablet edge. It also acts as the foundation for the smoothing and color coats. Generally two methods are used for subcoating. Dusting with powder and then drying follows one where the application of gum based solution and the routine repeated until the desired shape is achieved. The other method is where a suspension of dry powder in gum/sucrose solution is applied followed by drying the tablets. Thus subcoating is a sandwich of alternate layer of gum and powder. It is necessary to remove the bulk of the water after each application of coating syrup.

   c. Grossing/smoothing: The grossing/smoothing process is specifically for smoothing and filing the irregularity on the surface generated during subcoating. It also increases the tablet size to a predetermined dimension. If the subcoating is rough with high amount of irregularities, then the use of grossing syrup containing suspended solids will provide more rapid buildup and better filling qualities. Smoothing usually can be accomplished by the application of a simple syrup solution (approximately 60%–70% sugar solid). This syrup generally contains pigments, starch, gelatin, acacia, or opacifier if required. Small quantities of color suspension can be applied to impart a tint of the desired color when there are irregularities in coating.

   d. Color coating: This stage is often critical in the successful completion of a sugar coating process and involves the multiple application of syrup solution (60%–70% sugar solid) containing the requisite coloring matter. Mainly soluble dyes were used in the sugar coating to achieve the desired color, since the soluble dye will migrate to the surface during drying. But nowadays the insoluble certified lakes have virtually replaced the soluble dyes in pharmaceutical tablet coating. The most efficient process for color coating involves the use of a predispersed opacified lake suspension.

   e. Polishing: Sugar-coated tablets need to be polished to achieve a final elegance. Polishing is achieved by applying the mixture of waxes like beeswax, carnubawax, candelila wax, or hard paraffin wax to tablets in polishing pan.

II. Film Coating: Film coating is deposition of a thin film of polymer surrounding the tablet core. Conventional pan equipments may be used but nowadays more sophisticated equipments are employed to have a high degree of automation and coating time. The polymer is solubilized into solvent. Other additives like plasticizers and pigments are added. Resulting solution is sprayed onto a rotated tablet bed. The drying conditions cause removal of the solvent, giving thin deposition of coating material around each tablet core. Usually spray process is employed in preparation of film-coated tablets. Accela cota is the prototype of perforated cylindrical drum providing high drying air capacity. Fluidized bed equipment has made considerable impact where

tablets are moving in a stream of air passing through the perforated bottom of a cylindrical column. With a smaller cylindrical insert, the stream of cores is rising in the center of the device together with a spray mist applied in the middle of the bottom. For fluidized bed coating, very hard tablets (hardness > 20 N) have to be used. The fundamental requirements are independent of the actual type of equipments being used and include adequate means of atomizing the spray liquid for application to the tablet core, adequate mixing and agitation of tablet bed, and sufficient heat input in the form of drying air to provide the latent heat of evaporation of the solvent. This is particularly important with aqueous-based spraying and good exhaust facilities to remove dust and solvent laden air. The materials used in film coating include the following:

a. Film formers
   i. Hydroxypropyl methylcellulose (HPMC): It is available in different viscosity grades. It is a polymer of choice for air suspension and pan spray coating systems because of solubility characteristic in gastric fluid and organic and aqueous solvent systems. The advantages are that it does not affect tablet disintegration and drug availability; it is cheap, flexible, and highly resistant to heat, light, and moisture; it has no taste and odor; and color and other additives can be easily incorporated. The disadvantage are that when it used alone, the polymer has tendency to bridge or fill the debossed tablet surfaces. So mixture of HPMC and other polymers/plasticizers is used.
   ii. Methylhydroxy ethylcellulose (MHEC): It is available in wide variety of viscosity grades. It is not frequently used as HPMC because soluble in fewer organic solvents.
   iii. Ethylcellulose (EC): Depending on the degree of ethoxy substitution, different viscosity grades are available. It is completely insoluble in water and gastric fluids. Hence it is used in combination with water-soluble additives like HPMC and not alone. Unplasticized ethylcellulose films are brittle and require film modifiers to obtain an acceptable film formulation. Aqua coat is aqueous polymeric dispersion utilizing ethyl cellulose. These pseudolatex systems contain high solids, low-viscosity compositions that have coating properties quite different from regular ethyl cellulose solution.
   iv. Hydroxypropyl cellulose (HPC): It is soluble in water below 40°C (insoluble above 45°C), gastric fluid, and many polar organic solvents. HPC is extremely tacky as it dries from solution system. It is used for subcoat and not for color or glass coat. It gives very flexible film.
   v. Povidone: Degree of polymerization decides molecular weight of material. It is available in four viscosity grades i.e. K-15, K-30, K-60, and K-90. Average molecular weight of these grades is 10,000, 40,000, 160,000, and 360,000 respectively. K-30 is widely used as tablet binder and in tablet coating. It has excellent solubility in wide variety of organic solvents, water, gastric, and intestinal fluids. Povidone can be crosslinked with other materials to produce films with enteric properties. It is used to improve dispersion of colorants in coating solution.
   vi. Sodium carboxy methyl cellulose: It is available in medium, high, and extra high-viscosity grades. It is easily dispersed in water to form colloidal solutions but is insoluble in most organic solvents and hence not a material of choice for coating solution based on organic solvents. Films prepared by it are brittle but adhere well to tablets. Partially dried films of are tacky. So coating compositions must be modified with additives.
   vii. Polyethylene glycols (PEG): PEG with low-molecular weights (200–600) are liquid at room temperature and are used as plasticizers. High-molecular weights PEG (900–8000 series) are white, waxy solids at room temperature. Combination of PEG waxes with CAP gives films that are soluble in gastric fluids.
   viii. Acrylate polymers: It is marketed under the name of Eudragit®. Eudragit®E is cationic co-polymer. Only Eudragit®E is freely soluble in gastric fluid up to pH 5 and expandable and permeable above pH 5. This material is available as organic solution (12.5% in isopropanol/acetone), solid material, or 30% aqueous dispersion. Eudragit®RL & RS are copolymers with low content of quaternary ammonium groups. These are available only as organic solutions and solid materials. They produce films for delayed action (pH dependent).
b. Solvents: Mostly solvents are used either alone or in combination with water, ethanol, methanol, isopropanol, chloroform, acetone, methylene chloride, etc. Water is more used because there are no environmental and economic considerations. For drugs that readily hydrolyze in presence of water, nonaqueous solvents are used.
c. Plasticizers: As solvent is removed, most polymeric materials tend to pack together in three-dimensional honey comb arrangement. Both internal and external plasticizing techniques are used to modify the quality of film. Combination of plasticizer may be used to get desired effect. Concentration of plasticizer is expressed in relation to the polymer being plasticized. Recommended levels of plasticizers range from 1% to 50% by weight of the film former. Commonly used plasticizers are castor oil, PG, glycerin, lower molecular weight (200–400 series) PEG, surfactants, etc. For aqueous coating, PEG and PG are more used, while castor oil and spans are primarily used for organic-solvent–based coating solution. External plasticizer should be soluble in the solvent system used for dissolving the film former and plasticizer. The plasticizer and the film former must be at least partially soluble or miscible in each other.
d. Colorants: Colorants can be used in solution form or in suspension form. To achieve proper distribution of suspended colorants in the coating solution, requires the use of the powdered colorants (<10 microns). Most common colorants in use are certified FD & C or D & C colorants. These are synthetic dyes or lakes. Lakes are choice for sugar or film coating as they give reproducible results. Concentration of colorants in the coating solutions depends on the color

shade desired, the type of dye, and the concentration of opaquant-extenders. If very light shade is desired, concentration of less than 0.01% may be adequate; on the other hand, if a dark color is desired, a concentration of more than 2.0% may be required. The inorganic materials (e.g., iron oxide) and the natural coloring materials (e.g., anthrocyanins, carotenoids, etc) are also used to prepare coating solution. Magenta red dye is nonabsorbable in biologic system and resistant to degradation in the gastro intestinal track. Opasray® (opaque color concentrate for film coating) and Opadry® (complete film coating concentrate) are promoted as achieving less lot-to-lot color variation.

e. Opaquant-extenders: These are very fine inorganic powder used to provide more pastel colors and increase film coverage. These inorganic materials provide white coat or mask color of the tablet core. Colorants are very expensive and higher concentration is required. These inorganic materials are cheap. In presence of these inorganic materials, amount of colorants required decreases. Most commonly used materials are titanium dioxide, silicate (talc and aluminum silicates), carbonates (magnesium carbonates), oxides (magnesium oxide), and hydroxides (aluminum hydroxides).
f. Other components: Flavors, sweeteners, surfactants, antioxidants, antimicrobials, etc., may be incorporated into the coating solution.

III. Enteric Coating: The one-layer is applied as one homogenous layer, which can be whites-opaque or colored. The advantage is that is only one application needed. The two-layer system where the enteric formulation is applied first, followed by colored film. Both layers can be of enteric polymer or only the basic layer contains enteric polymer while top layer is fast disintegrating and water-soluble polymer. Polymers used for enteric coating include the following:
   a. Cellulose acetate phthalate (CAP): It is widely used in industry. Aquateric is reconstituted colloidal dispersion of latex particles. It is composed of solid or semisolid polymer spheres of CAP ranging in size from 0.05 to 3 microns. Cellulose acetate trimellitate (CAT) developed as an ammoniated aqueous formulation showed faster dissolution than a similar formulation of CAP. Disadvantages include: It dissolves above pH 6 only, delays absorption of drugs, is hygroscopic and permeable to moisture in comparison with other enteric polymer, and is susceptible to hydrolytic removal of phthalic and acetic acid changing film properties. CAP films are brittle and usually used with other hydrophobic film forming materials.
   b. Acrylate polymers: Eudragit®L & Eudragit®S are two forms of commercially available enteric acrylic resins. Both of them produce films resistant to gastric fluid. Eudragit®L & S are soluble in intestinal fluid at pH 6 & 7 respectively. Eudragit®L is available as an organic solution (Isopropanol), solid or aqueous dispersion. Eudragit®S is available only as an organic solution (Isopropanol) and solid.
   c. Hydroxy propyl methyl cellulose phthalate: HPMCP 50, 55, and 55-s (also called HP-50, HP-55, and HP-55-s) is widely used. HP-55 is recommended for general enteric preparation while HP-50 and HP-55-s for special cases. These polymers dissolve at a pH 5 to 5.5.
   d. Polyvinyl acetate phthalate: It is similar to HP-55 in stability and pH dependent solubility.
   e. Enteric coating can be combined with polysaccharides, which are enzyme degraded in colon, e.g., Cyclodextrin and galactomannan.

IV. Controlled-Release Coating: Polymers like modified acrylates, water insoluble cellulose (ethyl cellulose), etc., used for controlled-release coating.

V. Compressed Coating: This type of coating requires a specialization tablet machine. Compression coating is not widely used but it has advantages in some cases in which the tablet core cannot tolerate organic solvent or water and yet needs to be coated for taste masking or to provide delayed or enteric properties to the finished product and also to avoid incompatibility by separating incompatible ingredients.

VI. Electrostatic Coating: Electrostatic coating is an efficient method of applying coating to conductive substrates. A strong electrostatic charge is applied to the substrate. The coating material containing conductive ionic species of opposite charge is sprayed onto the charged substrate. Complete and uniform coating of corners and adaptability of this method to such relatively nonconductive substrate as pharmaceutical is limited.

VII. Dip Coating: Coating is applied to the tablet cores by dipping them into the coating liquid. The wet tablets are dried in a conventional manner in coating pan. Alternative dipping and drying steps may be repeated several times to obtain the desired coating. This process lacks the speed, versatility, and reliability of spray-coating techniques. Specialized equipment has been developed to dip-coat tablets, but no commercial pharmaceutical application has been obtained.

VIII. Vacuum Film Coating: Vacuum film coating is a new coating procedure that employs a specially designed baffled pan. The pan is hot water jacketed, and it can be sealed to achieve a vacuum system. The tablets are placed in the sealed pan, and the air in the pan is displaced by nitrogen before the desired vacuum level is obtained. The coating solution is then applied with airless spray system. The heated pan causes the evaporation, and the vapor is removed by the vacuum system. Because there is no high-velocity heated air, the energy requirement is low and coating efficiency is high. Organic solvent can be effectively used with this coating system with minimum environmental or safety concerns.

Formulations for tablet coating are often proprietary to various manufacturers as these address several formulation needs as described above. The suppliers of coating ingredients are often very open to sharing the coating technology and companies are highly encouraged to make use of them, more particularly where the coating materials have an open DMF available for regulatory filings. The following companies are a very good source of information:

Eudragit® (http://www.pharma-polymers.com/pharma-polymers/en/eudragit/).
Colorcon® (http://www.colorcon.com/products/coatings).
Methocel/Ethocel (http://www.dow.com/dowexcipients/applications/tablet_coating.htm).

The advantage of using these prepackaged formulations is consistency in color matching, as well as other considerations regarding ease of use. The most significant aspect remains the choice of colors, which often determines the method of manufacturing the coating solutions. With a limited choice of dyes and lakes available for selection, manufacturers often use a combination of several colors and dyes along with agents such as talc for opaqueness to obtain the desired color and protection.

Given below is a current listing of approved colors in various regulatory regions.

Approved Drug Colorants for Internal Use in Japan-1[a]

Name	CAS Number	Color Index Number	Precedent Limit	Compendia
Black Iron Oxide	12227-89-3	77499	1.539 mg	JPE
Caramel			1500 mg	JPE
Carbon Black	1333-86-4	77268:1	0.096 mg	JPE
Carmine	1390-65-4	75470	1.8 mg	JPE
β-Carotene	7235-40-7	40800	0.1%	JPE
Copper Chlorophyll			1.8 mg	Japan Pharmaceutical Codex
Glycyrrhiza Extract			300 mg	JP
Gold Leaf	7440-57-5		14 mg	JPE
Light Anhydrous Silicic Acid	7631-86-9		2.6 g	JP
Medicinal Carbon	16291-96-6		150 mg	JP
2-octyldodecyl Myristate	22766-83-2		100 mg	JPE
Orange Essence			15 mg	JPE
Powdered Green Tea			100 mg	JPE
Red Ferric Oxide	1309-37-1	77491	95.4 mg	JPE
Riboflavin	83-88-5		0.8 mg	JP
Riboflavin Butyrate			0.4 mg	JP
Riboflavin Sodium Phosphate			2 mg	JP
Rose Oil	8007-01-0		0.1 mg	NF
Rye Green Leaf Extract			2 mg	JPE
Sodium Copper Chlorophyllin			75 mg	Japan Pharmaceutical Codex
Sodium Hydroxide	1310-73-2		224 mg	JP
Talc	14807-96-6		3384 mg	JP
Titanium Oxide	13463-67-7	77891	384 mg	JP
Yellow Ferric Oxide	1310-14-1	77492	5.67 mg	JPE

[a]These colorants appear in the application column in the Japanese Pharmaceutical Excipients Directory 2007 (Japanese Version) as coloring agents. Precedent limits are quoted from the Japanese Pharmaceutical Excipients Directory 2007 (Japanese version). Each limit represents the maximum daily intake that a patient should consume from the use of a particular dosage form.

Approved Drug Colorants for Internal Use in Japan-2[*b]

Name	Alternate Name	Color Index Number	CAS Number	Precedent Limit
Amaranth[*d]	Red #2, Acid Red 27	16185	915-67-3	*c
Erythrosine[*d]	Red #3, Acid Red 51	45430	16423-68-0	*c
New Coccine (Ponceau4R)[*d]	Red #102, Acid Red 18	16255	2611-82-7	*c
Phloxine B	Red #104(1), Acid Red 92	45410	18472-87-2	*c
Rose Bengal	Red #105(1), Acid Red 94	45440	632-69-9	*c
Acid Red	Red #106, Acid Red 52	45100		*c
Tartrazine[*d]	Yellow #4, Acid Yellow 23	19140	1934-21-0	*c
Sunset Yellow FCF[*d]	Yellow #5	15985	2783-94-0	*c
Fast Green FCF	Green #3	42053	2353-45-9	*c
Brilliant Blue FCF[*d]	Blue #1	42090	3844-45-9	*c
Indigo Carmine[*d]	Blue #2, Acid Blue 74	73015	860-22-0	*c

[*b]Based on colors approved by the MHWs “Ministerial Ordinance to establish Tar colors which can be used in Pharmaceuticals”; No. 30; August 31, 1966. Aluminum lakes of these colors are also authorized.

[*c]Not more than 0.1% by weight of color (lake or dye) can be used in a dosage form. If one colorant was combined with other colorants, total weight of these colorants must be less than 0.1% of the final product.

[*d]These colorants make the list of the application column in the Japanese Pharmaceutical Excipients Directory 2007 (Japanese Version) as coloring agents.

Approved Drug Colorants for Use in Canada*

I. Colorants approved for internal and external drug use

Color	Alternate Name	Color Index Number	CAS Number
Acid Fuchsin D	D&C Red #33	17200	3567-66-6
Alizarin Cyanine Green F	D&C Green #5	61570	4403-90-1
Allura Red AC	FD&C Red #40	16035	25956-17-6
Amaranth	Delisted FD&C Red #2	16185	915-67-3
Anthocyanin (Derived from juice expressed from fresh edible fruits or vegetables)			
β-APO-8´ Carotenal	–	40820	1107-26-2
Brilliant Blue FCF Sodium Salt	FD&C Blue #0	42090	3844-45-8
Brilliant Blue FCF Ammonium Salt	D&C Blue #4	42090	6371-85-2
Canthaxanthin	–	40850	514-78-3
Caramel	–	–	–
Carbon Black	–	77266	1333-86-4
Carmine	–	75470	1260-17-9
Carmoisine	Azorubine	14720	3567-69-9
β-carotene	–	40800	7235-40-7
Chlorophyll	–	75810	479-61-8
Eosin YS Acid Form	D&C Red #21	45380:2	15086-94-9
Eosin YS Sodium Salt	D&C Red #22	45380	17372-87-1
Erythrosine	FD&C Red #3	45430	16423-68-0
Fast Green FCF	FD&C Green #3	42053	2353-45-9
Flaming Red	D&C Red #36	12085	2814-77-9
Helindone Pink CN	D&C Red #30	73360	2379-74-0
Indigo	D&C Blue #6	73000	482-89-3
Indigotine	FD&C Blue #2`	73015	860-22-0
Iron Oxides	Iron Oxide Red	77491	1309-37-1
	Iron Oxide Yellow	77492	51274-00-1
	Iron Oxide Black	77499	12227-89-3
Lithol Rubin B Sodium Salt	D&C Red #6	15850	5858-81-1
Lithol Rubin B Calcium Salt	D&C Red #7	15850:1	5281-04-9
Phloxine B Sodium Salt	D&C Red #28	45410	18472-87-2
Phloxine B Acid Form	D&C Red #27	45410:1	13473-26-2
Ponceau 4R	–	16255	2611-82-7
Ponceau SX	FD&C Red #4	14700	4548-53-2
Quinoline Yellow WS	D&C Yellow #10	47005	8004-92-0
Riboflavin	–	–	83-88-5
Sunset Yellow FCF	FD&C Yellow #6	15985	2783-94-0
Tartrazine	FD&C Yellow #5	19140	1934-21-0
Titanium Dioxide	–	77891	13463-67-7

II. Colorants approved for external drug use

Color	Alternate Name	Color Index Number	CAS Number
Acid Violet	Ext. D&C Violet #2	60730	–
Alizurol Purple SS	D&C Violet #2	60725	81-48-1
Annatto	–	75120	–
Bismuth Oxychloride	–	77163	–
Chromium Hydroxide Green	Pigment Green 18	77289	–
Dibromofluorescein (Solvent Red 72)	D&C Orange #5	45370:1	–
Deep Maroon	D&C Red #34	15880:1	6417-83-0
Ferric Ferrocyanide	–	77510	–
Guanine	–	75170	–
Orange II	D&C Orange #4	15510	633-96-5
Manganese Violet	–	77742	–
Mica	–	77019	–
Pyranine Concentrated	D&C Green #8	59040	6358-69-6
Quinizarin Green SS	D&C Green #6	61565	128-80-3
Toney Red	D&C Red #17	26100	85-86-9
Uranine Acid Form	D&C Yellow #7	45350:1	7/5/2321
Uranine Sodium Salt	D&C Yellow #8	45350	518-47-8
Zinc Oxide	–	77947	–

Approved Drug Colourants Listed by the European Union*

Note: Aluminum lakes prepared from colours mentioned in this list are also permitted.

Colour	E Number	Colour Index Number	Alternate Names
Allura Red AC	E129	16035	FD&C Red #40
Aluminum	E173	77000	–
Amaranth	E123	16185	Delisted FD&C Red #2
Anthocyanins	E163	–	–
Beet Root Red	E162	–	Betanin
Beta APO-8´-Carotenal	E160e	40820	–
Beta APO-8´-Carotenoic			–
Acidethyl Ester	E160f	40825	
Brilliant Black BN	E151	28440	Black PN
Brilliant Blue FCF	E133	42090	FD&C Blue #1
Brown HT	E155	20285	–
Calcium Carbonate	E170	77220	–
Canthaxanthin	E161g	40850	–
Caramel	E150a	–	–
Caramel,-Caustic Sulphite	E150b	–	–
Caramel,-Ammpnia	E150c	–	–
Caramel, Sulphite Ammonia	E150d	–	–
Carbon Vegetable Black	E153	77268:1	Carbo Medicinalis Vegetalis
Carmine	E120	75470	Carmine 40, Carminic Acid
Carmoisine	E122	14720	Azorubine
Carotene		75130	Alpha, Beta & Gamma Carotene
i. Mixed Carotenes	E160a(i)	75130	–
ii. Beta-Carotene	E160a(ii)	40800	–
Chlorophylls/Chlorophyllins		–	–
i. Chlorophylls	E140(i)	75810	–
ii. Chlorophyllins	E140(ii)	75815	–
Chlorophylls/Chlorophyllins			
Copper Complexes		75815	–
i. Copper Complexes	E141(i)		
Of Chlorophylls		–	–
ii. Copper Complexes	E141(ii)		
Of Chlorophyllins		–	–
Cochineal	E120	75470	Carminic Acid
Erythrosine	E127	45430	FD&C Red #3
Gold	E175	77480	–
Green S	E142	44090	Acid Brilliant Green BS
Indigotine	E132	73015	FD&C Blue #2, Indigo Carmine
Iron Oxides & Hydroxides	E172	77491	Iron Oxide Red
		77492	Iron Oxide Yellow
		77499	Iron Oxide Black
Lutein	E161b	–	–
Lycopene	E160d	–	–
Paprika Extract	E160c	–	Capsanthin, Capsorubin
Patent Blue V	E131	42051	Acid Blue 3
Ponceau 4R	E124	16255	Cochineal Red A
Quinoline Yellow[b]	E104	47005	China Yellow
Riboflavin		–	–
i. Riboflavin	E101(i)	–	–
ii. Riboflavin-5'-Phosphate	E101(ii)	–	–
Sunset Yellow FCF	E110	15985	FD&C Yellow #6, Orange Yellow S
Tartrazine	E102	19140	FD&C Yellow #5
Titanium Dioxide	E171	77891	–
Turmeric	E100	75300	Curcumin

This list is derived from Annex 1 of Directive 94/36/EC, colours permitted for use in foodstuffs. EMEA Guideline EMEA/CHMP/QWP/396951/2006 states that colourants mentioned in this annex are permitted for use in medicinal products.

*This is not D&C yellow #10. Although the C.I. numbers are the same, the dyes differ in composition. Quinoline yellow is primarily the disulfonated quinoline dye, whereas D&C yellow #10 is the monosulfonated color. Quinoline yellow is not accepted for use in the United States; conversely, D&C yellow #10 cannot be used in the EU.

Color Additives Exempt from Certification Permitted for Use in the United States*

Color	Color Index Number	CAS Number	21 CFR References			
			Food	Drug	Cosmetic	Medical Devices
Algae Meal (Dried)	–	–	73.275	–	–	–
Algae Meal (Haematococcus)	–	–	73.185	–	–	–
Alumina	77002	1332-73-6	–	73.1010	–	–
Aluminum Powder	77000	7429-90-5	–	73.1645	73.2645	–
Annatto Extract	75120	8015-67-6	73.30	73.1030	73.2030	–
Astaxanthin	–	–	73.35	–	–	–
Beta- Apo-8'-Carotenal	40820	1107-26-2	73.90	–	–	–
Beta Carotene	40800	7235-40-7	73.95	73.1095	73.2095	–
Beet Powder	–	57917-55-2	73.40	–	–	–
Bismuth Citrate	–	–	–	–	73.2110	–
Bismuth Oxychloride	77163	7787-59-9	–	73.1162	73.2162	–
Bronze Powder	77440	7440-50-8	–	73.1646	73.2646	–
		7740-66-6				
Calcium Carbonate	77220	471-34-1	–	73.1070	–	–
Canthaxanthin	40850	514-78-3	73.75	73.1075	–	–
Caramel	–	–	73.85	73.1085	73.2085	–
Carbazole Violet	51319	6358-30-1	–	–	–	73.3107
Carmine	75470	1390-65-4	73.100	73.1100	73.2087	–
Carrot Oil	–	–	73.300	–	–	–
Chlorophyllin Copper Complex	75810	–	–	73.1125	73.2125	73.3110
Chromium-Cobalt-Aluminum Oxide	77343	68187-11-1	–	73.1015	–	73.3110a
Chromium Hydroxide Green	77289	12182-82-0	–	73.1326	73.2326	–
Chromium Oxide Greens	77288	1308-38-9	–	73.1327	73.2327	73.3111
C.I. Vat Orange 1	59105	–	–	–	–	73.3112
Cochineal Extract	75470	1260-17-9	73.100	73.1100	–	–
Corn Endosperm Oil	–	–	73.315	–	–	–
Copper Powder	77400	7440-50-6	–	73.1647	73.2647	–
1,4-Bis [(2-hydroxyethyl) amino]-9,10-anthracenedione bis(2-propenoic) ester copolymers	–	10956-07-1	–	–	–	73.3100
1,4-Bis [(2-methylphenyl)amino]-9,10-anthracenedione	–	6737-68-4	–	–	–	73.3105
1,4-Bis[4-(2-methacryloxyethyl) phenylamino]-9,10-anthraquinone Copolymers	–	121888-69-5	–	–	–	73.3106
2-[[2,5-Diethoxy-4-[(4-methylphenyl) thiol]phenyl]azo]-1,3,5-benzenetriol	–	–	–	–	–	73.3115
16,23-Dihydrodinaptho[2,3-a:2′,3′-i] napth[2′,3′:6,7]indolo[2, 3-c]carbazole-5,10,15,17,22,24-hexone	70800	2475-33-4	–	–	–	73.3117
N,N′-(9,10-Dihydro-9,10-dioxo-1,5-anthracenediyl) bis-benzamide	61725	82-18-8	–	–	–	73.3118
7,16-Dichloro-6,15-dihydro-5,9,14,18-anthrazinetetrone	69825	130-20-1	–	–	–	73.3119
16,17-Dimethoxydinaphtho[1,2,3-cd:3′,2′,1′-lm] perylene-5,10 dione	59825	128-58-5	–	–	–	73.3120
4-[2,4-(Dimethylphenyl)azo]-2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one	–	6407-78-9	–	–	–	73.3122
Dihydroxy Acetone	–	62147-49-3	–	73.1150	73.2150	–
Disodium EDTA Copper	–	–	–	–	73.2120	–
6-Ethoxy-2-(6-ethoxy-3-oxobenzo [*b*]thien-2-(3*H*)-ylidene)benzo[*b*] thiophen-3-(2*H*)-one	73335	3263-31-8	–	–	–	73.3123
Ferric Ammonium Citrate	–	1185-57-5	–	73.1025	–	–
Ferric Ammonium Ferrocyanide	77510	25869-00-5	–	73.1298	73.2298	–
Ferric Ferrocyanide	77510	14038-43-8	–	73.1299	73.2299	–
Ferrous Gluconate	–	299-29-6	73.160	–	–	–
Ferrous Lactate	–	5905-52-2	73.165	–	–	–
Fruit Juice	–	–	73.250	–	–	–

Color Additives Exempt from Certification Permitted for Use in the United States* (*Continued*)

Color	Color Index Number	CAS Number	21 CFR References			
			Food	Drug	Cosmetic	Medical Devices
Grape Color Extract	–	–	73.169	–	–	–
Grape Skin Extract	–	–	73.170	–	–	–
Guaiazulene	–	489-84-9	–	–	73.2180	–
Guanine	75170	68-94-0 73-40-5	–	73.1329	73.2329	–
Henna	75480	83-72-7	–	–	73.2190	–
Iron Oxides, Synthetic	77491(Red) 77492(Yellow) 77499(Black)	1309-37-1 51274-00-1 12227-89-3	73.200	73.1200	73.2250	73.3125
Lead Acetate	–	6080-56-4	–	–	73.2396	–
Logwood Extract	75290	8005-33-2	–	73.1410	–	–
Manganese Violet	77742	10101-66-3	–	–	73.2775	–
Mica	77019	12001-26-2	–	73.1496	73.2496	–
Mica-Based Pearlescent Pigment	–	–	73.350	73.1350	–	73.3128
Paprika	–	–	73.340	–	–	–
Paprika Oleoresin	–	8023-77-6	73.345	–	–	–
Phaffia Yeast	–	–	73.355	–	–	–
Potassium Sodium Copper Chlorophyllin	75180	–	–	73.1125	73.2125	–
Phthalocyanine Green	74260	1328-53-6	–	–	–	73.3124
Poly(Hydroxyethyl Methacrylate)-Dye Copolymers	–	–	–	–	–	73.3121
Pyrogallol	76515	87-66-1	–	73.1375	–	–
Pyrophyllite	44004	8047-76-5	–	73.1400	73.2400	–
Riboflavin	–	83-88-5	73.450	–	–	–
Saffron	75100	42553-65-1 27876-94-4	73.500	–	–	–
Silver	77820	7440-22-4	–	–	73.2500	–
Sodium Copper Chlorophyllin	75815	28302-36-5	73.125	–	–	–
Tagetes Meal & Extract	75125	–	73.295	–	–	–
Talc	77019	14807-96-6	–	73.1550	–	–
Toasted Cotton Seed Meal	–	–	73.140	–	–	–
Titanium Dioxide	77891	13463-67-7	73.575	73.1575	73.2575	73.3126
Tomato Lycopene Extract And Concentrate			73.585	–	–	–
Turmeric	75300	458-37-7	73.600	–	–	–
Turmeric Oleoresin	75300	458-37-7	73.615	–	–	–
Ultramarine Blue	77007	57455-37-5	73.50	–	73.2725	–
Ultramarine Green	77013	–	–	–	73.2725	–
Ultramarine Pink	77007	127-96-9	–	–	73.2725	–
Ultramarine Red	77007	127-96-9	–	–	73.2725	–
Ultramarine Violet	77007	127-96-9	–	–	73.2725	–
Vegetable Juice	–	–	73.260	–	–	–
Vinyl Alcohol/Methyl Methacrylate Dye Reaction Products	–	–	–	–	–	73.3127
Zinc Oxide	77947	1314-13-2	–	73.1991	73.2991	–
Luminescent Zinc Sulfide	–	–	–	–	73.2995	–

*Based on 21 CFR 2007. Restrictions may exist limiting the use of some of these colors to specific applications (i.e., external drug use only, etc.). Additionally, there may be quantitative limits for the use of some colors. The specific 21 CFR reference for each color should be reviewed to determine potential restriction status.

Provisionally Listed Color Additives Subject to U.S. Certification*

Color	Common Name	Color Index Number	CAS Number	21 CFR References		
				Food	Drug	Cosmetic
FD&C Lakes	Lakes	See Individual Color	See Individual Color	82.51	82.51	82.51
D&C Lakes	Lakes	See Individual Color	See Individual Color	–	82.1051	82.1051
Ext. D&C Lakes	Lakes	See Individual Color	See Individual Color	–	82.2051	82.2051
FD&C Blue #1 Lake	Brilliant Blue FCF	42090:2	68921-42-6	82.101	82.101	82.101
FD&C Blue #2 Lake	Indigotine	73015:1	16521-38-3	82.102	82.102	82.102
D&C Blue #4 Lake	Alphazurine FG	42090	6371-85-3	–	82.1104	82.1104
FD&C Green #3 Lake	Fast Green FCF	42053	2353-45-9	82.203	82.203	82.203
D&C Green #5 Lake	Alizarin Cyanine Green F	61575	4403-90-1	–	82.1205	82.1205
D&C Green #6 Lake	Quinizarine Green SS	61565	128-80-3	–	82.1206	82.1206
D&C Orange #4 Lake	Orange II	15510:2	633-96-5	–	82.1254	82.1254
D&C Orange #5 Lake	Dibromofluorescein	45370:2	596-03-2	–	82.1255	82.1255
D&C Orange #10 Lake	Diiodofluorescein	45425:2	38577-97-8	–	82.1260	82.1260
D&C Orange #11 Lake	Erythrosine Yellowish Na	45425:2	38577-97-8	–	82.1261	81.1261
FD&C Red #4 Lake	Ponceau SX	14700	4548-53-2	82.304	82.304	82.304
D&C Red #6 Lake	Lithol Rubin B	15850:2	17852-98-1	–	82.1306	82.1306
D&C Red #7 Lake	Lithol Rubin B Ca	15850:1	5281-04-9	–	82.1307	82.1307
D&C Red #17 Lake	Toney Lake	26100	85-86-9	–	82.1317	82.1317
D&C Red #21 Lake	Tetrabromofluorescein	45380:3	15086-94-9	–	82.1321	82.1321
D&C Red #22 Lake	Eosine	45380:3	17372-87-1	–	82.1322	82.1322
D&C Red #27 Lake	Tetrachlorotetra-Bromofluorescein	45410:2	13473-26-2	–	82.1327	82.1327
D&C Red #28 Lake	Phloxine B	45410:2	18472-87-02	–	82.1328	82.1328
D&C Red #30 Lake	Helindone Pink CN	73360	2379-74-0	–	82.1330	82.1330
D&C Red #31 Lake	Brilliant Lake Red R	15800:1	6371-76-2	–	82.1331	82.1331
D&C Red #33 Lake	Acid Fuchsine	17200	3567-66-6	–	82.1333	82.1333
D&C Red #34 Lake	Lake Bordeaux B	15880:1	6417-83-0	–	82.1334	82.1334
D&C Red #36 Lake	Flaming Red	12085	2814-77-9	–	82.1336	82.1336
D&C Violet #2 Lake	Alizurol Purple SS	60725	81-48-1	–	82.1602	82.1602
FD&C Yellow #5 Lake	Tartrazine	19140:1	12225-21-7	82.705	82.705	82.705
FD&C Yellow #6 Lake	Sunset Yellow FCF	15985:1	15790-07-5	82.706	82.706	82.706
D&C Yellow #7 Lake	Fluorescein	45350:1	2321-07-5	–	82.1707	82.1707
Ext. D&C Yellow #7 Lake	Napthol Yellow S	10316	846-70-8	–	82.2707a	82.2707a
D&C Yellow #8 Lake	Uranine	45350	518-47-8	–	82.1708	82.1708
D&C Yellow #10 Lake	Quinoline Yellow WS	47005:1	68814-04-0	–	82.1710	82.1710

*Based on 21 CFR 2007. Restrictions may exist limiting the use of some of these colors to specific applications (i.e., external drug use only, etc.). Additionally there may be quantitative limits for the use of some colors. The specific 21 CFR reference for each color should be reviewed to determine potential restriction status.

List of Permanently Listed Color Additives Subject to U.S. Certification*

Color	Common Name	Color Index Number	CAS Number	21 CFR References			
				Food	Drug	Cosmetic	Medical Devices
D&C Black #2	Carbon Black	77266	1333-86-4	–	–	74.2052	–
D&C Black #3	Bone Black	77267	8021-99-6	–	–	74.2053	–
FD&C Blue #1	Brilliant Blue FCF	42090	2650-18-2	74.101	74.1101	74.2101	–
FD&C Blue #2	Indigotine	73015	860-22-0	74.102	74.1102	–	74.3102
D&C Blue #4	Alphazurine FG	42090	6371-85-3	–	74.1104	74.2104	–
D&C Blue #6	Indigo	73000	482-89-3	–	–	–	74.3106
D&C Blue #9	Indanthrene Blue	69825	130-20-1	–	74.1109	–	–
D&C Brown #1	Resorcin Brown	20170	1320-07-6	–	–	74.2151	–
FD&C Green #3	Fast Green FCF	42053	2353-45-9	74.203	74.1203	74.2203	–
D&C Green #5	Alizarin Cyanine Green F	61570	4403-90-1	–	74.1205	74.2205	–
D&C Green #6	Quinizarine Green SS	61565	128-80-3	–	74.1206	74.2206	74.3206
D&C Green #8	Pyranine Concentrated	59040	63-58-69-6	–	74.1208	74.2208	–
Orange B	–	19235	–	74.250	–	–	–
D&C Orange #4	Orange II	15510	633-96-5	–	74.1254	74.2254	–
D&C Orange #5	Dibromofluor Escein	45370:1	596-03-2	–	74.1255	74.2255	
D&C Orange #10	Diiodofluorescein	45425:1	38577-97-8	–	74.1260	74.2260	–
D&C Orange #11	Erythrosine Yellowish Na	45425	38577-97-8	–	74.1261	74.2261	
[Phthalocyaninato (2-)] Copper	Copper Phthalocyanine	74160	147-14-8	–	–	–	74.3045
FD&C Red #3	Erythrosine	45430	16423-68-0	74.303	74.1303	–	–
FD&C Red #4	Ponceau SX	14700	4548-53-2	–	74.1304	74.2304	–
D&C Red #6	Lithol Rubin B	15850	5858-81-1	–	74.1306	74.2306	–
D&C Red #7	Lithol Rubin B Ca	15850:1	4/9/5281	–	74.1307	74.2307	–
D&C Red #17	Toney Red	26100	85-86-9	–	74.1317	74.2317	74.3230
D&C Red #21	Tetrabromo Fluorescein	45380:2	15086-94-9	–	74.1321	74.2321	–
D&C Red #22	Eosine	45380	17372-87-1	–	74.1322	74.2322	–
D&C Red #27	Tetrachlorotetra-bromofluorescein	45410:1	13473-26-2	–	74.1327	74.2327	–
D&C Red #28	Phloxine B	45410	18472-87-2	–	74.1328	74.2328	–
D&C Red #30	Helindone Pink CN	73360	2379-74-0	–	74.1330	74.2330	–
D&C Red #31	Brilliant Lake Red R	15800:1	6371-76-2	–	74.1331	74.2331	–
D&C Red #33	Acid Fuchsine	17200	3567-66-6	–	74.1333	74.2333	–
D&C Red #34	Lake Bordeaux B	15880:1	6417-83-0	–	74.1334	74.2334	–
D&C Red #36	Flaming Red	12085	2814-77-9	–	74.1336	74.2336	–
D&C Red #39	Alba Red	13058	6371-55-7	–	74.1339	–	–
FD&C Red #40	Allura Red AC	16035	25956-17-6	74.340	74.1340	74.2340	–
FD&C Red #40 lake	Allura Red AC	16035:1	68583-95-9	74.340	74.1340	74.2340	–
Citrus Red #2	–	12156	6358-53-8	74.302	–	–	–
D&C Violet #2	Alizurol Purple SS	60725	81-48-1	–	74.1602	74.2602	74.3602
Ext. D&C Violet #2	Alizarin Violet	60730	4430-18-6	–	–	74.2602a	–
FD&C Yellow #5	Tartrazine	19140	1934-21-0	74.705	74.1705	74.2705	–
FD&C Yellow #6	Sunset Yellow FCF	15985	2783-94-0	74.706	74.1706	74.2706	–
D&C Yellow #7	Fluorescein	45350:1	7/5/2321	–	74.1707	74.2707	–
Ext. D&C Yellow #7	Napthol Yellow S	10316	846-70-8	–	74.1707a	74.2707a	–
D&C Yellow #8	Uranine	45350	518-47-8	–	74.1708	74.2708	–
D&C Yellow #10	Quinoline Yellow WS	47005	8004-92-0	–	74.1710	74.2710	74.3710
D&C Yellow #11	Quinoline Yellow SS	47000	8003-22-3	–	74.1711	74.2711	–

*Based on 21 CFR 2007. Restrictions may exist limiting the use of some of these colors to specific applications (i.e., external drug use only, etc.). Additionally, there may be quantitative limits for the use of some colors. The specific 21 CFR reference for each color should be reviewed to determine potential restriction status.

Another choice confronting manufacturers is whether to use an aqueous coating or an organic coating system; both have their advantages and disadvantages. While organic coatings provide greater protection against moisture uptake during the coating process (important for moisture-sensitive ingredients) and are easier to apply because of the fast evaporation of solvents, problems encountered with these coatings include environmental control of organic solvents going into the atmosphere, the need to perform solvent residue tests, and the need to have explosion-proof facilities, thus aqueous coating systems are often preferred.

CELLULOSE BASED

Cellulose acetate phthalate (CAP)

Caution: Check with regulatory authorities about approved states of all dyes before using them.

HYDROXYPROPYL METHYLCELLULOSE (METHOCEL, HPMC) AQUEOUS COATINGS

Methocel-based coatings in an aqueous base are the most popular coating options; two methods of making solutions are possible.

If a lake is used, then alcohol is also included (see, for example, Holberry Red).

A. Brite Rose

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methylcellulose 2910 (15 cps)	60.00 g
2.00	2	PEG-400 (low color)	20.00 g
2.00	3	PEG-8000	20.00 g
0.25	4	FD&C Red Dye No. 30 lake	2.50 g
2.00	5	Titanium dioxide (special coating grade)	20.00 g
QS	6	Deionized purified water	QS to 1 L

Manufacturing Directions

1. Charge 250 mL of water into a suitable container, and heat to 60°C to 70°C.
2. With gentle stirring, disperse the hydroxypropyl methyl cellulose onto the hot water; when the cellulose has wetted, quickly add 250 mL of cold water.
3. Stir until the dispersion is homogenous, although the solution of cellulose may not be complete.
4. Dissolve PEG-8000 in 50 mL of water, and then add to the step above.
5. Add PEG-400 to basic solution above.
6. Load a suitable size ball jar with the FD&C Red Dye No. 30 and titanium dioxide.
7. Add sufficient water to cover the pigment and balls.
8. Mill overnight or for 12 hours.
9. Other pigment reduction methods may be used to yield a particle size not greater than 1.0 μm.
10. Add milled pigments to the base solution from the step above, and bring the volume up with cold water.
11. Use within 7 days.

B. Cherry Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
2.00	2	PEG-400 (low color)	20.00 g
2.00	3	PEG-8000	20.00 g
1.80	4	FD&C Red Dye No. 3 lake	18.00 g
0.10	5	FD&C Red Dye No. 2 (Amaranth)	1.00 g
2.10	6	Titanium dioxide (special coating grade)	21.00 g
QS	7	Deionized purified water, USP	QS to 1 L

C. Geranium Rose

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
2.00	2	PEG-400 (low color), NF	20.00 g
2.00	3	PEG-8000	20.00 g
0.24	4	FD&C Red Dye No. 3 lake	2.00 g
QS	5	Deionized purified water, USP	QS to 1 L

D. Gloss

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/L
3.33	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	33.33 g
1.66	2	PEG-400 (low color), NF	16.66 g
QS	3	Deionized purified water, USP	QS to 1 L

E. Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
2.00	2	PEG-400 (low color), NF	20.00 g
2.00	3	PEG-8000	20.00 g
.50	4	FD&C Red Dye No. 3 lake	25.00 g
0.50	5	Titanium dioxide	5.00 g
QS	6	Deionized purified water, USP	QS to 1 L

F. Moderate Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
2.00	2	PEG-400 (low color), NF	20.00 g
2.00	3	PEG-8000	20.00 g
0.50	4	FD&C Yellow Dye No. 3 aluminum lake	5.00 g
2.50	5	Ponceau Red Dye 4R lake	25.00 g
1.00	6	Titanium dioxide (special coating grade), USP	10.00 g
QS	7	Deionized purified water, USP	QS to 1 L

G. Clear

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
0.10	2	Sorbic acid	1.00 g
2.00	3	Alcohol (200 proof), SD 3A	20.00 mL
2.00	4	PEG-400 (low color)[a]	20.00 g
2.00	5	PEG-8000 (optional)	20.00 g
QS	6	Deionized purified water	QS to 1 L

[a]Increase amount to 6.00 if item 5 is not used.

Manufacturing Directions

1. Charge approximately 500 mL of water into a suitable vessel.
2. Heat water to 65°C to 70°C.
3. Add the PEG-8000 to the hot water and dissolve (if used).
4. While maintaining gentle agitation, sprinkle the hydroxypropyl methyl cellulose onto the surface of the hot water solution.
5. Position stirring head to avoid excessive entrainment of air.
6. When the cellulose has been dispersed, add the PEG-400.
7. Continue to stir until dispersion is homogeneous, although solution of cellulose may not be complete.
8. Stop stirring, and allow solution to stand until entrained air is removed.
9. Dissolve sorbic acid in alcohol, and ensure that the solution is complete.
10. When the solution from the step above is clear, add 250 mL of cold water, mix well, and add sorbic acid solution.
11. Mix, then bring up to volume with cold water.
12. Store coating solution in well-filled, well-sealed containers.
13. Use within 3 months.

H. Green

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
0.10	2	Sorbic acid	1.00 g
2.00 v/v	3	Alcohol (200 proof), SD 3A	20.00 mL
2.00	4	PEG-400 (low color)	20.00 g
2.00	5	PEG-8000	20.00 g
1.00	6	Titanium dioxide (coating grade)	10.00 g
0.01	7	Dye Yellow E104 aluminum lake	0.10 g
0.0032	8	FD&C Blue Dye No. 1 lake (11 – 13%)	0.032 g
QS	9	Deionized purified water	QS to 1 L

I. Holberry Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
0.10	2	Sorbic acid	1.00 g
2.00 v/v	3	Alcohol (200 proof), SD 3A	20.00 mL
2.00	4	PEG-400 (low color)	20.00 g
2.00	5	PEG-8000	20.00 g
1.00	6	Titanium dioxide (coating grade)	10.00 g
1.50	7	FD&C Red Dye No. 40 lake (29%)	15.00 g
0.50	8	FD&C Blue Dye No. 3 lake	5.00 g
QS	9	Deionized purified water	QS to 1 L

J. Sun Orange

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/L
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00 g
0.17	2	Sorbic acid, NF	1.70 g
2.00 v/v	3	Alcohol (200 proof), SD 3A	20.00 mL
2.00	4	PEG-400 (low color), NF	20.00 g
2.00	5	PEG-8000	20.00 g
2.38	6	Titanium dioxide (coating grade), USP	23.80 g
2.47	7	FD&C Yellow Dye No. 5	24.70 g
0.16	8	FD&C Yellow Dye No. 6	1.60 g
QS	9	Deionized purified water, USP	QS to 1 L

K. Opadry Yellow

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Quantity/1000 Caplets (g)
10.00	1	Hydroxypropyl methyl cellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	PEG-4000	1.60
1.20	4	Titanium dioxide	1.20
0.30	5	FD&C Blue Dye No. 1 lake	0.30
0.50	6	FD&C Blue Dye No. 2 (dispersed)	0.50
0.75	7	Opadry-OY-S 29019 (clear)	0.75
QS	8	Purified water	225.00

Manufacturing Directions

1. The formula for this coating solution is prepared to obtain a weight gain of 10 mg per caplet (around 600 mg in weight).
2. Disperse item 1 in 175 g of purified water (70°C–80°C) while stirring.
3. Hold overnight for complete dispersion.
4. Disperse items 2 and 3 in 25 g of purified water (25°C–30°C).
5. Hold overnight for complete hydration.
6. Add mixture from previous step.
7. Homogenize using a homogenizer (gap setting = 1.5 mm).
8. Homogenize items 4, 5, and 6 in 50 g of hypromellose dispersion from the step above twice, using a homogenizer (gap setting = 1.5 mm).
9. Pass the dispersion twice through a 90-μm sieve.
10. (*Note*: This is a critical step; follow instructions closely to prevent foreign particles and spots.) Preparation of polishing solution: Disperse item 7 in 25 g of purified water with slow stirring.
11. Make a vortex by slow stirring and add the powder in such a way as to avoid foam formation.

L. Opadry Yellow

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Hydroxypropyl methyl cellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	PEG-4000	1.60
1.34	4	Titanium dioxide	1.34
0.046	5	Sunset Yellow E110, FCF	0.046
1.34	6	FD&C Yellow Dye No. 10 lake	1.34
0.75	7	Opadry-OY-S 29019 (clear)	0.75
QS	8	Purified water	225.00

M. Opadry Red

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Quantity/1000 Caplets (g)
10.00	1	Hydroxypropyl methyl cellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	PEG-4000	1.60
1.34	4	Titanium dioxide	1.34
0.15	5	Iron oxide red	0.15
0.75	6	Opadry-OY-S (clear)	0.75
QS	7	Purified water	225.00

N. Opadry Green

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Quantity/1000 Caplets(g)
10.00	1	Hydroxypropyl methyl cellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	PEG-4000	1.60
2.125	4	Titanium dioxide	2.125
0.053	5	FD&C Blue Dye No. 1 lake	0.053
0.15	6	FD&C Yellow Dye No. 10 lake	0.15
0.75	7	Opadry-OY-S (clear)	0.75
QS	8	Purified water	225.00

Manufacturing Directions

1. Disperse item 1 in 175 g of purified water (70°C–80°C) while stirring.
2. Keep overnight for complete dispersion.
3. Disperse items 2 and 3 in 25 g of purified water (25°C–30°C).
4. Keep overnight for complete hydration.
5. Add together and homogenize using homogenizer (gap setting = 1.5 mm).
6. Homogenize items 4, 5, and 6 in 50 g of hypromellose dispersion twice, using homogenizer (gap setting = 1.5 mm).
7. Pass the dispersion twice through a 90-μm sieve.
8. (*Note*: This is a critical step; follow instructions closely to prevent foreign particles and spots.) Disperse item 7 in 25 g of purified water while stirring slowly.
9. Make a vortex by slow stirring and add the powder in such a way as to avoid foam formation.
10. Follow the parameters for coating in Accela Cota:

Caplet load	620 g
Pan speed	4 rpm
Drying air temperature	70°C–75°C
Exhaust temperature	50°C–55°C
Fluid pressure	15 – 20 psi
Valve on spray gun	One revolution open
Atomizing pressure	55 psi
Nozzle orifice	1 mm
Nozzle distance to bed	250–280 mm
Difference of air pressure	–1.0 to –1.5 cm
Spray rate	200–225 g/min
Coating time	3.0–3.5 hours

11. Stir the dispersion at slow speed (6–10 rpm) continuously.
12. Spray the polishing solution under the same conditions as above, adjusting the spray rate to 180 g/min.
13. Check the caplet surface every 5 minutes for sticking.
14. If sticking tends to appear, stop the coating immediately.
15. When the spraying is over, roll the tablets in a pan for 10 minutes with cold air blowing onto the caplets.
16. Unload the film-coated caplets into stainless steel containers lined with polyethylene bags.
17. Appearance is a light green, film-coated caplet that is smooth, with no sticking or chipping on the caplet surface.
18. Weight gain per caplet is NLT 10 mg/tablet.

O. White Coating

Bill of Materials			
Scale(mg/tablet)	Item	Material Name	Quantity/1000 Tablets(g)
22.75	1	Hypromellose	22.75
4.54	2	Polyethylene glycol	4.54
12.50	3	Talc (fine powder)	12.50
10.00	4	Titanium dioxide	10.00
1.30	5	FD&C Yellow No. 10 lake	1.30
–	6	Purified water	~24.00
–	7	Ethanol (95%)	~21.00

HYDROXYPROPYL METHYLCELLULOSE OPAQUE ORGANIC COATING

A. Brite Green

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L(g)
1.00	1	Titanium dioxide	10.00
50.00 v/v	2	Alcohol (200 proof), SD 3A	~397.00
1.69	3	PEG-400 (low color), NF	16.90
0.02	4	FD&C Yellow Dye No. 5	0.20
0.0068	5	FD&C Blue Dye No. 1	0.068
4.00	6	Hydroxypropyl methyl cellulose 2910 (15 cps)	40.00
QS	7	Methylene chloride	~625.00

Manufacturing Directions

1. Charge titanium dioxide and QS with alcohol into a Ball mill.
2. Mill the material for 16 hours.
3. Charge 465 mL alcohol into a suitable mixing tank.
4. Start agitation.
5. Slowly add PEG-400 to mixing tank.
6. Mix for 5 minutes.
7. Add FD&C Yellow Dye to the mixing tank with continued agitation.
8. Rinse bottle with alcohol tapped from mixing tank.
9. Return rinse to mixing tank.
10. Add FD&C Blue Dye to the mixing tank, and rinse.
11. Mix for 2 hours.
12. Tap approximately 10 mL of solution from mixing tank after 1/2, 1, and 1.5 hours of mixing.
13. Put solution back into mixing tank. (*Note*: Tapping solution ensures that dye is not tapped into lower valve and/or pipeline.) Rinse the Ball mill with two rinses of 11.6 mL alcohol.
14. Reseal the Ball mill, and allow it to run for 2 to 5 minutes between rinses.
15. Empty content of the Ball mill and rinses into mixing tank.
16. Slow sprinkle hydroxypropyl methyl cellulose into mixing tank with constant agitation.
17. Agitate for an additional 15 minutes. (*Note*: Prevent the development of lumps by slowly sprinkling hydroxypropyl methyl cellulose into the alcohol.) After mixing 10 minutes, tap approximately 10 mL from the mixing tank and put back into tank to recirculate.
18. Add sufficient methylene chloride (~474 mL) to bring up to volume.
19. Continue agitation for 2 hours.
20. After 1/2, 1, and 1.5 hours, tap approximately 10 mL of solution from mixing tank and put back into mixing tank to recirculate.
21. (*Note*: No residue should be present in the solution when tapped at 1.5 hours; if some is present, then continue agitation and tap every 15 minutes until no residue is observed.) (*Caution*: Avoid contact with methylene chloride and vapors; they may have toxic effects when swallowed or inhaled.) (*Note*: Nitrogen pressure may be used to assist bottle filling.) Strain mixing tank contents through two-ply cheesecloth, or similar, into suitable approved containers (one half the total number of bottles). (*Note*: Lumps may obstruct spray nozzle.)

B. Red Mahogany

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L(g)
0.40	1	Titanium dioxide	4.00
45.00 v/v	2	Alcohol (200 proof), SD 3A	~375.30
0.40	3	Vanillin (crystals)	4.00
1.00	4	Propylene glycol	10.00
1.50	5	FD&C Red Dye No. 40 lake (29%)	15.00
1.00	6	Dye Brown lake blend	10.00
4.00	7	Hydroxypropyl methyl cellulose 2910 (15 cps)	40.00
QS	8	Methylene chloride	~530.40

C. Sun Orange

Bill of Materials			
Scale(%)	Item	Material Name	Quantity/L(g)
3.00 (w/v)	1	Titanium dioxide	30.00
50.00 (v/v)	2	Alcohol (200 proof), SD 3A	~397.00
2.11 (w/v)	3	Propylene glycol	21.10
3.11 (w/v)	4	FD&C Yellow Dye No. 5	31.10
0.20 (w/v)	5	FD&C Yellow Dye No. 6	2.00
4.00 (w/v)	6	Hydroxypropyl methyl cellulose 2910 (15 cps)	40.00
QS	7	Methylene chloride	~625.00

D. Dark Red

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L(g)
1.00	1	Titanium dioxide	10.00
20.00 v/v	2	Alcohol (200 proof), SD 3A	~200.00 mL
2.00	3	PEG-400 (low color)	20.00
0.02	4	Ponceau 4R dye (red)	20.00
0.0068	5	FD&C Blue Dye No. 1	0.068
2.95	6	Hydroxypropyl methyl cellulose 2910 (15 cps)	29.50
QS	7	Methylene chloride	QS to 1 L

E. Deep Yellow

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
2.00	1	Titanium dioxide	20.00 g
50.00	2	Alcohol (200 proof), SD 3A	~397.00 g
2.00	3	PEG-400 (low color)	20.00 g
2.00	4	FD&C Yellow Dye No. 5 lake	20.00 g
2.95	5	Hydroxypropyl methyl cellulose 2910 (15 cps)	29.50 g
QS	6	Methylene chloride	QS to 1 L

F. Pale Yellow

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
1.50	1	Titanium dioxide	15.00 g
50.00	2	Alcohol (200 proof), SD 3A	~397.00 g
2.00	3	PEG-400 (low color), NF	20.00 g
0.50	4	FD&C Yellow Dye No. 10 aluminum lake (14–17%)	5.00 g
2.95	5	Hydroxypropyl methyl cellulose 2910 (15 cps)	29.50 g
QS	6	Methylene chloride	QS to 1 L

G. Scarlet Red

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
2.00	1	Titanium dioxide	20.00 g
20.00	2	Alcohol (200 proof), SD 3A	~200.00 g
2.00	3	PEG-400 (low color), NF	20.00 g
2.00	4	FD&C Yellow Dye No. 7 lake	20.00 g
1.00	5	FD&C Yellow Dye No. 5 lake	10.00 g
2.95	6	Hydroxypropyl methyl cellulose 2910 (15 cps)	29.50 g
QS	7	Methylene chloride	QS to 1 L

HYDROXYPROPYL METHYL CELLULOSE/HYDROXYPROPYL CELLULOSE (KLUCEL®) COATING

A. White

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
2.00	1	Titanium dioxide	20.00 g
0.50	2	Hydroxypropyl cellulose, NC	5.00 g
45.00	3	Alcohol (200 proof), SD 3A	~450.00 g
2.00	4	Propylene glycol	20.00 g
4.50	5	Hydroxypropyl methyl cellulose 2910 (15 cps)	45.00 g
QS	6	Methylene chloride	QS to 1 L

Manufacturing Directions

1. Place titanium dioxide and sufficient methylene chloride into suitably sized ball jars to cover the balls.
2. Mill for not less than 16 hours.
3. While mixing alcohol, add and disperse hydroxypropyl methylcellulose, hydroxypropyl cellulose, and propylene glycol, followed by 250 mL of methylene chloride.
4. Continue mixing until the dissolution is complete.
5. While mixing the solution from the second step, empty into it the contents of the ball jar, rinse the balls and jar with methylene chloride, add the rinsing to the batch, and mix.
6. Bring the batch up to volume with methylene chloride, and mix well until homogeneous.
7. Strain the batch through muslin into suitable, approved bottles.
8. Seal and store.

HYDROXYPROPYL METHYL CELLULOSE/ETHYL CELLULOSE COATING

A. Reddish Orange Opaque

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
1.16	1	Titanium dioxide	11.60 g
45.00	2	Alcohol (dehydrated; 200 proof)	~450.00 g
0.20	3	Vanillin (crystals), NF	2.00 g
0.50	4	Albumen powder (white hen egg)	5.00 g
2.00	3	PEG-400 (low color), NF	20.00 g
1.30	4	FD&C Red Dye No. 3	13.00 g
0.05	5	FD&C Red Dye No. 2 (Amaranth), USP	0.50 g
0.20	6	FD&C Yellow Dye No. 6	2.00 g
2.95	5	Hydroxypropyl methyl cellulose 2910, USP (15 cps)	29.50 g
QS	6	Methylene chloride	QS to 1 L

Manufacturing Directions

1. Load vanillin, albumen, titanium dioxide, FD&C Red Dye No. 3, FD&C Red Dye No. 2, and FD&C Yellow Dye No. 6 into a suitable size ball jar.
2. Add sufficient methylene chloride to cover the pigments and balls.
3. Mill for 24 hours.
4. Measure 400 mL of alcohol into a suitable stainless steel container.
5. Sprinkle the hydroxypropyl methylcellulose/ethylcellulose onto the surface of the alcohol while stirring vigorously.
6. When the hydroxypropyl methyl cellulose/ethylcellulose has been wetted, quickly add 300 mL methylene chloride while stirring vigorously.
7. Add the PEG-400 to the solution from above, and rinse the container with the remaining alcohol; add the rinsings to the bulk.
8. Empty the contents of the ball jar from the first step into the coating solution from previous step, while stirring vigorously.
9. Rinse the ball jar with methylene chloride; add the rinsings to the bulk.
10. Bring up to volume with methylene chloride.

B. Subcoating Solution

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
45.00	1	Alcohol (190 proof), USP	450.00 mL
0.50	2	Hydroxypropyl cellulose, NF	5.00 g
4.50	3	Hydroxypropyl methyl cellulose 2910, USP (15 cps)	45.00 g
QS	4	Methylene chloride	QS to 1 L

HYDROXY METHYL CELLULOSE/HYDROXY CELLULOSE COATING

A. Blue

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
1.00	1	Hydroxy methyl cellulose	10.00 g
1.00	2	Hydroxy ethyl cellulose (15 cps)	10.00 g
0.312	3	Titanium dioxide	3.21 g
1.00	4	FD&C Blue Dye No. 1 lake (12%)	10.00 g
0.375	5	Castor oil (odorless)	3.75 g
0.375	6	Sorbitan monooleate	3.75 g
50.00	7	Alcohol (200 proof), SD 3A	500.00 mL
QS	8	Methylene chloride	QS to 1 L

Manufacturing Directions

1. Premix hydroxypropyl methyl cellulose and hydroxypropyl cellulose, and add to 440 mL alcohol with rapid agitation.
2. Mix for not less than 1 hour.
3. Charge FD&C Blue Dye and titanium dioxide into a ball mill.
4. Cover the balls and materials with 60 mL of alcohol, and mill for 16 hours.
5. Add contents to mixing tank, and add the castor oil and sorbitan monooleate.
6. Rinse the ball mill with methylene chloride, and add the rinsings to the mixing tank.
7. Bring up to a volume of 1 L with methylene chloride, and mix for at least 1 hour.

B. Clear (50:50)

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
1.00	1	Hydroxy methyl cellulose	10.00 g
1.00	2	Hydroxy ethyl cellulose, USP (15 cps)	10.00 g
0.375	3	Castor oil (odorless)	3.75 g
50.00	4	Alcohol (200 proof), SD 3A	500.00 mL
QS	5	Methylene chloride	QS to 1 L

HYDROXY METHYL CELLULOSE/ETHYL CELLULOSE COATING

A. Clear

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
1.00	1	Hydroxy methyl cellulose	10.00
1.00	2	Hydroxy ethyl cellulose, USP (15 cps)	10.00
0.375	3	Castor oil (odorless), USP	3.75
50.00	4	Alcohol (200 proof), SD 3A	500.00 mL
QS	5	Methylene chloride	QS to 1 L

Manufacturing Directions

1. Charge alcohol into mixing tank.
2. Turn on mixer to mixing speed; maintain mixing speed throughout preparation of coating solution.
3. Charge hydroxypropyl methyl cellulose and ethyl cellulose into the mixing tank.
4. Let mix for 1 hour.
5. Add methylene chloride (~500 mL) to bring the final volume up to 1 L.
6. Mix for 1 hour.
7. Solution need not be agitated at all times.
8. Keep tank tightly closed at all times.
9. Rubber stopper on bottles must be protected from methylene chloride with a polyethylene layer.

POLYVINYLPYRROLIDONE (PVP) COATINGS

A. Subcoating

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
20.00	1	Povidone USP K-29–32[a]	200.00 g
80.00	2	Alcohol (200 proof), SD 3A	800 mL

[a]May be substituted with Kollidon® VA 64 (polyvinylpyrrolidone/vinylacetate copolymer; 10%), and item 2 can be replaced with isopropyl alcohol.

Manufacturing Directions

1. Spray the solution onto the warm tablet cores (30°C–40°C) for a few minutes before continuing with the main aqueous coating procedure.
2. The amount of 0.4 mg/cm^2 tablet surface is sufficient for good subcoating protection.
3. No plasticizer is needed in this formulation due to the plasticity of Kollidon VA 64.

B. Kollidon® VA 64 (Polyvinylpyrrolidone/Vinylacetate Copolymer, BASF)

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg
5.00	1	Kollidon® VA 64	50.00 g
4.00	2	Lutrol E 6000	40.00 g
0.50	3	Glycerin, USP	5.00 g
1.50	4	Iron oxide or lake	15.00 g
3.00	5	Titanium dioxide	30.00 g
5.00	6	Talc	50.00 g
QS	7	Purified water	QS to 1 L

Manufacturing Directions

Pass the suspension through a disk mill prior to use and spray under the following conditions.

Sugar-Coating Pan

Spray gun	Walther WAXV with 1-mm nozzle
Spraying time	3 seconds
Pause	0.5 seconds
Dry air	6 seconds
Pause	3 seconds

Accela Cota (Continuous Spraying)

Spray gun	Walther WAXV with 0.8-mm nozzle
Temperature at inlet	45°C
Temperature at outlet	38°C
Spraying pressure	2 bar
Spraying time	~50 minutes

If the film is too sticky, a certain part of the Kollidon should be substituted by HPMC or sucrose.

Kollidon® VA 64 and Polyvinyl Alcohol

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg
5.0	1	Kollidon® VA 64	50.00 g
4.00	2	Lutrol E 6000	40.00 g
6.00	3	Polyvinyl alcohol	76.00 g
68.00	4	Purified water	680.00 g
0.50	5	Glycerin, USP	5.00 g
1.50	6	Iron oxide or lake	18.00 g
3.00	7	Titanium dioxide	37.00 g
5.00	8	Talc	50.00 g
QS	9	Purified water	168.00 g

Manufacturing Directions

1. Dissolve items 1 to 3 in item 4, add polyvinyl alcohol, and stir for 45 minutes, avoiding the formation of too many air bubbles.
2. Suspend the pigments and talc in 168 mL of water, and pass this mixture through a colloid mill.
3. To obtain the final coating suspension, mix this solution with the first solution.
4. Suggested conditions for coating using Accela-Cota are as follows.

Tablet core loading	5.0 kg
Amount of coating suspension	1.26 kg
Inlet air temperature	59°C
Outlet air temperature	46°C
Nozzle	1.0 mm
Rotation speed of the pan	15 rpm
Spraying pressure	2.0 bar
Spraying rate	15 g/min
Spraying time (continuously)	83 minutes
Final drying	5 minutes
Quantity of film former applied	$\sim$3 mg/cm^2

D. Kollidon® 30 and Shellac

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Quantity/kg(g)
2.00	1	Kollidon® 25 or 30	20.00
17.70	2	Shellac	177.00
18.50	3	Titanium dioxide	185.00
6.50	4	Talc	65.00
1.50	5	Cetyl alcohol	15.00
3.00	6	Sorbitan trioleate	30.00
5.00	7	Color lake	50.00
QS	8	Isopropanol or alcohol	458.00

Manufacturing Directions

1. Dissolve shellac and sorbitane trioleate in the warm solvent and then Kollidon and cetyl alcohol.
2. Add titanium dioxide, talc, and lake, and then mix in the colloid mill.
3. Application of the coating suspension: About 50 g of suspension is applied to 1 kg of tablet cores in a conventional coating pan or in an Accela-Cota pan (1–2 mg film formers/cm^2).

E. Kollidon® VA 64 and Hydroxypropyl Methyl Cellulose

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg
4.00	1	Kollidon® VA 64	53.00 g
1.00	2	Lutrol E 6000	12.00 g
6.00	3	Hydroxypropyl methyl cellulose	79.00 g
1.50	4	Iron oxide or lake	18.00 g
3.00	5	Titanium dioxide	37.00 g
4.00	6	Talc	50.00 g
QS	7	Purified water	QS to 1 kg

Manufacturing Directions

1. Dissolve Lutrol and Kollidon in a portion of the water, add hydroxypropyl methyl cellulose, and stir for 45 minutes, avoiding the formation of too many air bubbles.
2. Suspend the pigments and talc in a portion of the water, and pass this mixture through a colloid mill.
3. Mix the two portions.
4. Conditions for coating using Acela-Cota are as follows.

Tablet core loading	5.0 kg
Core size	9-mm biconvex
Amount of coating suspension applied	1.2 kg
Inlet air temperature	60°C
Outlet air temperature	40°C
Nozzle	1.0 mm
Rotation speed of the pan	12 rpm
Spraying pressure	2.0 bar
Spraying rate	50 g/min
Spraying time (continuously)	34 minutes
Final drying	2 minutes
Drying after spraying	5 minutes at 60°C
Quantity of film-former applied	3.14 mg/cm^2

F. Povidone, Ethyl Cellulose, and Talc

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
7.50	1	Povidone (PVP K-29-32), USP	75.00 g
4.25	2	Ethyl cellulose, NF	42.50 g
0.50	3	PEG-400, NF	5.00 g
5.00	4	Talc	50.00 g
45.00	5	Alcohol (200 proof), SD 3A	450.00 mL
QS	6	Methylene chloride, NF	QS to 1 L

Manufacturing Directions

1. Dissolve Povidone in alcohol and then add PEG-400.
2. Add ethyl cellulose to this solution.
3. Mix until evenly dispersed, then bring up to volume with methylene chloride with constant stirring.
4. Add talc to this solution, and stir to ensure distribution.
5. Solution should be freshly prepared and used within 10 days of manufacture.
6. Thoroughly disperse talc before use.
7. If batch is more than 200 L, do not add talc.
8. If coating solution is manufactured without talc, then solution should be used within 4 weeks.

CELLULOSE ACETATE PHTHALATE AND CARBOWAX COATINGS

A. Brite Green

Bill of Materials			
Scale(%, w/v)	Item	Material Name	Quantity/L
6.00	1	Cellulose acetate phthalate (carbowax)	60.00 g
1.86	2	Propylene glycol	18.65 g
0.66	3	Sorbitan monooleate (Span 80)	6.00 g
0.12	4	Castor oil (odorless)	1.25 g
0.85	5	FD&C Blue Dye No.1	0.85 g
3.11	6	FD&C Yellow Dye No. 5 lake	31.10 g
5.33	7	Titanium dioxide	53.30 g
21.58	8	Methylene chloride	215.00 g
QS	9	Acetone	QS to 1 L

Manufacturing Directions

1. Place methylene chloride in a suitably sized mixing tank.
2. While stirring, add propylene glycol, Span 80, and castor oil.
3. To this mixture add cellulose acetate phthalate, and allow to soak for overnight.
4. Load dyes and titanium dioxide into a suitable ball jar.
5. Add sufficient acetone to cover the raw materials and balls.
6. Ball mill overnight.
7. Melt carbowax with a portion of the acetone using gentle heat.
8. Add the melted carbowax to the mixture from the second step.
9. Empty contents of ball jar mill to this mixture.
10. Rinse the ball jar with acetone, and add rinsings.
11. Add acetone to volume and mix well.
12. If necessary, strain solution through gauge before storage or use.

B. Cherry Red

In the formulation given above, use, FD&C Red Dye No.3 (6.800 g), FD&C Red Dye No. 2 (Amaranth, USP; 1.00 g), and FD&C Yellow Dye (5.40 g).

C. Clear

Delete dyes.

D. Orange

Use FD&C Yellow Dye No. 6 (4.00 g) and FD&C Yellow Dye No. 5 (12.00 g).

SUGAR COATINGS

A. Basic

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg
4.00	1	Kollidon® VA 64	40.00 g
16.00	2	Sucrose	160.00 g
2.40	3	Titanium dioxide	24.00 g
1.20	4	Color lake	12.00 g
3.20	5	Lutrol E 4000	32.00 g
4.00	6	Talc	40.00 g
QS	7	Purified water	QS to 1 kg

Manufacturing Directions

1. Dissolve sucrose, Kollidon, and Lutrol in the water, and suspend the other components.
2. Pass through a colloid mill.
3. Use the following conditions for use in Accela-Cota.

Tablet core loading	5.00 kg
Amount of coating suspension	1.20 kg
Inlet air temperature	45°C
Outlet air temperature	35°C
Nozzle	0.80 mm
Rotation speed of the pan	15 rpm
Spraying pressure	2.0 bar
Spraying time (continuously)	50 minutes
Quantity of film-former applied	4.00 mg/cm^2

B. Automatic

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity, g/kg
4.00	1	Kollidon® 30	40.00
38.00	2	Sucrose	380.00
4.50	3	Titanium dioxide	45.00
QS	4	Color lake	QS
4.50	5	Calcium carbonate	45.00
14.50	6	Talc	145.00
QS	7	Purified water	QS to 1 kg

Manufacturing Directions

1. Dissolve sucrose in hot water, then mix with glycerol.
2. Dissolve Kollidon and suspend the other components.
3. Coating procedure: Coat 4 kg of tablet cores with a weight of 420 mg each by spraying with 2.5 kg of the above suspension in a conventional coating pan under the following conditions:

Spray phase	5 seconds
Interval	10 minutes
Drying phase (warm air)	10 minutes
Total coating time	16 hours

C. Manual, White

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg(g)
0.33	1	Kollidon® 30	3.36
0.29	2	Carmellose sodium	2.92
0.21	3	Aerosil® 200	2.14
QS	4	Color lake (white)	QS
1.62	5	Talc	16.20
0.10	6	Polysorbate or Cremophor RH40	1.00
1.40	7	Titanium dioxide	14.00
62.70	8	Sucrose	627.00
33.40	9	Purified water	334.00

Manufacturing Directions

1. Dissolve Kollidon, polysorbate or Cremophor, and sucrose in water, and suspend the other components in this solution.
2. Mix in a colloid mill.
3. Start with formulation without the color and then apply the color coat.
4. The polishing can be done by means of a solution of beeswax or PEG-6000.

ENTERIC COATINGS

A. Kollicoat® and Kollidon® Enteric Film Coating

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg
0.50	1	Titanium dioxide	5.00 g
2.00	2	Talc	20.00 g
0.50	3	Iron oxide	5.00 g
0.50	4	Kollidon® 25 or Kollidon® 30	5.00 g
50.00	5	Kollicoat® MAE 30 DP (methacrylic acid/ethyl acrylate copolymer, 1:1)	500.00 g
1.50	6	Triethyl citrate	15.00 g
QS	7	Purified water	QS to 1 kg

Manufacturing Directions/Conditions

Tablet core loading	5 kg
Core size	9-mm biconvex
Quantity of suspension applied	1890 g
Quantity of solids/cm^2	9 mg
Quantity of film-forming agent/cm^2	6 mg
Speed of the coating pan	12 rpm
Spray nozzle	0.8 mm
Spraying pressure	2.0 bar
Type of spraying	Continuous
Inlet air temperature	50°C
Outlet air temperature	~30°C
Spraying time	~60 minutes
Spraying rate	~30 g/min

EUDRAGIT® ENTERIC AQUEOUS

A. Brick Red

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg (g)
46.667	1	Distilled purified water	466.667
1.519	2	Talc (powder)	15.198
0.798	3	Titanium dioxide (special coating grade)	7.983
1.55	4	Iron oxide, red	15.50
0.426	5	Polysorbate 80	4.262
0.015	6	Dimethyl polysiloxane emulsion (30%)	0.155
47.60	7	Eudragit®; use Eudragit® L 30D-55	476.00
1.426	8	Triethyl citrate (Eudraflex®)	14.259

Manufacturing Directions

1. Weigh the quantity of water needed.
2. Put approximately 21.5% of the total quantity of water in a suitable mixing container.
3. Add talc powder, and stir vigorously until well suspended (approximately 20 minutes).
4. Add the following to this suspension, and mix thoroughly: titanium dioxide, iron oxide, Tween 80, and dimethyl polysiloxane emulsion (30%).
5. (*Note*: The pigments may requirehomogenizing with colloid, corrundum disc mill, or ball mill.) Put the Eudragit in a suitable mixing vessel, and add the following with continuous mixing: homogenized pigment mixture, Eudraflex (i.e., triethyl citrate), and remaining quantity of water. *Note*: When PEG-8000 is used as a plasticizer, it should be incorporated as a 10% aqueous solution.

B. Yellow

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg(g)
46.66	1	Distilled purified water	466.66
1.25	2	Talc (powder)	12.57
0.77	3	Titanium dioxide (special coating grade)	7.79
1.83	4	FD&C Yellow Dye No. 10 aluminum lake (14 to 17%)	18.36
0.42	5	Polysorbate 80	4.27
0.01	6	Dimethyl polysiloxane emulsion (30%)	0.12
47.6	7	Eudragit®; use methacrylic acid copolymer, NF (Eudragit® L 30D-55)	476.00
1.42	8	Triethyl citrate (Eudraflex®)	14.21

C. Brown

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg(g)
46.66	1	Distilled purified water	466.66
0.47	2	Titanium dioxide (special grade coating), USP	4.76
0.85	3	Iron oxide, black	8.53
2.26	4	Iron oxide, red	22.61
0.25	5	Iron oxide, yellow	2.57
0.42	6	Polysorbate 80	4.26
0.01	7	Dimethyl polysiloxane emulsion	0.09
47.63	8	Eudragit®; use Eudragit® L 30D-55	476.33
1.42	9	Triethyl citrate (Eudraflex®)	14.28

D. Dark Orange

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg(g)
46.66	1	Distilled purified water	466.66
2.51	2	Talc (powder)	25.18
0.39	3	Titanium dioxide (special coating grade)	3.92
0.93	4	FD&C Yellow Dye No. 6 aluminum lake	9.32
0.42	5	Polysorbate 80	4.29
0.01	6	Dimethyl polysiloxane emulsion (30%)	0.13
47.63	7	Eudragit®; use Eudragit® L 30D-55	476.33
1.42	8	Triethyl citrate (Eudraflex®)	14.28

E. Orange

Bill of Materials			
Scale(%, w/w)	Item	Material Name	Quantity/kg(g)
46.66	1	Distilled purified water	466.66
2.60	2	Talc (powder)	26.00
0.78	3	Titanium dioxide (special coating grade)	7.84
0.46	4	FD&C Yellow Dye No. 6 aluminum lake	4.66
0.42	5	Polysorbate 80	4.27
0.01	6	Dimethyl polysiloxane emulsion (30%)	0.11
47.61	7	Eudragit®; use Eudragit® L 30D-55	476.16
1.42	8	Triethyl citrate (Eudraflex®)	14.29

F. Dispersed Orange

Bill of Materials			
Scale(mg/tablet)	Item	Material Name	Quantity/1000 Tablets(g)
0.92	1	Opagloss NA 7150	0.92
7.07	2	Methacrylic acid copolymer (Eudragit® L 100–55)	7.07
0.09	3	Sodium hydroxide pellets (caustic soda)	0.09
0.73	4	PEG-6000	0.73
2.50	5	Talc (fine powder)	2.50
0.10	6	Simethicone emulsion 30% (simethicone antifoam M30)	0.10
0.27	7	Povidone (PVP K-25)	0.27
50.00	8	Sucrose	50.00
0.54	9	Povidone (PVP K-25)	0.54
0.36	10	Titanium dioxide	0.36
0.36	11	FD&C Yellow Dye No. 10 lake	0.36
0.04	12	Dispersed orange[a]	0.04
1.07	13	Sucrose	1.07
0.38	14	Polishing emulsion	0.38
–	15	Purified water	65.41

[a]Dispersed orange: This material is the aluminum lake of Sunset Yellow FCF (E110).

HYDROXYPROPYL METHYL CELLULOSE PHTHALATE ENTERIC COATING

A. Clear Enteric

Bill of Materials			
Scale(%)	Item	Material Name	Quantity/kg
20.00 (v/v)	1	Acetone	200.00 mL
10.00 (v/v)	2	Purified Water	100.00 mL
4.00 (w/v)	3	Hydroxypropyl methyl cellulose	40.00 g
0.30 (w/v)	4	Vanillin (crystals)	3.00 g
0.40 (w/v)	5	Acetylated monoglycerides	4.00 g
QS	6	Alcohol (200 proof), SD 3A	QS to 1 L

Manufacturing Directions

1. Charge acetone, purified water, and 470 mL of alcohol into a suitable mixing tank.
2. Add hydroxypropyl methylcellulose phthalate, vanillin crystals (if used), and the distilled acetylated monoglycerides.
3. Mix until a clear solution is obtained.
4. Bring up to 1 L with alcohol, and record volume used.
5. Mix for 1 hour.

B. Orchid Pink Opaque

Bill of Materials			
Scale (%)	Item	Material Name	Quantity/kg
20.00 (v/v)	1	Acetone	200.00 mL
10.00 (v/v)	2	Purified water	100.00 mL
8.00 (w/v)	3	Hydroxypropyl methylcellulose phthalate	80.00 g
0.80 (w/v)	4	Diacetylated monoglycerides	8.00 g
0.06 (w/v)	5	Dye Red D&C No. 30 Lake	0.60 g
0.006 (w/v)	6	FD&C Blue Dye No. 2 aluminum lake (14%)	0.06 g
0.70 (w/v)	7	Titanium dioxide	7.00 g
QS	8	Alcohol (200 proof), SD 3A	1

C. Light Apricot Orange

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Quantity/kg
20.00 (v/v)	1	Acetone	200.00 mL
10.00 (v/v)	2	Purified water	100.00 mL
8.00	3	Hydroxypropyl methyl cellulose phthalate	80.00 g
0.80	4	Diacetylated monoglycerides	8.00 g
0.10	5	FD&C Yellow Dye No. 10 aluminum lake (14–17%)	1.00 g
0.06	6	FD&C Red Dye No. 3 aluminum lake (14%)	0.60 g
0.70	7	Titanium dioxide	7.00 g
QS	8	Alcohol (200 proof), SD 3A	To 1 kg

Part IV

Composition of Proprietary Products Approved in the US

Composition of Proprietary Products Approved in the US

- ABILIFY® (aripiprazole) tablets are available in 5-, 10-, 15-, 20-, and 30-mg strengths. Inactive ingredients include cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.
- ACCOLATE (Zafirlukast) is supplied as 10- and 20-mg tablets for oral administration. Inactive ingredients: Film-coated tablets containing croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose, povidone, hypromellose, and titanium dioxide.
- ACEON® (perindopril erbumine) tablets are available in 2-, 4-, and 8-mg strengths for oral administration. In addition to perindopril erbumine, each tablet contains the following inactive ingredients: colloidal silica (hydrophobic), lactose, magnesium stearate, and microcrystalline cellulose. The 4- and 8-mg tablets also contain iron oxide.
- ACIPHEX® delayed-release tablets is rabeprazole sodium and is available for oral administration as delayed-release, enteric-coated tablets containing 20 mg of rabeprazole sodium. Inactive ingredients are carnauba wax, crospovidone, diacetylated monoglycerides, ethylcellulose, hydroxypropyl cellulose, hypromellose phthalate, magnesium stearate, mannitol, sodium hydroxide, sodium stearyl fumarate, talc, titanium dioxide, and yellow ferric oxide as a coloring agent.
- Actiq (oral transmucosal fentanyl citrate) is formulated as a white to off-white solid drug matrix on a handle that is radiopaque and is fracture resistant (ABS plastic) under normal conditions when used as directed. Actiq is designed to be dissolved slowly in the mouth in a manner to facilitate transmucosal absorption. The handle allows the Actiq unit to be removed from the mouth if signs of excessive opioid effects appear during administration. Active ingredient: Fentanyl citrate, USP is a highly lipophilic compound (octanol–water partition coefficient at pH 7.4 is 816:1) that is freely soluble in organic solvents and sparingly soluble in water (1:40). The pK_a's of the tertiary nitrogen are 7.3 and 8.4. Actiq is available in six strengths equivalent to 200, 400, 600, 800, 1200, or 1600 mcg fentanyl base that is identified by the text on the solid drug matrix, the dosage unit handle tag, the blister package, and the shelf carton. Inactive ingredients: Hydrated dextrates, citric acid, dibasic sodium phosphate, artificial berry flavor, magnesium stearate, modified food starch, and confectioner's sugar.
- ACTONEL (risedronate sodium tablets) tablet for oral administration contains the equivalent of 5, 30, or 35 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate. Inactive ingredients: Crospovidone, ferric oxide red (35-mg tablets only), ferric oxide yellow (5 and 35-mg tablets only), hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, and titanium dioxide.
- ACTONEL with CALCIUM is a co-package product containing ACTONEL (risedronate sodium tablets, 35 mg) for once weekly dosing and calcium carbonate tablets, USP (1250 mg, equivalent to 500 mg of elemental calcium) for daily dosing for the remaining 6 days of the week. Each package contains a 28-day course of therapy. Each ACTONEL tablet in the ACTONEL with CALCIUM co-package contains the equivalent of 35 mg of anhydrous risedronate sodium in the form of the hemi-pentahydrate with small amounts of monohydrate. Inactive ingredients—ACTONEL: Crospovidone, ferric oxide red, ferric oxide yellow, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, silicon dioxide, and titanium dioxide. CALCIUM: Pregelatinized starch, sodium starch glycolate, FD&C Blue #2, magnesium stearate, polyethylene glycol 3350, hypromellose, Opaspray Light Blue, and polysorbate 80.
- ACTOPLUS MET™ (pioglitazone hydrochloride and metformin hydrochloride) tablets containing 15 mg of pioglitazone hydrochloride (as the base) with 500 mg of metformin hydrochloride (15 mg/500 mg) or 15 mg of pioglitazone hydrochloride (as the base) with 850 mg of metformin hydrochloride (15 mg/850 mg) formulated with the following excipients: povidone USP, microcrystalline cellulose NF, croscarmellose sodium NF, magnesium stearate NF, hypromellose 2910 USP, polyethylene glycol 8000 NF, titanium dioxide USP, and talc USP.
- ACTOPLUS MET™ (pioglitazone hydrochloride and metformin hydrochloride) tablets contain two oral antihyperglycemic drugs. ACTOPLUS MET is available as a tablet for oral administration containing 15 mg of pioglitazone hydrochloride (as the base) with 500 mg of metformin hydrochloride (15 mg/500 mg) or 15 mg of pioglitazone hydrochloride (as the base) with 850 mg of metformin hydrochloride (15 mg/850 mg) formulated with the following excipients: povidone USP, microcrystalline cellulose NF, croscarmellose sodium NF, magnesium stearate NF, hypromellose 2910 USP, polyethylene glycol 8000 NF, titanium dioxide USP, and talc USP.
- ACTOS (pioglitazone hydrochloride) is available as a tablet for oral administration containing 15, 30, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropyl cellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.
- ACTOS (pioglitazone hydrochloride) is available as a tablet for oral administration containing 15, 30, or 45 mg of pioglitazone (as the base) formulated with the following excipients: lactose monohydrate NF, hydroxypropyl cellulose NF, carboxymethylcellulose calcium NF, and magnesium stearate NF.

- ADIPEX-P tablets contain the inactive ingredients cornstarch, lactose (anhydrous), magnesium stearate, microcrystalline cellulose, pregelatinized starch, sucrose, and FD&C Blue #1.
- ALDOCLOR (methyldopa-chlorothiazide) combines two antihypertensives: methyldopa and chlorothiazide is supplied as tablets for oral use, each containing 250 mg of methyldopa and 250 mg of chlorothiazide. Each tablet contains the following inactive ingredients: calcium disodium edetate, cellulose, citric acid, D&C Yellow 10 aluminum lake, ethylcellulose, FD&C Yellow 6 aluminum lake, gelatin, glycerin, guar gum, hydroxypropyl methylcellulose, magnesium stearate, starch, talc, titanium dioxide, and FD&C Blue 2 aluminum lake.
- ALDORIL Methyldopa is supplied as tablets in four strengths for oral use: ALDORIL 15 contains 250 mg of methyldopa and 15 mg of hydrochlorothiazide. ALDORIL 25 contains 250 mg of methyldopa and 25 mg of hydrochlorothiazide. ALDORIL D30 contains 500 mg of methyldopa and 30 mg of hydrochlorothiazide. ALDORIL D50 contains 500 mg of methyldopa and 50 mg of hydrochlorothiazide. Each tablet contains the following inactive ingredients: calcium disodium edetate, calcium phosphate, cellulose, citric acid, colloidal silicon dioxide, ethylcellulose, guar gum, hydroxypropyl methylcellulose, magnesium stearate, propylene glycol, talc, and titanium dioxide. ALDORIL 15 and ALDORIL D30 also contain iron oxide.
- ALKERAN (melphalan) is a film-coated tablet containing 2 mg of melphalan and the inactive ingredients colloidal silicon dioxide, crospovidone, hypromellose, macrogol/PEG 400, magnesium stearate, microcrystalline cellulose, and titanium dioxide.
- ALTOPREV™ lovastatin extended-release tablets are designed for once-a-day oral administration and deliver 10, mg, 40, or 60 mg of lovastatin. In addition to the active ingredient lovastatin, each tablet contains the following inactive ingredients: acetyltributyl citrate, butylated hydroxyanisole, candelilla wax, cellulose acetate, confectioner's sugar (contains cornstarch), FD&C yellow # 6, glyceryl monostearate, hypromellose, hypromellose phthalate, lactose, methacrylic acid copolymer, type B, polyethylene glycols (PEG 400, PEG 8000), polyethylene oxides, polysorbate 80, propylene glycol, silicon dioxide, sodium chloride, sodium lauryl sulfate, synthetic black iron oxide, red iron oxide, talc, titanium dioxide, and triacetin.
- AMPRAL® (acamprosate calcium) tablet contains acamprosate calcium 333 mg, equivalent to 300 mg of acamprosate. Inactive ingredients in CAMPRAL tablets include crospovidone, microcrystalline cellulose, magnesium silicate, sodium starch glycolate, colloidal anhydrous silica, magnesium stearate, talc, propylene glycol, and Eudragit® L30D or equivalent. Sulfites are used in the synthesis of the drug substance and traces of residual sulfites may be present in the drug product.
- ANADROL® (oxymetholone) tablets for oral administration contain 50 mg of the steroid oxymetholone. Inactive ingredients: lactose, magnesium stearate, povidone, and starch.
- Appearex® is a biotin preparation. Each Appearex® tablet contains as its active ingredient 2.5 mg of biotin, a dose clinically proven to improve nail strength and quality. Inactive ingredients include lactose monohydrate, cornstarch, povidone (K25), and magnesium stearate.
- ARICEPT® (donepezil hydrochloride) is a film-coated tablet containing 5 or 10 mg of donepezil hydrochloride. Inactive ingredients are lactose monohydrate, cornstarch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. The film coating contains talc, polyethylene glycol, hypromellose, and titanium dioxide. Additionally, the 10-mg tablet contains yellow iron oxide (synthetic) as a coloring agent. ARICEPT® ODT tablets are available for oral administration. Each ARICEPT® ODT tablet contains 5 or 10 mg of donepezil hydrochloride. Inactive ingredients are carrageenan, mannitol, colloidal silicon dioxide, and polyvinyl alcohol. Additionally, the 10-mg tablet contains ferric oxide (yellow) as a coloring agent.
- ARIMIDEX® (anastrozole) tablets for oral administration contain 1 mg of anastrozole, a nonsteroidal aromatase inhibitor. Each tablet contains as inactive ingredients: lactose, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, povidone, sodium starch glycolate, and titanium dioxide.
- AROMASIN® tablets for oral administration contain 25 mg of exemestane. Each AROMASIN tablet contains the following inactive ingredients: mannitol, crospovidone, polysorbate 80, hypromellose, colloidal silicon dioxide, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, simethicone, polyethylene glycol 6000, sucrose, magnesium carbonate, titanium dioxide, methylparaben, and polyvinyl alcohol.
- ARTHROTEC (diclofenac sodium/misoprostol) oral tablets are white to off-white, round, biconvex, and approximately 11 mm in diameter. Each tablet consists of an enteric-coated core containing 50 mg (ARTHROTEC 50) or 75 mg (ARTHROTEC 75) diclofenac sodium surrounded by an outer mantle containing 200 mcg misoprostol. Inactive ingredients in ARTHROTEC: colloidal silicon dioxide, crospovidone, hydrogenated castor oil, hypromellose, lactose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, povidone (polyvidone) K-30, sodium hydroxide, starch (corn), talc, and triethyl citrate.
- Asacol delayed-release tablet for oral administration contains 400 mg of mesalamine, an anti-inflammatory drug. The Asacol delayed-release tablets are coated with acrylic based resin, Eudragit S (methacrylic acid copolymer B, NF), which dissolves at pH 7 or greater, releasing mesalamine in the terminal ileum and beyond for topical anti-inflammatory action in the colon. Inactive ingredients: Each tablet contains colloidal silicon dioxide, dibutyl phthalate, edible black ink, iron oxide red, iron oxide yellow, lactose, magnesium stearate, methacrylic acid copolymer B (Eudragit S), polyethylene glycol, povidone, sodium starch glycolate, and talc.
- ATACAND (candesartan cilexetil) is available for oral use as tablets containing either 4, 8, 16, or 32 mg of candesartan cilexetil and the following inactive ingredients: hydroxypropyl cellulose, polyethylene glycol, lactose, cornstarch, carboxymethylcellulose calcium, and magnesium stearate. Ferric oxide (reddish brown) is added to the 8-, 16-, and 32- mg tablets as a colorant.
- ATACAND HCT (candesartan cilexetil-hydrochlorothiazide). ATACAND HCT 16-12.5 contains 16 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide. ATACAND HCT 32-12.5 contains 32 mg of candesartan cilexetil and 12.5 mg of hydrochlorothiazide. The inactive ingredients of the tablets are calcium carboxymethylcellulose, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, cornstarch, polyethylene glycol 8000, and ferric oxide (yellow). Ferric oxide (reddish brown) is also added to the 16-12.5 mg tablet as colorant.

- Aygestin (norethindrone acetate tablets, USP)—5-mg oral tablets contain the following inactive ingredients: lactose, magnesium stearate, and microcrystalline cellulose.
- Beelith. Each tablet contains magnesium oxide 600 mg and pyridoxine hydrochloride (vitamin B6) 25 mg equivalent to vitamin B6 20 mg. Each tablet yields 362 mg of magnesium and supplies 90% of the Adult U.S. Recommended Daily Allowance (RDA) for magnesium and 1000% of the Adult RDA for vitamin B6. Inactive ingredients FD&C Yellow No. 6, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide. May also contain D&C Yellow No. 10, FD&C Yellow No. 5 (Tartrazine), hydroxypropyl cellulose, polydextrose, stearic acid, and/or triacetin.
- Bethanol chloride. Each tablet for oral administration contains 5, 10, 25, or 50 mg of bethanechol chloride, USP. Tablets also contain the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and (25 and 50 mg) D&C Yellow #10 and FD&C Yellow #6.
- BIAXIN Clarithromycin tablet (clarithromycin tablets, USP) contains 250 or 500 mg of clarithromycin and the following inactive ingredients: 250-mg tablets—hypromellose, hydroxypropyl cellulose, croscarmellose sodium, D&C Yellow No. 10, FD&C Blue No. 1, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, stearic acid, talc, titanium dioxide, and vanillin. 500-mg tablets—hypromellose, hydroxypropyl cellulose, colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10, magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, sorbic acid, sorbitan monooleate, titanium dioxide, and vanillin. Each yellow oval film-coated BIAXIN XL tablet (clarithromycin extended-release tablets) contains 500 mg of clarithromycin and the following inactive ingredients: cellulosic polymers, D&C Yellow No. 10, lactose monohydrate, magnesium stearate, propylene glycol, sorbic acid, sorbitan monooleate, talc, titanium dioxide, and vanillin.
- BIAXIN® Filmtab® (clarithromycin tablets, USP) oval film-coated immediate-release tablet contains 500 mg of clarithromycin and the following inactive ingredients: hypromellose, hydroxypropyl cellulose, colloidal silicon dioxide, croscarmellose sodium, D&C Yellow No. 10, magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, sorbic acid, sorbitan monooleate, titanium dioxide, and vanillin.
- BiDil is a fixed-dose combination of isosorbide dinitrate and hydralazine hydrochloride. Each BiDil tablet for oral administration contains 20 mg of isosorbide dinitrate and 37.5 mg of hydralazine hydrochloride. The inactive ingredients in BiDil tablets include anhydrous lactose, microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, hypromellose, FD&C Yellow No. 6 aluminum lake, polyethylene glycol, titanium dioxide, polysorbate 80.
- BLOCADREN (Timolol Maleate) is supplied as tablets in three strengths containing 5, 10, or 20 mg timolol maleate for oral administration. Inactive ingredients are cellulose, FD&C Blue 2, magnesium stearate, and starch.
- Buphenyl® (sodium phenylbutyrate) tablets for oral administration contain sodium phenylbutyrate. Each tablet of Buphenyl contains 500 mg of sodium phenylbutyrate and the inactive ingredients microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide.
- CADUET® contains amlodipine besylate. CADUET tablets are formulated for oral administration in several combination strengths from 2.5/10 to 10/80 mg. Each tablet also contains calcium carbonate, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, polysorbate 80, hydroxypropyl cellulose, purified water, colloidal silicon dioxide (anhydrous), magnesium stearate, Opadry® II White 85F28751 (polyvinyl alcohol, titanium dioxide, PEG 3000 and talc), or Opadry® II Blue 85F10919 (polyvinyl alcohol, titanium dioxide, PEG 3000, talc and FD&C blue #2). Combinations of atorvastatin with 2.5 and 5 mg amlodipine are film coated white, and combinations of atorvastatin with 10 mg amlodipine are film coated blue.
- Calcium polycarbophil 625 mg (equivalent to 500-mg polycarbophil). Inactive ingredients: calcium carbonate, caramel, crospovidone, hypromellose, light mineral oil, magnesium stearate, microcrystalline cellulose, povidone, silicon dioxide, and sodium lauryl sulfate
- CANESTIN synthetic conjugated estrogens tablets contain a blend of nine synthetic estrogenic substances. The estrogenic substances are sodium estrone sulfate, sodium equilin sulfate, sodium 17(α)-dihydroequilenin sulfate, sodium 17(α)-estradiol sulfate, sodium 17(β)-dihydroequilenin sulfate, sodium 17(α)-dihydroequilenin sulfate, sodium 17(β)-dihydroequilenin sulfate, sodium equilenin sulfate, and sodium 17(β)-estradiol sulfate. Tablets for oral administration are available in 0.3-, 0.45-, 0.625-, 0.9-, and 1.25-mg strengths of synthetic conjugated estrogens. Tablets also contain the following inactive ingredients: ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, polysorbate 80, pregelatinized starch, titanium dioxide, and triethyl citrate; 0.3-mg tablets also contain FD&C Blue No. 2 aluminum lake and D&C Yellow No. 10 aluminum lake; 0.45-mg tablets also contain FD&C Yellow No. 6/Sunset Yellow FCF lake; 0.625-mg tablets also contain FD&C Red No. 40 aluminum lake; 0.9-mg tablets do not contain additional color additives; 1.25-mg tablets also contain FD&C Blue No. 2 aluminum lake.
- Captopril tablet for oral administration contains 12.5, 25, 50, or 100 mg of captopril and the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, crospovidone, microcrystalline cellulose and stearic acid.
- CARDURA® XL (doxazosin mesylate extended-release tablets) contains doxazosin mesylate. CARDURA XL is an extended-release tablet for oral use and is designed to deliver 4 or 8 mg of doxazosin as the free base. Each 4- and 8-mg tablet contains 5.1 and 10.2 mg doxazosin mesylate (includes a 5% overage) to provide 4 and 8 mg doxazosin as a free base, respectively. The inactive ingredients for CARDURA XL: polyethylene oxide, sodium chloride, hypromellose, red ferric oxide, titanium dioxide, magnesium stearate, cellulose acetate, Macrogol®, pharmaceutical glaze, and black iron oxide. CARDURA XL is similar in appearance to a conventional tablet. It consists, however, of an osmotically active drug core surrounded by a semipermeable membrane. The core itself is divided into two layers: an "active" layer containing the drug and a "push" layer containing pharmacologically inert (but osmotically active) components. The membrane surrounding the tablet is permeable to water but not to drug or osmotic excipients. As water from the gastrointestinal tract enters the tablet, pressure increases in the osmotic layer and "pushes" against the drug layer, resulting in the release of drug through a small, laser-drilled orifice in the

membrane on the drug side of the tablet. CARDURA XL utilizes GITS (Gastrointestinal Therapeutic System), which is designed to provide a controlled rate of delivery of doxazosin into the gastrointestinal lumen, which is independent of pH or gastrointestinal (GI) motility. The function of CARDURA XL depends upon the existence of an osmotic gradient between the contents of the bilayer core and fluid in the GI tract. Drug delivery is essentially constant as long as the osmotic gradient remains constant, and then gradually falls to zero. The biologically inert components of the tablet remain intact during GI transit and are eliminated in the feces as an insoluble shell.

- CASODEX® (bicalutamide) tablets for oral administration contain 50 mg of bicalutamide. The inactive ingredients of CASODEX tablets are lactose, magnesium stearate, methylhydroxypropyl cellulose, polyethylene glycol, polyvidone, sodium starch glycolate, and titanium dioxide.
- CEFTIN tablets film-coated and contain the equivalent of 250 or 500 mg of cefuroxime as cefuroxime axetil. CEFTIN tablets contain the inactive ingredients colloidal silicon dioxide, croscarmellose sodium, hydrogenated vegetable oil, hypromellose, methylparaben, microcrystalline cellulose, propylene glycol, propylparaben, sodium benzoate, sodium lauryl sulfate, and titanium dioxide.
- CELEBREX (celecoxib) oral capsules contain either 100, 200, or 400 mg of celecoxib. The inactive ingredients in CELEBREX capsules: croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate, and titanium dioxide.
- Celexa® (citalopram HBr) 10-mg tablets are film-coated, oval shaped containing citalopram HBr in strengths equivalent to 10-mg citalopram base. Celexa 20-mg and 40-mg tablets are film-coated, oval, scored tablets containing citalopram HBr in strengths equivalent to 20 or 40 mg of citalopram base. The tablets also contain the following inactive ingredients: copolyvidone, cornstarch, croscarmellose sodium, glycerin, lactose monohydrate, magnesium stearate, hypromellose, microcrystalline cellulose, polyethylene glycol, and titanium dioxide. Iron oxides are used as coloring agents in the beige (10 mg) and pink (20 mg) tablets.
- CHANTIX™ tablets contain the active ingredient, varenicline (as the tartrate salt). CHANTIX is supplied for oral administration in two strengths: a 0.5-mg capsular biconvex, white to off-white, film-coated tablet and a 1-mg capsular biconvex, light blue film-coated tablet. Each 0.5-mg CHANTIX tablet contains 0.85 mg of varenicline tartrate equivalent to 0.5 mg of varenicline free base; each 1-mg CHANTIX tablet contains 1.71 mg of varenicline tartrate equivalent to 1 mg of varenicline free base. The following inactive ingredients are included in the tablets: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, Opadry® White (for 0.5 mg), Opadry® Blue (for 1 mg), and Opadry® Clear.
- Chlorpheniramine-Ibuprofen-Pseudoephedrine tablet. Active ingredients (in each caplet): chlorpheniramine maleate (2 mg), ibuprofen (200 mg), pseudoephedrine HCl (30 mg). Inactive ingredients: carnauba wax, croscarmellose sodium, FD&C red no. 40 aluminum lake, FD&C yellow no. 6 aluminum lake, glyceryl behenate, hypromellose, iron oxide black, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized starch, propylene glycol, silicon dioxide, starch, and titanium dioxide. Active ingredients (in each caplet): chlorpheniramine maleate (2 mg), Ibuprofen (200 mg), Pseudoephedrine HCl (30 mg). Inactive ingredients: carnauba wax, croscarmellose sodium, FD&C Red No. 40 aluminum lake, FD&C Yellow No. 6 aluminum lake, glyceryl behenate, hypromellose, iron oxide black, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized starch, propylene glycol, silicon dioxide, starch, and titanium dioxide.
- CIALIS® (tadalafil) is available as film-coated, almond-shaped tablets for oral administration. Each tablet contains 5, 10, or 20 mg of tadalafil and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, iron oxide, lactose monohydrate, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide, and triacetin.
- CIPRO XR (ciprofloxacin extended-release tablets) contains ciprofloxacin, a synthetic broad-spectrum antimicrobial agent for oral administration. CIPRO XR tablets are coated, bilayer tablets consisting of an immediate-release layer and an erosion-matrix type controlled-release layer. The tablets contain a combination of two types of ciprofloxacin drug substance, ciprofloxacin hydrochloride and ciprofloxacin betaine (base). The drug substance is a faintly yellowish to light yellow crystalline substance. CIPRO XR is available in 500- and 1000-mg (ciprofloxacin equivalent) tablet strengths. CIPRO XR tablets are nearly white to slightly yellowish, film-coated, oblong-shaped tablets. Each CIPRO XR 500-mg tablet contains 500 mg of ciprofloxacin as ciprofloxacin HCl (287.5 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin (212.6 mg, calculated on the dried basis). Each CIPRO XR 1000-mg tablet contains 1000 mg of ciprofloxacin as ciprofloxacin HCl (574.9 mg, calculated as ciprofloxacin on the dried basis) and ciprofloxacin (425.2 mg, calculated on the dried basis). The inactive ingredients are crospovidone, hypromellose, magnesium stearate, polyethylene glycol, silica colloidal anhydrous, succinic acid, and titanium dioxide.
- Citracal Prenatal Rx is a scored, white, modified oval shaped multivitamin/multimineral tablet. Each tablet contains: vitamin A (vitamin A palmitate), 2700 IU; vitamin C (ascorbic acid), 120 mg; calcium (calcium citrate), 125 mg; iron (carbonyl iron, ferrous gluconate), 27 mg; vitamin D3 (cholecalciferol), 400 IU; vitamin E (dl-tocopheryl acetate), 30 IU; thiamin (vitamin B1), 3 mg; riboflavin (vitamin B2), 3.4 mg; niacinamide (vitamin B3), 20 mg; pyridoxine HCl (vitamin B6), 20 mg; folic acid 1 mg; iodine (potassium iodide), 150 mcg; zinc (zinc oxide), 25 mg; copper (cupric oxide), 2 mg; docusate sodium, 50 mg; calcium (as Ultradense® calcium citrate), 200 mg; polyethylene glycol; croscarmellose sodium; polyvinyl alcohol-part hydrolyzed; color added;, magnesium silicate; and magnesium stearate.
- CLARINEX (desloratadine) tablets are light blue, round, film-coated tablets containing 5 mg of desloratadine, an antihistamine, to be administered orally. It also contains the following excipients: dibasic calcium phosphate dihydrate USP, microcrystalline cellulose NF, cornstarch NF, talc USP, carnauba wax NF, white wax NF, coating material consisting of lactose monohydrate, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, and FD&C Blue #2 Aluminum Lake.
- CLARINEX RediTabs® brand of desloratadine orally disintegrating tablets. Each RediTabs tablet contains either 5 or 2.5 mg of desloratadine. It also contains the following inactive ingredients: mannitol USP, microcrystalline

cellulose NF, pregelatinized starch, NF, sodium starch glycolate, USP, magnesium stearate NF, butylated methacrylate copolymer, crospovidone, NF, aspartame NF, citric acid USP, sodium bicarbonate USP, colloidal silicon dioxide, NF, ferric oxide red NF, and tutti-frutti flavoring.

- CLARINEX-D® 24-hour extended-release tablets are light blue oval shaped tablets containing 5 mg of desloratadine in the tablet coating for immediate-release and 240 mg of pseudoephedrine sulfate, USP in the tablet core for extended-release. The inactive ingredients contained in CLARINEX-D® 24-hour extended-release tablets are hypromellose USP, ethylcellulose NF, dibasic calcium phosphate dihydrate USP, magnesium stearate NF, povidone USP, silicone dioxide NF, talc USP, polyacrylate dispersion, polyethylene glycol NF, simethicone USP, Blue Lake Blend 50726 (FD&C Blue No. 2 Lake, titanium dioxide USP and edetate disodium USP), and ink (Opacode® S-1-17746 or Opacode® S-1-4159).
- CLINORIL (Sulindac) is available in 150- and 200-mg tablets for oral administration. Each tablet contains the following inactive ingredients: cellulose, magnesium stearate, starch. Sulindac is a nonsteroidal, anti-inflammatory indene derivative.
- CLORPRES® is a combination of clonidine hydrochloride and chlorthalidone. CLORPRES® is available as tablets for oral administration in three dosage strengths: 0.1 mg/15 mg, 0.2 mg/15 mg, and 0.3 mg/15 mg of clonidine hydrochloride/chlorthalidone, respectively. The inactive ingredients are ammonium chloride, colloidal silicon dioxide, croscarmellose sodium (Type A), magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, D&C yellow #10.
- Clozapine tablets, for oral administration, are available containing 25 and 100 mg of clozapine. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, crospovidone, lactose (monohydrate), magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. In addition, the 25-mg tablet contains FD&C red #40 lake and the 100-mg tablet contains FD&C blue #2 lake.
- COMBIVIR tablets are combination tablets containing lamivudine and zidovudine. Lamivudine (EPIVIR®, 3TC®) and zidovudine (RETROVIR®, azidothymidine, AZT, or ZDV) are synthetic nucleoside analogues with activity against human immunodeficiency virus (HIV). COMBIVIR tablets are for oral administration. Each film-coated tablet contains 150 mg of lamivudine, 300 mg of zidovudine, and the inactive ingredients colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide. Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C. Zidovudine is a white to beige, odorless, crystalline solid with a solubility of 20.1 mg/mL in water at 25°C.
- Combunox™ tablet contains oxycodone HCl, USP 5 mg, and ibuprofen, USP 400 mg. Combunox tablets include sodium starch glycolate, microcrystalline cellulose, colloidal silicon dioxide, stearic acid, calcium stearate, carboxymethylcellulose, povidone, and Opadry® II White, Y-22 7719 coloring agent. Opadry® II White, Y-22 7719 coloring agent consists of titanium dioxide, polydextrose, hypromellose, triacetin, and polyethylene glycol 8000.
- Comtan® (entacapone) is available as tablets containing 200-mg entacapone. The inactive ingredients of the Comtan tablet are microcrystalline cellulose, mannitol, croscarmellose sodium, hydrogenated vegetable oil, hydroxypropyl methylcellulose, polysorbate 80, glycerol 85%, sucrose, magnesium stearate, yellow iron oxide, red oxide, and titanium dioxide.
- CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin. CONCERTA® uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within 1 hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, which in turn controls drug delivery. Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of CONCERTA®. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components.
- COREG (Carvedilol) is a white, oval, film-coated tablet containing 3.125, 6.25, 12.5, or 25 mg of carvedilol. The 6.25-, 12.5-, and 25-mg tablets are TILTAB® tablets. Inactive ingredients consist of colloidal silicon dioxide, crospovidone, hypromellose, lactose, magnesium stearate, polyethylene glycol, polysorbate 80, povidone, sucrose, and titanium dioxide.
- Covera-HS (verapamil hydrochloride) for oral administration as pale yellow, round, film-coated tablets containing 240 mg of verapamil hydrochloride and as lavender, round, film-coated tablets containing 180 mg of verapamil hydrochloride. Inactive ingredients are black ferric oxide, BHT, cellulose acetate, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, magnesium stearate, polyethylene glycol, polyethylene oxide, polysorbate 80, povidone, sodium chloride, titanium dioxide, and coloring agents: 240-mg FD&C Blue No. 2 Lake and D&C Yellow No. 10 Lake; 180-mg FD&C Blue No. 2 Lake and D&C Red No. 30 Lake. System components and performance: The Covera-HS formulation has been designed to initiate the release of verapamil 4 to 5 hours after ingestion. This delay is introduced by a layer between the active drug core and outer semipermeable membrane. As water from the gastrointestinal tract enters the tablet, this delay coating is solubilized and released. As tablet hydration continues, the osmotic layer expands and pushes against the drug layer, releasing drug through precision laser-drilled orifices in the outer membrane at a constant rate. This

controlled rate of drug delivery in the gastrointestinal lumen is independent of posture, pH, gastrointestinal motility, and fed or fasting conditions. The biologically inert components of the delivery system remain intact during GI transit and are eliminated in the feces as an insoluble shell.

- COZAAR (losartan potassium) is available as tablets for oral administration containing either 25, 50, or 100 mg of losartan potassium and the following inactive ingredients: microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hypromellose, titanium dioxide, D&C yellow No. 10 aluminum lake and FD&C blue No. 2 aluminum lake. COZAAR 25-, 50-, and 100-mg tablets contain potassium in the following amounts: 2.12 mg (0.054 mEq), 4.24 mg (0.108 mEq), and 8.48 mg (0.216 mEq), respectively. COZAAR 25 mg, COZAAR 50 mg, and COZAAR 100 mg may also contain carnauba wax.
- CRESTOR® (rosuvastatin calcium) tablets for oral administration contain 5, 10, 20, or 40 mg of rosuvastatin and the following inactive ingredients: microcrystalline cellulose NF, lactose monohydrate NF, tribasic calcium phosphate NF, crospovidone NF, magnesium stearate NF, hypromellose NF, triacetin NF, titanium dioxide USP, yellow ferric oxide, and red ferric oxide NF.
- DARANIDE (Dichlorphenamide) is supplied as tablets, for oral administration, each containing 50 mg of dichlorphenamide. Inactive ingredients are D&C Yellow 10, lactose, magnesium stearate, and starch.
- DARAPRIM (pyrimethamine) tablet contains 25 mg of pyrimethamine and the inactive ingredients corn and potato starch, lactose, and magnesium stearate.
- Darvocet (Propoxyphene Napsylate). Each tablet of Darvocet A500™ contains 100 mg of propoxyphene napsylate and 500 mg of acetaminophen. Each tablet also contains anhydrous lactose, colloidal silicon dioxide, crospovidone, magnesium stearate (powder), microcrystalline cellulose, povidone, pregelatinized cornstarch, and stearic acid (powder). Film coating is composed of carnauba wax, hypromellose 2910 6cP, polyethylene glycol, purified water, sodium citrate, titanium dioxide, FD&C Red No. 40 Aluminum Lake, and FD&C Yellow No. 6 Aluminum Lake.
- DECADRON (dexamethasone tablets, USP) tablets, for oral administration, are supplied in two potencies, 0.5 and 0.75 mg. Inactive ingredients are calcium phosphate, lactose, magnesium stearate, and starch. Tablets DECADRON 0.5 mg also contain D&C Yellow 10 and FD&C Yellow 6. Tablets DECADRON 0.75 mg also contain FD&C Blue 1.
- DEPAKOTE (Divalproex sodium) is a stable coordination compound composed of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Divalproex sodium occurs as a white powder with a characteristic odor. DEPAKOTE tablets are for oral administration. DEPAKOTE tablets are supplied in three dosage strengths containing divalproex sodium equivalent to 125, 250, or 500 mg of valproic acid. Inactive ingredients DEPAKOTE tablets: cellulosic polymers, diacetylated monoglycerides, povidone, pregelatinized starch (contains cornstarch), silica gel, talc, titanium dioxide, and vanillin. In addition, 125-mg tablets contain FD&C Blue No. 1 and FD&C Red No. 40, 250-mg tablets contain FD&C Yellow No. 6 and iron oxide, and 500-mg tablets contain D&C Red No. 30, FD&C Blue No. 2, and iron oxide. DEPAKOTE ER 250- and 500-mg tablets are for oral administration. DEPAKOTE ER tablets contain divalproex sodium in a once-a-day extended-release formulation equivalent to 250 and 500 mg of valproic acid. Inactive ingredients for DEPAKOTE ER 250- and 500-mg tablets: FD&C Blue No. 1, hypromellose, lactose, microcrystalline cellulose, polyethylene glycol, potassium sorbate, propylene glycol, silicon dioxide, titanium dioxide, and triacetin. In addition, 500-mg tablets contain iron oxide and polydextrose.
- DESOXYN (methamphetamine hydrochloride tablets, USP), contain 5 mg of methamphetamine hydrochloride for oral administration. Inactive ingredients: cornstarch, lactose, sodium paraminobenzoate, stearic acid, and talc.
- DETROL tablets contain tolterodine tartrate. DETROL tablets for oral administration contain 1 or 2 mg of tolterodine tartrate. The inactive ingredients are colloidal anhydrous silica, calcium hydrogen phosphate dihydrate, cellulose microcrystalline, hypromellose, magnesium stearate, sodium starch glycolate (pH 3.0–5.0), stearic acid, and titanium dioxide.
- DEXEDRINE (dextroamphetamine sulfate) is the dextro isomer of the compound dl-amphetamine sulfate. Each triangular, orange, scored tablet is debossed SKF and E19 and contains dextroamphetamine sulfate, 5 mg. Inactive ingredients consist of calcium sulfate, FD&C Yellow No. 5 (tartrazine), FD&C Yellow No. 6, gelatin, lactose, mineral oil, starch, stearic acid, sucrose, talc, and trace amounts of other inactive ingredients.
- Didronel tablets contain either 200 or 400 mg of etidronate disodium. Inactive ingredients: Each tablet contains magnesium stearate, microcrystalline cellulose, and starch.
- DIGITEK (digoxin) is one of the cardiac (or digitalis) glycosides. Each tablet contains the labeled amount of digoxin USP and the following inactive ingredients: cornstarch, croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, lactose monohydrate and anhydrous lactose, silicon dioxide and stearic acid. In addition, the 125-mcg (0.125-mg) tablet contains D&C Yellow No. 10 Aluminum Lake.
- DILAUDID TABLET contains hydromorphone hydrochloride. In addition, the tablets include lactose anhydrous, and magnesium stearate. DILAUDID 8-mg tablet may contain traces of sodium metabisulfite. Color coded tablets (for oral administration) containing 2-mg hydromorphone hydrochloride (orange tablet) and D&C red #30 Lake dye, D&C yellow #10 Lake dye, lactose, and magnesium stearate, 4-mg hydromorphone hydrochloride (yellow tablet) and D&C yellow #10 Lake dye, lactose, and magnesium stearate.
- Diovan HCT® (valsartan and hydrochlorothiazide, USP) tablets are formulated for oral administration to contain valsartan and hydrochlorothiazide, USP 80/12.5 mg, 160/12.5 mg, and 160/25 mg. The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, and titanium dioxide.
- Diovan® (valsartan) is available as tablets for oral administration, containing 40, 80, 160, or 320 mg of valsartan. The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides (yellow, black and/or red), magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.
- Disulfiram tablet for oral administration contains 250 or 500 mg of disulfiram, USP. Tablets also contain colloidal

silicon dioxide, anhydrous lactose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, and stearic acid.

- DOLOBID. Diflunisal tablets DOLOBID contain the following inactive ingredients: cellulose, FD&C Yellow 6, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, starch, talc, and titanium dioxide.
- DOSTINEX tablets contain 0.5 mg of cabergoline. Inactive ingredients consist of leucine, USP, and lactose, NF.
- Each MOTRIN® IB tablet and caplet contains ibuprofen 200 mg. Tablets and caplets: carnauba wax, cornstarch, FD&C Yellow #6, hypromellose, iron oxide, polydextrose, polyethylene glycol, silicon dioxide, stearic acid, and titanium dioxide.
- EES (Erythromycin ethylsuccinate) is an ester of erythromycin suitable for oral administration. E.E.S. 400® Filmtab® tablets: Each tablet contains erythromycin ethylsuccinate equivalent to 400 mg of erythromycin. Inactive ingredients: Cellulosic polymers, confectioner's sugar (contains cornstarch), cornstarch, D&C Red No. 30, D&C Yellow No. 10, FD&C Red No. 40, magnesium stearate, polacrilin potassium, polyethylene glycol, propylene glycol, sodium citrate, sorbic acid, and titanium dioxide.
- Effexor (venlafaxine hydrochloride) tablets contain venlafaxine hydrochloride equivalent to 25, 37.5, 50, 75, or 100 mg of venlafaxine. Inactive ingredients consist of cellulose, iron oxides, lactose, magnesium stearate, and sodium starch glycolate.
- ENABLEX® (darifenacin) is an extended-release tablet that contains 7.5 or 15 mg of darifenacin as its hydrobromide salt. ENABLEX is a once-a-day extended-release tablet and contains the following inactive ingredients: dibasic calcium phosphate anhydrous, hydroxypropyl methylcellulose (hypromellose), lactose monohydrate, magnesium stearate, titanium dioxide, and triacetin. The 15-mg tablet also contains FD&C Yellow No. 6 Aluminum Lake.
- Encora™ is a prescription vitamin and mineral nutritional supplement with essential fatty acids consisting of two capsules and two tablets on each blister card designated for AM and PM oral administration as follows. AM tablet is an oval-shaped, light pink film-coated tablet containing the following ingredients: calcium (calcium carbonate), 400 mg; vitamin D3 (cholecalciferol), 200 IU; vitamin C (as Ester-C® †), 25 mg; folic acid, USP, 2 mg; and vitamin B6 (pyridoxine hydrochloride, USP), 25 mg. PM tablet is an oval-shaped, purple film-coated tablet containing the following ingredients: calcium (calcium carbonate), 600 mg; vitamin D3 (cholecalciferol), 600 IU; vitamin C (as Ester-C®), 25 mg; folic acid, USP, 0.5 mg; and vitamin B6 (pyridoxine hydrochloride, USP), 12.5 mg. AM and PM capsule is a pink soft gelatin capsule containing the following ingredients: essential fatty acids (omega-3), 650 mg; DHA and EPA, 550 mg; α-linolenic acid (ALA), 100 mg; linoleic acid (LA), 10 mg; and vitamin E (dl-tocopheryl acetate), 50 IU. Ester-C® is a patented pharmaceutical grade material consisting of calcium ascorbate and calcium theonate. Eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA) ratio is approximately 2.7:1. Inactive ingredients (tablets): acacia, butylated hydroxyanisole, butylated hydroxytoluene, colloidal silicon dioxide, cornstarch, croscarmellose sodium, D&C Red No. 27 aluminum lake, hydrolyzed gelatin, lecithin, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, stearic acid, sucrose, talc, titanium dioxide, and vegetable oil. The AM tablet also contains FD&C Blue No. 2 aluminum lake. The PM tablet also contains FD&C Blue No. 1 aluminum lake. Inactive ingredients (capsule): D&C Red No. 33, ethyl vanillin, FD&C Red No. 40, gelatin, glycerin, soybean oil, and titanium dioxide.
- ENJUVIA (synthetic conjugated estrogens, B) tablets contain a blend of ten synthetic estrogenic substances. The estrogenic substances are sodium estrone sulfate, sodium equilin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17α-estradiol sulfate, sodium 17β-dihydroequilenin sulfate, sodium 17α-dihydroequilenin sulfate, sodium 17β-dihydroequilenin sulfate, sodium equilenin sulfate, sodium 17β-estradiol sulfate, and sodium Δ8, 9-dehydroestrone sulfate. ENJUVIA tablets for oral administration are available in 0.3-, 0.45-, 0.625-, and 1.25-mg strengths of synthetic conjugated estrogens, B. These tablets contain the following inactive ingredients: ascorbyl palmitate, butylated hydroxyanisole, colloidal silicon dioxide, edetate disodium dehydrate, plasticized ethylcellulose, hypromellose, lactose monohydrate, magnesium stearate, purified water, iron oxide red, titanium dioxide, polyethylene glycol, polysorbate 80, triacetate, and triacetin/glycerol. In addition, the 0.45-mg tablets contain iron oxide black and iron oxide yellow, and the 1.25-mg tablets contain iron oxide yellow.
- EPHEDRINE-GUAIFENESI. Active ingredients (in each tablet): Ephedrine HCl, USP, 12.5 mg; Guaifenesin, USP, 200 mg. Inactive ingredients: crospovidone, D&C yellow no. 10 aluminum lake, FD&C yellow no. 6 aluminum lake, magnesium stearate, microcrystalline cellulose, povidone, and silicon dioxide (colloidal).
- EPIVIR (also known as 3TC) is a lamivudine, a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C. EPIVIR tablets are for oral administration. Each 150-mg film-coated tablet contains 150 mg of lamivudine and the inactive ingredients hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide. Each 300-mg film-coated tablet contains 300 mg of lamivudine and the inactive ingredients black iron oxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.
- EPIVIR-HBV is lamivudine, a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C. EPIVIR-HBV tablets are for oral administration. Each tablet contains 100 mg of lamivudine and the inactive ingredients hypromellose, macrogol 400, magnesium stearate, microcrystalline cellulose, polysorbate 80, red iron oxide, sodium starch glycolate, titanium dioxide, and yellow iron oxide.
- EPZICOM tablets contain the following two synthetic nucleoside analogues: abacavir sulfate (ZIAGEN®, also a component of TRIZIVIR®) and lamivudine (also known as EPIVIR® or 3TC). EPZICOM tablets are for oral administration. Each orange, film-coated tablet contains the active ingredients 600 mg of abacavir as abacavir sulfate and 300 mg of lamivudine and the inactive ingredients magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film (Opadry® orange YS 1–13065-A) that is made of FD&C Yellow No. 6, hypromellose, polyethylene glycol 400, polysorbate 80, and titanium dioxide. Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25°C. In vivo, abacavir

sulfate dissociates to its free base, abacavir. All dosages for abacavir sulfate are expressed in terms of abacavir. Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

- EryPed chewable tablets contain erythromycin ethylsuccinate equivalent to 200 mg of erythromycin and is scored for division into half-dose (100 mg) portions. Inactive ingredients: EryPed chewable tablets: Citric acid, confectioner's sugar (contains cornstarch), magnesium aluminum silicate, magnesium stearate, sodium carboxymethylcellulose, sodium citrate, and artificial flavor.
- ERY-TAB (erythromycin delayed-release tablets) are available in three dosage strengths, each white oval tablet containing either 250, 333, or 500 mg of erythromycin as the free base. ERY-TAB tablets comply with USP Drug Release Test 1. Inactive ingredients : Ammonium hydroxide, colloidal silicon dioxide, croscarmellose sodium, crospovidone, diacetylated monoglycerides, hydroxypropyl cellulose, hypromellose, hypromellose phthalate, magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, sodium citrate, sorbitan monooleate, talc, and titanium dioxide.
- ERYTHROCIN STEARATE Filmtab tablets (erythromycin stearate tablets, USP) containing the stearate salt of erythromycin in a unique film coating. Inactive ingredients: 250-mg tablet—Cellulosic polymers, cornstarch, D&C Red No. 7, polacrilin potassium, polyethylene glycol, povidone, propylene glycol, sodium carboxymethylcellulose, sodium citrate, sorbic acid, sorbitan monooleate, and titanium dioxide. 500-mg tablet—Cellulosic polymers, cornstarch, FD&C Red No. 3, magnesium hydroxide, polacrilin potassium, povidone, propylene glycol, sorbitan monooleate, titanium dioxide, and vanillin.
- Erythromycin Base Filmtab (erythromycin tablets, USP) are available in two strengths containing either 250 or 500 mg of erythromycin base. Inactive ingredients: Colloidal silicon dioxide, croscarmellose sodium, crospovidone, D&C Red No. 30 Aluminum Lake, hydroxypropyl cellulose, hypromellose, hydroxypropyl methylcellulose phthalate, magnesium stearate, microcrystalline cellulose, povidone, polyethylene glycol, propylene glycol, sodium citrate, sodium hydroxide, sorbic acid, sorbitan monooleate, talc, and titanium dioxide.
- ESKALITH contains lithium carbonate, a white, light alkaline powder. ESKALITH CR controlled-release tablets: Each round, yellow, biconvex tablet, debossed with SKF and J10 on one side and scored on the other side, contains lithium carbonate, 450 mg. Inactive ingredients consist of alginic acid, gelatin, iron oxide, magnesium stearate, and sodium starch glycolate. ESKALITH CR tablets 450 mg are designed to release a portion of the dose initially and the remainder gradually; the release pattern of the controlled-release tablets reduces the variability in lithium blood levels seen with the immediate-release dosage forms.
- ESTRATEST® tablets: Each dark green, capsule shaped, sugar-coated oral tablet contains: 1.25 mg of Esterified Estrogens, USP, and 2.5 mg of Methyltestosterone, USP. ESTRATEST® H.S. (half-strength) tablets: Each light green, capsule shaped, sugar-coated oral tablet contains 0.625 mg of Esterified Estrogens, USP, and 1.25 mg of Methyltestosterone, USP. Esterified Estrogens, USP is a mixture of the sodium salts of the sulfate esters of the estrogenic substances, principally estrone, that are of the type excreted by pregnant mares. Esterified Estrogens contain not less than 75.0% and not more than 85.0% of sodium estrone sulfate, and not less than 6.0% and not more than 15.0% of sodium equilin sulfate, in such proportion that the total of these two components is not less than 90.0%. ESTRATEST and ESTRATEST H.S. tablets contain the following inactive ingredients: acacia, acetylated monoglycerides, calcium carbonate, carboxymethylcellulose sodium, carnauba wax NF, citric acid, colloidal silicon dioxide, gelatin, iron oxide, lactose, magnesium stearate, methylparaben, microcrystalline cellulose, pharmaceutical glaze, povidone, propylene glycol, propylparaben, shellac glaze, sodium benzoate, sodium bicarbonate, sorbic acid, starch, sucrose, talc, titanium dioxide, and tribasic calcium phosphate. ESTRATEST tablets also contain: FD&C Blue No. 1 Lake, FD&C Yellow No. 6 Lake, and D&C Yellow No. 10 Lake. ESTRATEST H.S. tablets also contain: D&C Yellow No. 10 Lake, FD&C Blue No. 1 Lake, FD&C Blue No. 2 Lake, FD&C Yellow No. 6 Lake, and FD&C Red No. 40 Lake.
- EVISTA® (raloxifene hydrochloride) tablet contains 60 mg of raloxifene HCl, which is the molar equivalent of 55.71 mg of free base. Inactive ingredients include anhydrous lactose, carnauba wax, crospovidone, FD&C Blue No. 2 aluminum lake, hypromellose, lactose monohydrate, magnesium stearate, modified pharmaceutical glaze, polyethylene glycol, polysorbate 80, povidone, propylene glycol, and titanium dioxide.
- FACTIVE (gemifloxacin mesylate). Each white to off-white, oval, film-coated FACTIVE tablet has breaklines and GE 320 debossed on both faces and contains gemifloxacin mesylate equivalent to 320 mg gemifloxacin. The inactive ingredients are crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, and titanium dioxide.
- Famvir® (famciclovir) contains famciclovir. Tablets for oral administration: Each white, film-coated tablet contains famciclovir. The 125-mg and 250-mg tablets are round and the 500-mg tablets are oval. Inactive ingredients consist of hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycols, sodium starch glycolate, and titanium dioxide.
- FazaClo® (clozapine, USP) is available as scored, yellow, orally disintegrating tablets of 25 and 100 mg for oral administration without water. Each orally disintegrating tablet contains clozapine equivalent to 25 or 100 mg. Active ingredient: Each 25-mg orally disintegrating tablet contains 3.1 mg aspartame, thus, 1.74 mg phenylalanine. Each 100-mg orally disintegrating tablet contains 12.4 mg aspartame, thus, 6.96 mg phenylalanine.
- Femara® (letrozole tablets) for oral administration contains 2.5 mg of letrozole. Femara® (letrozole tablets) is available as 2.5-mg tablets for oral administration. Inactive ingredients: Colloidal silicon dioxide, ferric oxide, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, maize starch, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, talc, and titanium dioxide.
- Ferrets tablets are for use as a dietary iron supplement. Each tablet contains: Iron (from 325 mg ferrous fumarate) 106 mg. Other ingredients: Microcrystalline cellulose, sodium starch glycolate, magnesium stearate, Opadry II clear, and Opadry II Red 40L15175.
- FLEXERIL 5 mg (Cyclobenzaprine HCl) is supplied as a 5-mg tablet for oral administration. FLEXERIL 10 mg (Cyclobenzaprine HCl) is supplied as a 10-mg tablet for oral administration. FLEXERIL 5 mg (Cyclobenzaprine HCl) tablets contain the following inactive ingredients: hydroxypropyl cellulose, hypromellose, lactose,

magnesium stearate, starch, titanium dioxide, Yellow D&C #10 Aluminum Lake HT, and Yellow FD&C #6 Aluminum Lake. FLEXERIL 10 mg (Cyclobenzaprine HCl) tablets contain the following inactive ingredients: hydroxypropyl cellulose, hypromellose, iron oxide, lactose, magnesium stearate, starch, and titanium dioxide.

- Flumadine® (rimantadine hydrochloride) film-coated tablet contains 100 mg of rimantadine hydrochloride plus hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, FD&C Yellow No. 6 Lake, and FD&C Yellow No. 6. The film coat contains hydroxypropyl methylcellulose and polyethylene glycol.
- Focalin™ (dexmethylphenidate hydrochloride) is the *d*-threoenantiomer of racemic methylphenidate hydrochloride, which is a 50/50 mixture of the *d*-threo and *l*-threoenantiomers. Focalin is a central nervous system (CNS) stimulant, available in three tablet strengths. Each tablet contains dexmethylphenidate hydrochloride 2.5, 5, or 10 mg for oral administration. Focalin also contains the following inert ingredients: pregelatinized starch, lactose monohydrate, sodium starch glycolate, microcrystalline cellulose, magnesium stearate, and FD&C Blue No. 1 #5516 aluminum lake (2.5-mg tablets), D&C Yellow Lake #10 (5-mg tablets); the 10-mg tablet contains no dye.
- FORTAMET™ (metformin hydrochloride) extended-release tablets are designed for once-a-day oral administration and deliver 500 or 1000 mg of metformin hydrochloride. In addition to the active ingredient metformin hydrochloride, each tablet contains the following inactive ingredients: candelilla wax, cellulose acetate, hypromellose, magnesium stearate, polyethylene glycols (PEG 400, PEG 8000), polysorbate 80, povidone, sodium lauryl sulfate, synthetic black iron oxides, titanium dioxide, and triacetin.
- FOSAMAX (alendronate sodium) tablets for oral administration contain 6.53, 13.05, 45.68, 52.21 or 91.37 mg of alendronate monosodium salt trihydrate, which is the molar equivalent of 5, 10, 35, 40 and 70 mg, respectively, of free acid, and the following inactive ingredients: microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, and magnesium stearate. Tablets FOSAMAX 10 mg also contain carnauba wax.
- FOSAMAX PLUS D contains alendronate sodium, contains 91.37 mg of alendronate monosodium salt trihydrate, the molar equivalent of 70 mg of free acid, and 70 mcg of cholecalciferol equivalent to 2800 International Units (IU) vitamin D. Each tablet contains the following inactive ingredients: microcrystalline cellulose, lactose anhydrous, medium chain triglycerides, gelatin, croscarmellose sodium, sucrose, colloidal silicon dioxide, magnesium stearate, butylated hydroxytoluene, modified food starch, and sodium aluminum silicate.
- FOSRENOL® contains lanthanum carbonate (2:3) hydrate. Each FOSRENOL®, white to off-white, chewable tablet contains lanthanum carbonate hydrate equivalent to 250, 500, 750, or 1000 mg of elemental lanthanum and the following inactive ingredients: dextrates (hydrated) NF, colloidal silicon dioxide NF, and magnesium stearate NF.
- FROVA (frovatriptan succinate) tablet for oral administration contains 3.91 mg of frovatriptan succinate, equivalent to 2.5 mg of frovatriptan base. Each tablet also contains the inactive ingredients lactose NF, microcrystalline cellulose NF, colloidal silicon dioxide NF, sodium starch glycolate NF, magnesium stearate NF, hydroxypropyl methylcellulose USP, polyethylene glycol 3000 USP, triacetin USP, and titanium dioxide USP.
- Furosemide tablet for oral administration contains 20, 40, or 80 mg of furosemide and the following inactive ingredients: colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, pregelatinized starch and stearic acid. Furosemide tablets, USP 20, 40, and 80 mg meet USP Dissolution Test 1.
- GABITRIL (tiagabine HCl) tablets contain the following inactive ingredients: Ascorbic acid, colloidal silicon dioxide, crospovidone, hydrogenated vegetable oil wax, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, stearic acid, and titanium dioxide. In addition, individual tablets contain the following ingredients: 2-mg tablets—FD&C Yellow No. 6. 4-mg tablets—D&C Yellow No. 10. 12-mg tablets—D&C Yellow No. 10 and FD&C Blue No. 1. 16-mg tablets—FD&C Blue No. 2.
- Gleevec® (imatinib mesylate) film-coated tablets contain imatinib mesylate equivalent to 100 or 400 mg of imatinib free base. Inactive ingredients: colloidal silicon dioxide (NF), crospovidone (NF), hydroxypropyl methylcellulose (USP), magnesium stearate (NF), and microcrystalline cellulose (NF). Tablet coating: ferric oxide, red (NF); ferric oxide, yellow (NF); hydroxypropyl methylcellulose (USP); polyethylene glycol (NF); and talc (USP).
- Gris-PEG® tablets contain ultramicrosize crystals of griseofulvin. Active ingredient: griseofulvin ultramicrosize 125 mg. Inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, methylcellulose, methylparaben, polyethylene glycol 400 and 8000, polyvinylpyrrolidone, and titanium dioxide. Or, active ingredient: griseofulvin ultramicrosize 250 mg. Inactive ingredients: colloidal silicon dioxide, magnesium stearate, methylcellulose, methylparaben, polyethylene glycol 400 and 8000, povidone, sodium lauryl sulfate, and titanium dioxide.
- Guanidine (amino-methanamidine) tablet contains 125 mg of guanidine hydrochloride with no color additive in the base. It also contains the following inactive ingredients: colloidal silicon dioxide, magnesium stearate, mannitol, and microcrystalline cellulose.
- HYDROCORTONE (Hydrocortisone) tablets contain 10 mg of hydrocortisone in each tablet. Inactive ingredients are lactose, magnesium stearate, and starch.
- HYZAAR 50-12.5 (losartan potassium-hydrochlorothiazide), HYZAAR 100-12.5 (losartan potassium-hydrochlorothiazide), and HYZAAR 100-25 (losartan potassium-hydrochlorothiazide) are available for oral administration in two tablet combinations of losartan and hydrochlorothiazide. HYZAAR 50-12.5 contains 50 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. HYZAAR 100-12.5 contains 100 mg of losartan potassium and 12.5 mg of hydrochlorothiazide. HYZAAR 100-25 contains 100 mg of losartan potassium and 25 mg of hydrochlorothiazide. Inactive ingredients are microcrystalline cellulose, lactose hydrous, pregelatinized starch, magnesium stearate, hydroxypropyl cellulose, hypromellose, and titanium dioxide. HYZAAR 50-12.5 and HYZAAR 100-25 also contain D&C yellow No. 10 aluminum lake. HYZAAR 50-12.5, HYZAAR 100-12.5, and HYZAAR 100-25 may also contain carnauba wax. HYZAAR 50-12.5 contains 4.24 mg (0.108 mEq) of potassium, HYZAAR 100-12.5 contains 8.48 mg (0.216 mEq) of potassium, and HYZAAR 100-25 contains 8.48 mg (0.216 mEq) of potassium.

- IBUPROFEN. Active ingredient: Each tablet, caplet, gel caplet, or liquigel capsule contains ibuprofen (200 mg). Inactive ingredients: Tablets and caplets—acetylated monoglyceride, beeswax and/or carnauba wax, croscarmellose sodium, iron oxides, lecithin, methylparaben, microcrystalline cellulose, pharmaceutical glaze, povidone, propylparaben, silicon dioxide, simethicone, sodium benzoate, sodium lauryl sulfate, starch, stearic acid, sucrose, and titanium dioxide. Gel Caplets—croscarmellose sodium, FD&C red no. 40, FD&C yellow no. 6, gelatin, glycerin, hypromellose, iron oxides, medium chain triglycerides, pharmaceutical ink, propyl gallate, silicon dioxide, sodium lauryl sulfate, starch, stearic acid, titanium dioxide, and triacetin.
- Ibuprofen 50 mg. Inactive ingredients: (Grape flavor) artificial flavor, aspartame, cellulose acetate phthalate, D&C Red No. 30 Lake, FD&C Blue No. 2 Lake, gelatin, magnasweet, magnesium stearate, mannitol, microcrystalline cellulose, silicon dioxide, and sodium starch glycolate. Active ingredient (in each tablet): ibuprofen 100 mg. Inactive ingredients: acetylated monoglycerides, carnauba wax, colloidal silicon dioxide, croscarmellose sodium, iron oxides, methylparaben, microcrystalline cellulose, povidone, pregelatinized starch, propylene glycol, propylparaben, shellac, sodium benzoate, starch, stearic acid, sucrose, and titanium dioxide. Active ingredient: Each brown, oval capsule contains solubilized ibuprofen, a pain reliever, equal to 200 mg of ibuprofen (present as the free acid and potassium salt). Inactive ingredients: D&C Yellow No. 10, FD&C Green No. 3, FD&C Red No. 40, gelatin, light mineral oil, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan, and sorbitol. Active ingredients (in each caplet): Ibuprofen (200 mg) and pseudoephedrine HCl (30 mg). Inactive ingredients: carnauba or equivalent wax, croscarmellose sodium, iron oxide, methylparaben, microcrystalline cellulose, propylparaben, silicon dioxide, sodium benzoate, sodium lauryl sulfate, starch, stearic acid, sucrose, and titanium dioxide. Active ingredients (in each tablet or caplet): Ibuprofen (200 mg) and pseudoephedrine HCl (30 mg). Inactive Ingredients (tablets and caplets): carnauba or equivalent wax, croscarmellose sodium, iron oxides, methylparaben, microcrystalline cellulose, propylparaben, silicon dioxide, sodium benzoate, sodium lauryl sulfate, starch, stearic acid, sucrose, and titanium dioxide.
- Ibuprofen 50 mg. Inactive ingredients: (White grape flavor) artificial flavor, carboxymethylcellulose sodium, citric acid, edetate disodium, glycerin, microcrystalline cellulose, polysorbate 80, propylene glycol, purified water, sodium benzoate, sorbitol solution, sucrose, and xanthan gum. Inactive ingredients: (grape flavor) artificial flavor, carboxymethyl cellulose sodium, citric acid, edetate disodium, FD&C blue no. 1, FD&C red no. 40, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution, sucrose, and xanthan gum
- IMDUR (Isosorbide mononitrate (ISMN) tablets contain 30, 60, or 120 mg of isosorbide mononitrate in an extended-release formulation. The inactive ingredients are aluminum silicate, colloidal silicon dioxide, hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, paraffin wax, polyethylene glycol, titanium dioxide, and trace amounts of ethanol.
- IMITREX tablets sumatriptan (as the succinate) contains 35, 70, or 140 mg of sumatriptan succinate equivalent to 25, 50, or 100 mg of sumatriptan, respectively. Each tablet also contains the inactive ingredients croscarmellose sodium, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, and sodium bicarbonate. Each 100-mg tablet also contains hypromellose, iron oxide, titanium dioxide, and triacetin.
- Indapamide tablet for oral administration contains 1.25 or 2.5 mg of indapamide and the following inactive ingredients: anhydrous lactose, colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized starch, sodium lauryl sulfate, and titanium dioxide. Additionally, the 1.25 mg product contains glyceryl triacetate and D&C Red No. 30 Aluminum Lake and the 2.5 mg product contains triacetin.
- Inderal (propranolol hydrochloride) LA capsules contain the following inactive ingredients: cellulose, ethylcellulose, gelatin capsules, hypromellose, and titanium dioxide. In addition, Inderal LA 60-, 80-, and 120-mg capsules contain D&C Red No. 28 and FD&C Blue No. 1; Inderal LA 160-mg capsules contain FD&C Blue No. 1.
- INTELECTOL® tablet contains vinpocetine 5 mg. Other ingredients: Lactose, hydroxypropyl cellulose, magnesium stearate, and talc.
- INVERSINE® (Mecamylamine HCl) is supplied as tablets for oral use, each containing 2.5-mg mecamylamine HCl. Inactive ingredients are acacia, calcium phosphate, D&C Yellow 10, FD&C Yellow 6, lactose, magnesium stearate, starch, and talc.
- IRESSA® (gefitinib tablets) contain 250 mg of gefitinib and are available as brown film-coated tablets for daily oral administration. It is a white-colored powder. Gefitinib is a free base. The molecule has pK a s of 5.4 and 7.2 and therefore ionizes progressively in solution as the pH falls. Inactive ingredients of IRESSA tablets (core): Lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, and magnesium stearate. Inactive ingredients of IRESSA tablets (coating): Hypromellose, polyethylene glycol 300, titanium dioxide, red ferric oxide, and yellow ferric oxide.
- KALETRA (lopinavir/ritonavir) film-coated tablets are available for oral administration in a strength of 200 mg of lopinavir and 50 mg of ritonavir with the following inactive ingredients: copovidone, sorbitan monolaurate, colloidal silicon dioxide, and sodium stearyl fumarate. The following are the ingredients in the film coating: hypromellose, titanium dioxide, polyethylene glycol 400, hydroxypropyl cellulose, talc, colloidal silicon dioxide, polyethylene 3350, yellow ferric oxide E172, and polysorbate 80.
- K-DUR® 20 product is an immediately dispersing extended-release oral dosage form of potassium chloride containing 1500 mg of microencapsulated potassium chloride, USP equivalent to 20 mEq of potassium in a tablet. The K-DUR® 10 product is an immediately dispersing extended-release oral dosage form of potassium chloride containing 750 mg of microencapsulated potassium chloride, USP equivalent to 10 mEq of potassium in a tablet. K-DUR is a tablet formulation (not enteric coated or wax matrix) containing individually microencapsulated potassium chloride crystals which disperse upon tablet disintegration. In simulated gastric fluid at 37°C and in the absence of outside agitation, K-DUR begins disintegrating into microencapsulated crystals within seconds and completely disintegrates within 1 minute. The microencapsulated crystals are formulated to provide an extended release of potassium chloride. Inactive ingredients:

crospovidone, ethylcellulose, hydroxypropyl cellulose, magnesium stearate, and microcrystalline cellulose.

- Keppra® (levetiracetam) tablets and as a clear, colorless, grape-flavored liquid (100 mg/mL) for oral administration. Inactive ingredients: colloidal silicon dioxide, cornstarch, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 4000, povidone, talc, titanium dioxide, and coloring agents. The individual tablets contain the following coloring agents: 250-mg tablets—FD&C Blue No. 2; 500-mg tablets—yellow iron oxide; 750-mg tablets—FD&C Blue No. 2, FD&C Yellow No. 6 and red iron oxide.
- KETEK® tablets contain telithromycin. KETEK tablets are light-orange, oval, film-coated tablets, each containing 400-mg telithromycin, plus the following inactive ingredients: cornstarch, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, red ferric oxide, talc, titanium dioxide, and yellow ferric oxide.
- K-PHOS® ORIGINAL (sodium free) tablet contains potassium acid phosphate 500 mg. Each tablet yields approximately 114 mg of phosphorus and 144 mg of potassium or 3.7 mEq. Inactive ingredients: Magnesium stearate, microcrystalline cellulose, starch, and syloid. Each tablet of K-PHOS® NEUTRAL contains 852 mg of dibasic sodium phosphate anhydrous, 155 mg of monobasic potassium phosphate, and 130 mg of monobasic sodium phosphate monohydrate. Each tablet yields approximately 250 mg of phosphorus, 298 mg of sodium (13.0 mEq), and 45 mg of potassium (1.1 mEq). Inactive ingredients: Magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate, and sugar.
- K-TAB (potassium chloride extended-release tablets) 750 mg of potassium chloride, USP, equivalent to 10 mEq of potassium in a film-coated (not enteric-coated), wax matrix tablet. This formulation is intended to slow the release of potassium so that the likelihood of a high localized concentration of potassium chloride within the gastrointestinal tract is reduced. The expended inert, porous, wax/polymer matrix is not absorbed and may be excreted intact in the stool. Inactive ingredients: Castor oil, cellulosic polymers, colloidal silicon dioxide, D&C Yellow No. 10, magnesium stearate, paraffin, polyvinyl acetate, titanium dioxide, vanillin, and vitamin E.
- LAMICTAL (lamotrigine), tablets are supplied for oral administration as 25-mg (white), 100-mg (peach), 150-mg (cream), and 200- mg (blue) tablets. Each tablet contains the labeled amount of lamotrigine and the following inactive ingredients: lactose; magnesium stearate; microcrystalline cellulose; povidone; sodium starch glycolate; FD&C Yellow No. 6 Lake (100-mg tablet only); ferric oxide, yellow (150-mg tablet only); and FD&C Blue No. 2 Lake (200-mg tablet only). LAMICTAL chewable dispersible tablets are supplied for oral administration. The tablets contain 2 mg (white), 5 mg (white), or 25 mg (white) of lamotrigine and the following inactive ingredients: blackcurrant flavor, calcium carbonate, low-substituted hydroxypropyl cellulose, magnesium aluminum silicate, magnesium stearate, povidone, saccharin sodium, and sodium starch glycolate.
- LAMISIL® (terbinafine hydrochloride tablets) terbinafine hydrochloride (equivalent to 250 mg base). Inactive ingredients: colloidal silicon dioxide, NF; hydroxypropyl methylcellulose, USP; magnesium stearate, NF; microcrystalline cellulose, NF; sodium starch glycolate, NF.
- LANOXIN (digoxin) is supplied as 125-mcg (0.125-mg) or 250-mcg (0.25-mg) tablets for oral administration. Each tablet contains the labeled amount of digoxin USP and the following inactive ingredients: corn and potato starches, lactose, and magnesium stearate. In addition, the dyes used in the 125-mcg (0.125-mg) tablets are D&C Yellow No. 10 and FD&C Yellow No. 6.
- LEUKERAN (chlorambucil) is available in tablet form for oral administration. Each film-coated tablet contains 2 mg chlorambucil and the inactive ingredients colloidal silicon dioxide, hypromellose, lactose (anhydrous), macrogol/PEG 400, microcrystalline cellulose, red iron oxide, stearic acid, titanium dioxide, and yellow iron oxide.
- LEVITRA® is formulated as orange, round, film-coated tablets containing 2.5, 5, 10, and 20 mg of vardenafil, respectively. In addition to the active ingredient, vardenafil HCl, each tablet contains microcrystalline cellulose, crospovidone, colloidal silicon dioxide, magnesium stearate, hypromellose, polyethylene glycol, titanium dioxide, yellow ferric oxide, and red ferric oxide.
- Levonorgestrel. Twenty-one pink active tablets each containing 0.10 mg of levonorgestrel. The inactive ingredients present are cellulose, hypromellose, iron oxide, lactose, magnesium stearate, polacrilin potassium, polyethylene glycol, titanium dioxide, and wax E. Seven light-green inert tablets, each containing cellulose, FD&C blue no. 1, hypromellose, iron oxide, lactose, magnesium stearate, polacrilin potassium, polyethylene glycol, titanium dioxide, and wax E.
- LEVOTHROID® (levothyroxine sodium tablets, USP) contains synthetic crystalline L-3, 3′, 5, 5′-tetraiodothyronine sodium salt [levothyroxine (T 4) sodium]. Inactive ingredients: Microcrystalline cellulose, calcium phosphate dibasic, povidone and magnesium stearate. The following are the coloring additives per tablet strength: 25 FD&C Yellow No. 6 Aluminum Lake; 50 None; 75 FD&C Blue No. 2 Aluminum Lake, FD&C Red No. 40 Aluminum Lake; 88 FD&C Yellow No. 6 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, D&C Yellow No. 10 Aluminum Lake; 100 FD&C Yellow No. 6 Aluminum Lake, D&C Yellow No. 10 Aluminum Lake; 112 D&C Red No. 27 Aluminum Lake, D&C Red No. 30 Aluminum Lake; 125 FD&C Blue No. 1 Aluminum Lake, FD&C Red No. 40 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake; 137 FD&C Blue No. 1 Aluminum Lake; 150 FD&C Blue No. 2 Aluminum Lake; 175 FD&C Blue No. 1 Aluminum Lake, D&C Red No. 30 Aluminum Lake, D&C Red No. 27 Aluminum Lake; 200 FD&C Red No. 40 Aluminum Lake; 300 FD&C Yellow No. 6 Aluminum Lake, FD&C Blue No.1 Aluminum Lake, D&C Yellow No. 10 Aluminum Lake.
- Lexapro® (escitalopram oxalate) tablets are film-coated, round tablets containing escitalopram oxalate in strengths equivalent to 5, 10, and 20 mg escitalopram base. The 10- and 20-mg tablets are scored. The tablets also contain the following inactive ingredients: talc, croscarmellose sodium, microcrystalline cellulose/colloidal silicon dioxide, and magnesium stearate. The film coating contains hypromellose, titanium dioxide, and polyethylene glycol.
- LEXIVA (fosamprenavir calcium) tablets are available for oral administration in a strength of 700 mg of fosamprenavir as fosamprenavir calcium (equivalent to approximately 600 mg of amprenavir). Each 700-mg tablet contains the inactive ingredients colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and povidone K30. The tablet film-coating

contains the inactive ingredients hypromellose, iron oxide red, titanium dioxide, and triacetin.

- Librium is available as capsules containing 5, 10, or 25 mg chlordiazepoxide HCl. Each capsule also contains cornstarch, lactose and talc. Gelatin capsule shells may contain methyl and propyl parabens and potassium sorbate, with the following dye systems: 5-mg capsules—FD&C Yellow No. 6 plus D&C Yellow No. 10 and either FD&C Blue No. 1 or FD&C Green No. 3. 10-mg capsules—D&C Yellow No. 10 and either FD&C Blue No. 1 plus FD&C Red No. 3 or FD&C Green No.3 plus FD&C Red No. 40. 25-mg capsules—D&C Yellow No. 10 and either FD&C Green No. 3 or FD&C Blue No. 1
- LIPITOR® (atorvastatin calcium) tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate, USP; candelilla wax, FCC; croscarmellose sodium, NF; hydroxypropyl cellulose, NF; lactose monohydrate, NF; magnesium stearate, NF; microcrystalline cellulose, NF; Opadry White YS-1–7040 (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80, NF; simethicone emulsion.
- LOFIBRA® (fenofibrate tablets) is a lipid regulating agent available as tablets for oral administration. Each tablet contains 54 or 160 mg of fenofibrate. Each 54 mg LOFIBRA® tablet contains the following inactive ingredients: colloidal silicone dioxide, croscarmellose sodium, crospovidone, iron oxide yellow, lactose monohydrate, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone, sodium lauryl sulfate, sodium starch glycolate, sodium stearyl fumarate, talc, titanium dioxide, xanthan gum, and D&C yellow #10 lake. Each 160 mg LOFIBRA® tablet contains the following inactive ingredients: colloidal silicone dioxide, croscarmellose sodium, crospovidone, lactose monohydrate, lecithin, microcrystalline cellulose, polyvinyl alcohol, povidone, sodium lauryl sulfate, sodium starch glycolate, sodium stearyl fumarate, talc, titanium dioxide, and xanthan gum.
- LORATIDINE. Active ingredient (in each tablet): Loratadine 10 mg. Inactive ingredients (Loratadine orally disintegrating tablets): artificial & natural flavor, aspartame, citric acid, colloidal silicon dioxide, corn syrup solids, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, modified food starch, and sodium bicarbonate. Inactive ingredients (Loratadine swallow tablets): lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate
- LORATIDINE-PSEUDOEPHEDRINE. Active ingredients (in each tablet): Loratadine (5 mg) and pseudoephedrine sulfate (120 mg). Inactive ingredients: croscarmellose sodium, dibasic calcium phosphate, hypromellose, lactose monohydrate, magnesium stearate, pharmaceutical ink, povidone, and titanium dioxide.
- Lortab. Hydrocodone bitartrate and acetaminophen is supplied in tablet form for oral administration. Each Lortab 2.5/500 tablet contains hydrocodone bitartrate (2.5 mg) and acetaminophen (500 mg). In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, stearic acid and sugar spheres, which are composed of starch derived from corn, sucrose, and FD&C Red #3. Each Lortab 5/500 tablet contains hydrocodone bitartrate (5 mg) and acetaminophen (500 mg). In addition, each tablet contains the following inactive ingredients: cornstarch, FD&C Blue # 1 Lake, gelatin, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, sodium starch glycolate, and sugar spheres. Each Lortab 7.5/500 tablet contains hydrocodone bitartrate (7.5 mg) and acetaminophen (500 mg). In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, stearic acid, and sugar spheres, which are composed of starch derived from corn, sucrose, FD&C Blue #1 and D&C Yellow #10. Each Lortab 10/500 tablet contains hydrocodone bitartrate (10 mg) and acetaminophen (500 mg). In addition, each tablet contains the following inactive ingredients: D&C Red No. 27 Aluminum Lake, D&C Red No. 30 Aluminum Lake, colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, starch (corn), and stearic acid.
- Lotensin HCT is a combination of benazepril hydrochloride and hydrochlorothiazide USP. The tablets are formulated for oral administration with a combination of 5, 10, or 20 mg of benazepril hydrochloride and 6.25, 12.5, or 25 mg of hydrochlorothiazide USP. The inactive ingredients of the tablets are cellulose compounds, crospovidone, hydrogenated castor oil, iron oxides (10/12.5-mg, 20/12.5-mg, and 20/25-mg tablets), lactose, polyethylene glycol, talc, and titanium dioxide.
- Lotensin is supplied as tablets containing 5, 10, 20, and 40 mg of benazepril hydrochloride for oral administration. The inactive ingredients are colloidal silicon dioxide, crospovidone, hydrogenated castor oil (5-, 10-, and 20-mg tablets), hypromellose, iron oxides, lactose, magnesium stearate (40-mg tablets), microcrystalline cellulose, polysorbate 80, propylene glycol (5- and 40-mg tablets), starch, talc, and titanium dioxide.
- LOTRONEX tablets is alosetron hydrochloride (HCl) and is a white to beige solid that has a solubility of 61 mg/mL in water, 42 mg/mL in 0.1M hydrochloric acid, 0.3 mg/mL in pH 6 phosphate buffer, and <0.1 mg/mL in pH 8 phosphate buffer. LOTRONEX tablets are supplied for oral administration as 0.5-mg (white) and 1-mg (blue) tablets. The 0.5-mg tablet contains 0.562 mg alosetron HCl equivalent to 0.5 mg alosetron and the 1-mg tablet contains 1.124 mg alosetron HCl equivalent to 1 mg of alosetron. Each tablet also contains the inactive ingredients: lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The white film-coat for the 0.5-mg tablet contains hypromellose, titanium dioxide, and triacetin. The blue film-coat for the 1-mg tablet contains hypromellose, titanium dioxide, triacetin, and indigo carmine.
- MALARONE (atovaquone and proguanil hydrochloride) is a fixed-dose combination of the antimalarial agents atovaquone and proguanil hydrochloride. MALARONE tablets and MALARONE pediatric tablets are for oral administration. Each MALARONE tablet contains 250 mg of atovaquone and 100 mg of proguanil hydrochloride and each MALARONE pediatric tablet contains 62.5 mg of atovaquone and 25 mg of proguanil hydrochloride. The inactive ingredients in both tablets are low-substituted hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, poloxamer 188, povidone K30, and sodium starch glycolate. The tablet coating contains hypromellose, polyethylene glycol 400, polyethylene glycol 8000, red iron oxide, and titanium dioxide.
- MAVIK (Trandolapril) tablets contain 1, 2, or 4 mg of trandolapril for oral administration. Each tablet also contains cornstarch, croscarmellose sodium, hypromellose, iron oxide, lactose, povidone, and sodium stearyl fumarate.

- MAXALT contains rizatriptan benzoate. MAXALT tablets and MAXALT-MLT orally disintegrating tablets are available for oral administration in strengths of 5 and 10 mg (corresponding to 7.265 or 14.53 mg of the benzoate salt, respectively). Each compressed tablet contains the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, pregelatinized starch, ferric oxide (red), and magnesium stearate. Each lyophilized orally disintegrating tablet contains the following inactive ingredients: gelatin, mannitol, glycine, aspartame, and peppermint flavor.
- MAXZIDE® (triamterene and hydrochlorothiazide) combines triamterene with hydrochlorothiazide. Each MAXZIDE® tablet contains: Triamterene, USP 75 mg; Hydrochlorothiazide, USP 50 mg. Each MAXZIDE®-25 MG tablet contains: Triamterene, USP 37.5 mg; hydrochlorothiazide, USP 25 mg. MAXZIDE® and MAXZIDE®-25 MG tablets for oral administration contain the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, powdered cellulose, sodium lauryl sulfate, and D&C Yellow #10. MAXZIDE®-25 MG tablets also contain FD&C Blue #1.
- MEBARAL (mephobarbital) is available as tablets for oral administration. Inactive ingredients: Lactose, starch, stearic acid, and talc.
- Melatonin. Each tablet contains Melatonin 3 mg, methylcobalamin (vitamin B12), 1 mg; folic acid, 0.4 mg.
- MEPHYTON Phytonadione tablets containing 5 mg of phytonadione are yellow, compressed tablets, scored on one side. Inactive ingredients are acacia, calcium phosphate, colloidal silicon dioxide, lactose, magnesium stearate, starch, and talc.
- MEVACOR® (Lovastatin), tablets are supplied as 10-, 20-, and 40-mg tablets for oral administration. In addition to the active ingredient lovastatin, each tablet contains the following inactive ingredients: cellulose, lactose, magnesium stearate, and starch. Butylated hydroxyanisole (BHA) is added as a preservative. Tablets MEVACOR 10 mg also contain red ferric oxide and yellow ferric oxide. Tablets MEVACOR 20 mg also contain FD&C Blue 2. Tablets MEVACOR 40 mg also contain D&C Yellow 10 aluminum lake and FD&C Blue 2 aluminum lake.
- MIDAMOR (Amiloride HCl) is available for oral use as tablets containing 5 mg of anhydrous amiloride HCl. Each tablet contains the following inactive ingredients: calcium phosphate, D&C Yellow 10, iron oxide, lactose, magnesium stearate, and starch.
- Minocycline hydrochloride tablets for oral administration contain minocycline HCl equivalent to 50, 75, or 100 mg of minocycline. In addition, 50-, 75-, and 100-mg tablets contain the following inactive ingredients: Colloidal silicon dioxide, lactose anhydrous, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate. The 50-mg tablets also contain Opadry White which contains titanium dioxide, hydroxypropyl methylcellulose, polyethylene glycol, and polysorbate 80. The 75- and 100-mg tablets contain Opadry Gray which contains titanium dioxide, hydroxypropyl methylcellulose, polyethylene glycol, and iron oxide black.
- MIRADON tablets contain a synthetic anticoagulant, anisindione, an indanedione derivative. Each tablet contains 50 mg anisindione. They also contain: cornstarch, FD&C Red No. 3, gelatin, lactose, and hydrogenated cotton-seed oil.
- MS CONTIN® Controlled-release tablets 15, 30, 60, 100, and 200 mg of morphine sulfate and further contain the following inactive ingredients: cetostearyl alcohol, hydroxyethyl cellulose, hypromellose, magnesium stearate, polyethylene glycol, talc, and titanium dioxide. MS CONTIN® controlled-release tablets 15 mg also contains FD&C Blue No. 2, lactose and polysorbate 80. MS CONTIN® controlled-release tablets 30 mg also contains D&C Red No. 7, FD&C Blue No. 1, lactose and polysorbate 80. MS CONTIN® controlled-release tablets 60 mg also contains D&C Red No. 30, D&C Yellow No. 10, hydroxypropyl cellulose, and lactose. MS CONTIN® controlled-release tablets 100 mg also contains black iron oxide. MS CONTIN® controlled-release tablets 200 mg also contains D&C Yellow No. 10, FD&C Blue No. 1, and hydroxypropyl cellulose.
- Myfortic® (mycophenolic acid) delayed-release tablets are an enteric formulation of mycophenolate sodium that delivers the active moiety mycophenolic acid (MPA). Myfortic is available for oral use as delayed-release tablets containing either 180 or 360 mg of mycophenolic acid. Inactive ingredients include colloidal silicon dioxide, crospovidone, lactose anhydrous, magnesium stearate, povidone (K-30), and starch. The enteric coating of the tablet consists of hypromellose phthalate, titanium dioxide, iron oxide yellow, and indigotine (180 mg) or iron oxide red (360 mg).
- MYLERAN (busulfan) film-coated tablet contains 2 mg busulfan and the inactive ingredients hypromellose, lactose (anhydrous), magnesium stearate, pregelatinized starch, triacetin, and titanium dioxide.
- Nadolol tablet for oral administration contains 20, 40, or 80 mg of nadolol and the following inactive ingredients: croscarmellose sodium, lactose (anhydrous), magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, and D&C Yellow #10 Aluminum Lake.
- Namenda® (memantine hydrochloride) capsule-shaped, film-coated tablets containing 5 and 10 mg of memantine hydrochloride. The tablets also contain the following inactive ingredients: microcrystalline cellulose/colloidal silicon dioxide, talc, croscarmellose sodium, and magnesium stearate. In addition the following inactive ingredients are also present as components of the film coat: hypromellose, titanium dioxide, polyethylene glycol 400, FD&C yellow #6 and FD&C blue #2 (5-mg tablets), and hypromellose, titanium dioxide, macrogol/polyethylene glycol 400 and iron oxide black (10-mg tablets).
- Neurontin® (gabapentin) tablets are elliptical film-coated tablets containing 600 and 800 mg of gabapentin. The inactive ingredients for the tablets are poloxamer 407, copolyvidonum, cornstarch, magnesium stearate, hydroxypropyl cellulose, talc, candelilla wax, and purified water.
- NEXAVAR film-coated tablet contains sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide, and ferric oxide red.
- Nicomide® tablets for oral administration are peach-colored, oval-shaped tablets imprinted "Sirius" in blue ink on one side. Each oral tablet provides nicotinamide, USP, 750 mg; zinc oxide, USP, 25 mg; cupric oxide, USP 1.5 mg; folic acid, USP 500 mcg. Nicomide® has been designed to provide biphasic delivery of each of the active ingredients in order to minimize the potential for competitive antagonism in absorption of its ingredients. The biphasic

delivery system facilitates the immediate release of 750 mg nicotinamide, 1.5 mg cupric oxide, and 500 mcg folic acid as well as the sustained release of 25 mg zinc oxide. The biphasic delivery system also minimizes the potential for drug interaction induced deficiency states and impaired absorptions of other therapeutic agents. Inactive ingredients: Carnauba wax powder, ethyl cellulose, FD&C Blue # 1, FD&C Yellow # 6 Aluminum Lake, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, propylene glycol, shellac, stearic acid, and titanium dioxide.

- NIRAVAM™ (alprazolam orally disintegrating tablets) contains either 0.25, 0.5, 1, or 2 mg of alprazolam and the following inactive ingredients: colloidal silicon dioxide, cornstarch, crospovidone, magnesium stearate, mannitol, methacrylic acid copolymer, microcrystalline cellulose, natural and artificial orange flavor, sucralose, and sucrose. In addition, the 0.25- and 0.5-mg tablets contain yellow iron oxide.
- Nystatin Vaginal tablets, USP, are available as oval-shaped compressed tablets for intravaginal administration, each containing 100,000 units Nystatin, USP. Inactive ingredients include cornstarch, ethylcellulose, anhydrous lactose, microcrystalline cellulose, polyethylene glycol, and stearic acid.
- OptiNate™ is a prescription prenatal/postnatal multivitamin/mineral capsule and tablet combination with essential fatty acids. Each tablet contains elemental iron (carbonyl iron), 90 mg; biotin, 30 mcg; pantothenic acid (calcium pantothenate, USP), 6 mg; calcium (calcium carbonate, USP), 200 mg; copper (cupric oxide), 2 mg; zinc (zinc oxide, USP), 15 mg; folate, 1 mg (*l*-methylfolate as Metafolin® 600 mcg) (folic acid, USP 400 mcg); vitamin D3 (cholecalciferol), 400 IU; vitamin E (dl-tocopheryl acetate), 10 IU; vitamin C (ascorbic acid, USP), 120 mg; vitamin B1 (thiamine mononitrate), 3 mg; vitamin B2 (riboflavin, USP), 3.4 mg; vitamin B6 (pyridoxine HCl), 20 mg; vitamin B12 (cyanocobalamin), 12 mcg; niacinamide, USP, 20 mg; magnesium (magnesium oxide, USP), 30 mg; docusate sodium, USP, 50 mg. Each L-Vcaps™ capsule contains docosahexaenoic acid (DHA) 250 mg. DHA is contained in the oil derived from microalgae. Other ingredients (OptiNate™ Omega-3L-Vcaps™): Hypromellose, iron oxide, beeswax, ascorbyl palmitate, mixed tocopherols, and other ingredients. Other ingredients (OptiNate™ tablets): Calcium phosphate dibasic, carnauba wax, crospovidone, dextrin, dl-tocopherol, gelatin, hypromellose, lactose, magnesium stearate, mono- and diglycerides, polacrilin, pregelatinized starch, propylene glycol, silicon dioxide, sodium benzoate, partially hydrogenated soybean oil, starch, stearic acid, sucrose, titanium dioxide, and other ingredients.
- ORAP® (pimozide) tablet contains either 1 or 2 mg of pimozide and the following inactive ingredients: calcium stearate, microcrystalline cellulose, lactose anhydrous, and cornstarch.
- OxyContin® (oxycodone hydrochloride controlled-release) tablets contain the following inactive ingredients: ammonio methacrylate copolymer, hypromellose, lactose, magnesium stearate, polyethylene glycol 400, povidone, sodium hydroxide, sorbic acid, stearyl alcohol, talc, titanium dioxide, and triacetin. The 10-mg tablets also contain hydroxypropyl cellulose. The 20-mg tablets also contain polysorbate 80 and red iron oxide. The 40-mg tablets also contain polysorbate 80 and yellow iron oxide. The 80-mg tablets also contain FD&C blue No. 2, hydroxypropyl cellulose, and yellow iron oxide. The 160-mg tablets also contain FD&C blue No. 2 and polysorbate 80.
- Pacerone® (Amiodarone HCl) tablets are available in four strengths, containing 100, 200, 300, and 400 mg amiodarone hydrochloride, for oral administration. The 100-mg tablets are white tablets with the following inactive ingredients: anhydrous lactose, colloidal silicone dioxide, cornstarch, magnesium stearate, and povidone. The 200-mg tablets are pink, scored tablets with the following inactive ingredients: lactose monohydrate, magnesium stearate, povidone, pregelatinized cornstarch, sodium starch glycolate, stearic acid, FD&C Red 40, and FD&C Yellow 6. The 300-mg tablets are peach, scored tablets with the following inactive ingredients: colloidal silicone dioxide, cornstarch, anhydrous lactose, magnesium stearate, povidone, and FD&C Yellow 6 Lake. The 400-mg tablets are light yellow, scored tablets with the following inactive ingredients: colloidal silicon dioxide, cornstarch, lactose monohydrate, magnesium stearate, povidone, and D&C Yellow 10 Aluminum Lake.
- Pacerone® (Amiodarone HCl) tablets are available in four strengths, containing 100, 200, 300, and 400 mg of amiodarone hydrochloride, for oral administration. The 100-mg tablets are white tablets with the following inactive ingredients: anhydrous lactose, colloidal silicone dioxide, cornstarch, magnesium stearate and povidone. The 200-mg tablets are pink, scored tablets with the following inactive ingredients: lactose monohydrate, magnesium stearate, povidone, pregelatinized cornstarch, sodium starch glycolate, stearic acid, FD&C Red 40, and FD&C Yellow 6. The 300-mg tablets are peach, scored tablets with the following inactive ingredients: colloidal silicone dioxide, cornstarch, anhydrous lactose, magnesium stearate, povidone, and FD&C Yellow 6 Lake. The 400-mg tablets are light yellow, scored tablets with the following inactive ingredients: colloidal silicon dioxide, cornstarch, lactose monohydrate, magnesium stearate, povidone, and D&C Yellow 10 Aluminum Lake.
- PARCOPA™ (carbidopa-levodopa orally disintegrating tablets) is a combination of carbidopa and levodopa. PARCOPA™ 25/100 contains 25 mg of carbidopa and 100 mg of levodopa. PARCOPA™ 10/100 contains 10 mg of carbidopa and 100 mg of levodopa. PARCOPA™ 25/250 contains 25 mg of carbidopa and 250 mg of levodopa. Inactive ingredients are aspartame, citric acid, crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, natural and artificial mint flavor, and sodium bicarbonate. PARCOPA™ 10/100 and 25/250 also contain FD&C blue #2 HT aluminum lake. PARCOPA™ 25/100 also contains yellow 10 iron oxide.
- PARNATE, tranylcypromine sulfate rose-red, film-coated tablet contains tranylcypromine sulfate equivalent to 10 mg of tranylcypromine. Inactive ingredients consist of cellulose, citric acid, croscarmellose sodium, D&C Red No. 7, FD&C Blue No. 2, FD&C Red No. 40, FD&C Yellow No. 6, gelatin, iron oxide, lactose, magnesium stearate, talc, titanium dioxide, and trace amounts of other inactive ingredients.
- PAXIL CR (paroxetine hydrochloride) enteric, film-coated, controlled-release tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 12.5 mg (yellow), 25 mg (pink), and 37.5 mg (blue). One layer of the tablet consists of a degradable barrier layer and the other contains the active material in a hydrophilic matrix. Inactive ingredients consist of hypromellose, polyvinylpyrrolidone, lactose monohydrate, magnesium stearate, colloidal

silicon dioxide, glyceryl behenate, methacrylic acid copolymer type C, sodium lauryl sulfate, polysorbate 80, talc, triethyl citrate, and one or more of the following colorants: Yellow ferric oxide, red ferric oxide, D&C Red No. 30, D&C Yellow No. 6, D&C Yellow No. 10, FD&C Blue No. 2. Each film-coated tablet contains paroxetine hydrochloride equivalent to paroxetine as follows: 10 mg, yellow (scored); 20 mg, pink (scored); 30 mg, blue; 40 mg, green. Inactive ingredients consist of dibasic calcium phosphate dihydrate, hypromellose, magnesium stearate, polyethylene glycols, polysorbate 80, sodium starch glycolate, titanium dioxide, and one or more of the following: D&C Red No. 30, D&C Yellow No. 10, FD&C Blue No. 2, and FD&C Yellow No. 6.

- PCE (erythromycin particles in tablets). The coating protects the antibiotic from the inactivating effects of gastric acidity and permits efficient absorption of the antibiotic in the small intestine. PCE is available in two strengths containing either 333 or 500 mg of erythromycin base. PCE 500-mg tablets contain no synthetic dyes or artificial colors. Inactive ingredients: PCE 333-mg tablets: Cellulosic polymers, citrate ester, colloidal silicon dioxide, D&C Red No. 30, hydrogenated vegetable oil wax, lactose, magnesium stearate, microcrystalline cellulose, povidone, propylene glycol, sodium starch glycolate, stearic acid, and vanillin. PCE 500-mg tablets: Cellulosic polymers, citrate ester, colloidal silicon dioxide, crospovidone, hydrogenated vegetable oil wax, iron oxide, microcrystalline cellulose, polyethylene glycol, povidone, propylene glycol, stearic acid, talc, titanium dioxide, and vanillin.
- PEGANONE (ethotoin tablets, USP) are available in a dosage strength of 250 mg. Inactive ingredients Acacia, lactose, sodium carboxymethylcellulose, stearic acid, and talc.
- Peri-Colace® (docusate sodium and standardized senna concentrate) is a combination stimulant laxative and stool softener. Peri-Colace® tablets contains the following active ingredient: 50 mg of docusate sodium and 8.6 mg of sennosides. Inactive ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, dicalcium phosphate, FD&C Blue No. 2, FD&C Red No. 40, hypromellose, magnesium stearate, microcrystalline cellulose, PEG 400, sodium benzoate, stearic acid, and titanium dioxide.
- Phenergan. Each tablet of Phenergan contains 12.5, 25, or 50 mg promethazine HCl. The inactive ingredients present are lactose, magnesium stearate, and methylcellulose. Each dosage strength also contains the following: 12.5 mg—FD&C Yellow 6 and saccharin sodium; 25 mg—saccharin sodium; 50 mg—FD&C Red 40. Each rectal suppository of Phenergan contains 12.5, 25, or 50 mg promethazine HCl with ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter.
- PLAVIX (clopidogrel bisulfate) for oral administration is provided as pink, round, biconvex, debossed film-coated tablets containing 97.875 mg of clopidogrel bisulfate, which is the molar equivalent of 75 mg of clopidogrel base. Each tablet contains hydrogenated castor oil, hydroxypropyl cellulose, mannitol, microcrystalline cellulose, and polyethylene glycol 6000 as inactive ingredients. The pink film coating contains ferric oxide, hypromellose 2910, lactose monohydrate, titanium dioxide, and triacetin. The tablets are polished with Carnauba wax.
- PLENDIL (felodipine) is available as tablets containing 2.5, 5, or 10 mg of felodipine for oral administration. In addition to the active ingredient felodipine, the tablets contain the following inactive ingredients: 2.5-mg tablets-–hydroxypropyl cellulose, lactose, FD&C Blue 2, sodium stearyl fumarate, titanium dioxide, yellow iron oxide, and other ingredients. 5- and 10-mg tablets—cellulose, red and yellow oxide, lactose, polyethylene glycol, sodium stearyl fumarate, titanium dioxide, and other ingredients.
- PLETAL (cilostazol) tablets for oral administration are available in 50 mg triangular and 100 mg round, white debossed tablets. Each tablet, in addition to the active ingredient, contains the following inactive ingredients: carboxymethylcellulose calcium, cornstarch, hydroxypropyl methylcellulose 2910, magnesium stearate, and microcrystalline cellulose.
- PRANDIN® (repaglinide) tablets contain 0.5, 1, or 2 mg of repaglinide. In addition each tablet contains the following inactive ingredients: calcium hydrogen phosphate (anhydrous), microcrystalline cellulose, maize starch, polacrilin potassium, povidone, glycerol (85%), magnesium stearate, meglumine, and poloxamer. The 1- and 2-mg tablets contain iron oxides (yellow and red, respectively) as coloring agents.
- PreCare® Chewables are prescription prenatal multivitamin/mineral nutritional supplement tablets. Each orange colored, flavored, oval, chewable tablet contains: Folic Acid, USP, 1 mg; vitamin B6 (pyridoxine HCl), 2 mg; vitamin C (as Ester-C®)*, 50 mg; vitamin D3 (cholecalciferol), 6 mcg; vitamin E (dl-tocopheryl acetate), 3.5 IU; calcium (calcium carbonate), 250 mg; copper (cupric oxide), 2 mg; iron (including MicroMask® ferrous fumarate), 40 mg; magnesium (magnesium oxide, USP), 50 mg; zinc (zinc oxide, USP), 15 mg.* Ester-C® is a patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate. Inactive ingredients: Citric acid, FD&C yellow #6 lake, flow agents, natural and artificial nonnutritive and nutritive sweetening agents, and natural and artificial flavors.
- PreCare® Prenatal is a prescription prenatal multivitamin/mineral nutritional supplement. Each dye-free, peach film-coated caplet contains Folic Acid, USP 1 mg; vitamin B1 (thiamine mononitrate, USP) 3 mg; vitamin B2 (riboflavin, USP) 3.4 mg; vitamin B3 (niacinamide) 20 mg; vitamin B6 (pyridoxine HCl, USP) 50 mg; vitamin B12 (cyanocobalamin) 12 mcg; vitamin C (as Ester-C) 50 mg; vitamin D3 (cholecalciferol) l6 mcg; vitamin E (dl-tocopheryl acetate) 3.5 IU; Calcium (as CalciPure™ calcium carbonate) 250 mg; Copper (cupric oxide) 2 mg; Iron (as MicroMask® ferrous fumarate) 40 mg; Magnesium (magnesium oxide, USP) 50 mg; Zinc (zinc oxide, USP) 15 mg. Inactive ingredients: Natural oils, natural wax, cellulose polymers, flow agents, and other ingredients. Dye free.
- PRECOSE® (acarbose tablets) is available as 25-, 50-, and 100-mg tablets for oral use. The inactive ingredients are starch, microcrystalline cellulose, magnesium stearate, and colloidal silicon dioxide.
- PREFEST regimen provides for a single oral tablet to be taken once daily. The estrogenic component of PREFEST is estradiol, USP. It is a white, crystalline solid. The progestational component of PREFEST is micronized norgestimate, a white powder. Each tablet for oral administration contains 1.0 mg estradiol alone or 1.0 mg estradiol and 0.09 mg of norgestimate, and the following inactive ingredients: croscarmellose sodium, microcrystalline cellulose, magnesium stearate, ferric oxide red, and lactose monohydrate.
- Prelief tablets : Each tablet contains 345 mg calcium glycerophosphate (65 mg of elemental calcium). The tablets also contain 0.25% magnesium stearate as a processing aid.

Two tablets are equivalent to 690 mg calcium glycerophosphate (130 mg of elemental calcium).

- Premarin® (conjugated estrogens tablets, USP) for oral administration contains a mixture of conjugated estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17α-dihydroequilenin, 17α-estradiol, and 17β-dihydroequilenin. Tablets for oral administration are available in 0.3 mg, 0.45 mg, 0.625 mg, 0.9 mg, and 1.25 mg strengths of conjugated estrogens. Premarin 0.3-, 0.45-, 0.625-, 0.9-, and 1.25-mg tablets also contain the following inactive ingredients: calcium phosphate tribasic, hydroxypropyl cellulose, microcrystalline cellulose, powdered cellulose, hypromellose, lactose monohydrate, magnesium stearate, polyethylene glycol, sucrose, and titanium dioxide. The 0.3-mg tablets also contain D&C Yellow No. 10 and FD&C Blue No. 2. The 0.45-mg tablets also contain FD&C Blue No. 2. The 0.625-mg tablets also contain FD&C Blue No. 2 and FD&C Red No. 40. The 0.9-mg tablets also contain: D&C Red No. 30 and D&C Red No. 7. The 1.25-mg tablets also contain black iron oxide, D&C Yellow No. 10, and FD&C Yellow No. 6.
- PremCal is a combination calcium and vitamin D nutritional supplement that offers three different strengths of vitamin D3 per tablet—500 IU, 750 IU, and 1000 IU with 500 mg of elemental calcium as the carbonate. PremCal is indicated in those requiring higher than the currently recommended doses of vitamin D such as vitamin D deficiency, premenstrual syndrome, osteoporosis, osteomalacia, or malabsorption. Ingredients: PremCal tablets are supplied in three different strengths of vitamin D3 (light, 500 IU; regular, 750 IU; extra strength,1000 IU) with a constant amount of calcium 500 mg as calcium carbonate and 15 mg of magnesium oxide. Each tablet also contains hypromellose, croscarmellose sodium, malto dextrin, povidone, stearic acid, magnesium stearate, triacetin, polyethylene glycol, and silicon dioxide. Free of sugar, soy, wheat, gluten, corn, shellfish, and artificial colors.
- PremesisRx®. Each blue tablet contains vitamin B6 (as pyridoxine HCl), 75 mg; vitamin B12 (cyanocobalamin), 12 mcg; folic acid, USP, 1 mg; calcium (as calcium carbonate), 200 mg. Inactive ingredients: Natural waxes, cellulose polymers, FD&C blue No. 1 aluminum lake, D&C yellow No. 10 aluminum lake, flow agents, and other ingredients.
- PREMPRO™ 0.3 mg/1.5 mg therapy consists of a single tablet containing 0.3 mg of the conjugated estrogens (CE) found in Premarin® tablets and 1.5 mg of medroxyprogesterone acetate (MPA) for oral administration. PREMPRO 0.45 mg/1.5 mg therapy consists of a single tablet containing 0.45 mg of the conjugated estrogens found in Premarin tablets and 1.5 mg of medroxyprogesterone acetate for oral administration. PREMPRO 0.625 mg/2.5 mg therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 2.5 mg of medroxyprogesterone acetate for oral administration. PREMPRO 0.625 mg/5 mg therapy consists of a single tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate for oral administration. PREMPHASE® therapy consists of two separate tablets, a maroon Premarin tablet containing 0.625 mg of conjugated estrogens that is taken orally on days 1 through 14 and a light-blue tablet containing 0.625 mg of the conjugated estrogens found in Premarin tablets and 5 mg of medroxyprogesterone acetate that is taken orally on days 15 through 28. Premarin (conjugated estrogens tablets, USP) for oral administration contains a mixture obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17 (α)-dihydroequilenin, 17 (α)-estradiol, and 17 (β)-dihydroequilenin.
- PREVACID® NapraPAC™ 375 is a combination package containing NAPROSYN 375-mg tablets and PREVACID 15-mg capsules. PREVACID® NapraPAC™ 500 is a combination package containing NAPROSYN 500-mg tablets and PREVACID 15-mg capsules. NAPROSYN tablets contain 250, 375, or 500 mg of naproxen (active ingredient) and croscarmellose sodium, iron oxides, povidone, and magnesium stearate (inactive ingredients). PREVACID capsules contain enteric-coated granules consisting of lansoprazole (15 mg) [active ingredient], hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide [inactive ingredients]. Components of the gelatin capsule include gelatin, titanium dioxide, D&C Red No. 28, FD&C Blue No. 1, FD&C Green No. 3, and FD&C Red No. 40 [inactive ingredients]. PREVACID I.V. The active ingredient in PREVACID I.V. (lansoprazole) for injection is a substituted benzimidazole, 2-[[[3-methyl-4-(2, 2, 2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole, a compound that inhibits gastric acid secretion. PREVACID I.V. for injection contains 30 mg of the active ingredient lansoprazole, 60-mg mannitol, 10-mg meglumine, and 3.45-mg sodium hydroxide and is supplied as a sterile, lyophilized powder for I.V. (intravenous) use. The solution of PREVACID I.V. for injection has a pH of approximately 11 following the first reconstitution with sterile water for injection, USP, and approximately 10.2, 10.0, or 9.5 after further dilution with either 0.9% sodium chloride injection, USP, lactated Ringer's injection, USP, or 5% dextrose injection, USP, respectively.
- PREVACID for delayed-release orally disintegrating tablets contain the active ingredient, lansoprazole in the form of enteric-coated microgranules. The tablets are available in 15-mg and 30-mg dosage strengths. Each tablet contains lansoprazole and the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, magnesium carbonate, hydroxypropyl cellulose, hypromellose, titanium dioxide, talc, mannitol, methacrylic acid, polyacrylate, polyethylene glycol, glyceryl monostearate, polysorbate 80, triethyl citrate, ferric oxide, citric acid, crospovidone, aspartame, artificial strawberry flavor, and magnesium stearate.
- ProAmatine® (midodrine hydrochloride) tablets. Dosage form: 2.5-, 5-, and 10-mg tablets for oral administration. Active ingredient: Midodrine hydrochloride, 2.5, 5, and 10 mg. Inactive ingredients: colloidal silicone dioxide NF, cornstarch NF, FD&C Blue No. 2 Lake (10-mg tablets), FD&C Yellow No. 6 Lake (5-mg tablet), magnesium stearate NF, microcrystalline cellulose NF, Talc USP.
- Proflavanol 90 tablet contains the following: vitamin C (Poly C, a blend of calcium, zinc, potassium, and magnesium ascorbates), 300 mg; grape seed extract, 90 mg; ascorbyl palmitate, 12 mg.

- ProSom (estazolam), tablets are scored and contain either 1 or 2 mg of estazolam. Inactive ingredients: colloidal silicon dioxide, lactose, povidone, stearic acid, and sodium starch glycolate. In addition, the 2-mg tablets contain FD&C Red No. 40.
- PROTONIX® (pantoprazole sodium) delayed-release tablets is supplied as a delayed-release tablet for oral administration, available in 2 strengths. Each delayed-release tablet contains 45.1 or 22.6 mg of pantoprazole sodium sesquihydrate (equivalent to 40 or 20 mg pantoprazole, respectively) with the following inactive ingredients: calcium stearate, crospovidone, hypromellose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate.
- PROVIGIL (modafinil) tablets contain 100 or 200 mg of modafinil and the following inactive ingredients: lactose, microcrystalline cellulose, pregelatinized starch, croscarmellose sodium, povidone, and magnesium stearate.
- Prozac® (fluoxetine hydrochloride) contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol), 20 mg (64.7 μmol), or 40 mg (129.3 μmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and other inactive ingredients. The 10- and 20-mg Pulvules also contain FD&C Blue No. 1, and the 40-mg Pulvule also contains FD&C Blue No. 1 and FD&C Yellow No. 6. Each tablet contains fluoxetine hydrochloride equivalent to 10 mg (32.3 μmol) of fluoxetine. The tablets also contain microcrystalline cellulose, magnesium stearate, crospovidone, hypromellose, titanium dioxide, polyethylene glycol, and yellow iron oxide. In addition to the above ingredients, the 10-mg tablet contains FD&C Blue No. 1 aluminum lake, and polysorbate 80.
- PURINETHOL (mercaptopurine) tablet contains 50 mg of mercaptopurine and the inactive ingredients corn and potato starch, lactose, magnesium stearate, and stearic acid.
- Ranexa™ (ranolazine) film-coated, extended-release tablets containing 500 mg of ranolazine. Inactive ingredients of the 500-mg tablet include carnauba wax, hypromellose, magnesium stearate, methacrylic acid copolymer (Type C), microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium hydroxide, titanium dioxide, and FD&C Yellow #6 Lake.
- Rapamune® (sirolimus) is available as a white, triangular-shaped tablet containing 1-mg sirolimus, and as a yellow to beige triangular-shaped tablet containing 2-mg sirolimus, ascorbyl palmitate, and polysorbate 80. Rapamune the inactive ingredients in Rapamune® tablets include sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20, 000, glyceryl monooleate, carnauba wax, and other ingredients. The 2-mg dosage strength also contains iron oxide yellow 10 and iron oxide brown 70.
- RELAFEN (nabumetone) oval-shaped, film-coated tablet contains 500 or 750 mg of nabumetone. Inactive ingredients consist of hypromellose, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium lauryl sulfate, sodium starch glycolate, and titanium dioxide. The 750-mg tablets also contain iron oxides.
- RELPAX® (eletriptan) tablets for oral administration contains 24.2 or 48.5 mg of eletriptan hydrobromide equivalent to 20 or 40 mg of eletriptan, respectively. Each tablet also contains the inactive ingredients microcrystalline cellulose NF, lactose NF, croscarmellose sodium NF, magnesium stearate NF, titanium dioxide USP, hypromellose, triacetin USP and FD&C Yellow No. 6 aluminum lake.
- REQUIP (ropinirole hydrochloride) film-coated TILTAB® tablet with beveled edges contains ropinirole hydrochloride equivalent to ropinirole, 0.25, 0.5, 1, 2, 3, 4, or 5 mg. Inactive ingredients consist of: croscarmellose sodium, hydrous lactose, magnesium stearate, microcrystalline cellulose, and one or more of the following: carmine, FD&C Blue No. 2 aluminum lake, FD&C Yellow No. 6 aluminum lake, hypromellose, iron oxides, polyethylene glycol, polysorbate 80, and titanium dioxide.
- RESCRIPTOR tablets contain delavirdine mesylate. Each RESCRIPTOR tablet, for oral administration, contains 100 or 200 mg of delavirdine mesylate (henceforth referred to as delavirdine). Inactive ingredients consist of lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, colloidal silicon dioxide, and carnauba wax. In addition, the 100-mg tablet contains Opadry White YS-1-7000-E and the 200-mg tablet contains hypromellose, Opadry White YS-1-18202-A and Pharmaceutical Ink Black.
- RETROVIR (zidovudine) film-coated tablet contains 300 mg of zidovudine and the inactive ingredients hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.
- REVATIO™ is the citrate salt of sildenafil. REVATIO (sildenafil citrate) is formulated as white, film-coated round tablets equivalent to 20 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose monohydrate, and triacetin.
- RILUTEK® (riluzole) is a member of the benzothiazole class. RILUTEK is available as a capsule-shaped, white, film-coated tablet for oral administration containing 50 mg of riluzole. Each tablet is engraved with "RPR 202" on one side. Inactive ingredients (core): anhydrous dibasic calcium phosphate, USP; microcrystalline cellulose, NF; anhydrous colloidal silica, NF; magnesium stearate, NF; croscarmellose sodium, NF. Inactive ingredients (film coating): hypromellose, USP; polyethylene glycol 6000; titanium dioxide, USP.
- Ritalin-SR®: Ritalin hydrochloride, methylphenidate hydrochloride USP, is available as tablets of 5, 10, and 20 mg for oral administration; Ritalin-SR is available as sustained-release tablets of 20 mg for oral administration. Inactive ingredients (Ritalin tablets): D&C Yellow No. 10 (5- and 20-mg tablets), FD&C Green No. 3 (10-mg tablets), lactose, magnesium stearate, polyethylene glycol, starch (5- and 10-mg tablets), sucrose, talc, and tragacanth (20-mg tablets). Inactive ingredients (Ritalin-SR tablets): Cellulose compounds, cetostearyl alcohol, lactose, magnesium stearate, mineral oil, povidone, titanium dioxide, and zein.
- ROZEREM™ (ramelteon) tablet includes the following inactive ingredients: lactose monohydrate, starch, hydroxypropyl cellulose, magnesium stearate, hypromellose, copovidone, titanium dioxide, yellow ferric oxide, polyethylene glycol 8000, and ink containing shellac and synthetic iron oxide black.
- Seasonale® (levonorgestrel/ethinyl estradiol tablets) is an extended-cycle oral contraceptive consisting of 84 pink

active tablets each containing 0.15 mg of levonorgestrel, a synthetic progestogen, and 0.03 mg of ethinyl estradiol as well 7 white inert tablets (without hormones). Each pink active tablet contains the following inactive ingredients: anhydrous lactose NF, FD&C Blue No. 1, FD&C Red No. 40, hydroxypropyl methylcellulose USP, microcrystalline cellulose NF, polyethylene glycol NF, magnesium stearate NF, polysorbate 80 NF, and titanium dioxide USP. Each white inert tablet contains the following inactive ingredients: anhydrous lactose NF, hydroxypropyl methylcellulose USP, microcrystalline cellulose NF, and magnesium stearate NF.

- Sedapap®Butalbital and acetaminophen is supplied in tablet form for oral administration. Each Sedapap® tablet contains Butalbital (50 mg) and acetaminophen (650 mg). In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, crospovidone, microcrystalline cellulose, povidone, pregelatinized starch, and stearic acid.
- SENOKOT tablets: Each tablet contains 8.6 mg of sennosides. Active ingredient: Standardized Senna Concentrate. Inactive ingredients: croscarmellose sodium, dicalcium phosphate, hypromellose, magnesium stearate, microcrystalline cellulose, and mineral oil. SENOKOT-S tablets: Each tablet contains 8.6 mg sennosides and 50 mg of docusate sodium. Active ingredients: Docusate Sodium and standardized senna concentrate. Inactive ingredients: carnauba wax, colloidal silicon dioxide, croscarmellose sodium, dicalcium phosphate, D&C Yellow #10, FD&C Yellow #6, hypromellose, magnesium stearate, microcrystalline cellulose, PEG 8000, sodium benzoate, stearic acid, and titanium dioxide.
- Sensipar™ (cinacalcet hydrochloride) tablets are formulated as light-green, film-coated, oval-shaped tablets for oral administration in strengths of 30, 60, and 90 mg of cinacalcet HCl as the free base equivalent (33, 66, and 99 mg as the hydrochloride salt, respectively). Inactive ingredients: Sensipar™ tablets are composed of the active ingredient, and the following inactive ingredients: pregelatinized starch, microcrystalline cellulose, povidone, crospovidone, colloidal silicon dioxide, and magnesium stearate. Tablets are coated with color (Opadry® II green) and clear film-coat (Opadry® clear), carnauba wax, and Opacode® black ink.
- SEROQUEL (quetiapine fumarate) is supplied for oral administration as 25 mg (round, peach), 50 mg (round, white), 100 mg (round, yellow), 200 mg (round, white), 300 mg (capsule-shaped, white), and 400 mg (capsule-shaped, yellow) tablets. Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol, and titanium dioxide. The 25-mg tablets contain red ferric oxide and yellow ferric oxide and the 100-mg tablets contain only yellow ferric oxide.
- SPECTRACEF® tablets contain cefditoren pivoxil. The tablets contain 200 mg of cefditoren as cefditoren pivoxil and the following inactive ingredients: croscarmellose sodium, D-mannitol, hydroxypropyl cellulose, hypromellose, magnesium stearate, sodium caseinate (a milk protein), and sodium tripolyphosphate. The tablet coating contains carnauba wax, hypromellose, polyethylene glycol, and titanium dioxide. Tablets are printed with ink containing D&C Red No. 27, FD&C Blue No. 1, propylene glycol, and shellac.
- Stalevo® (carbidopa, levodopa, and entacapone) is a combination of carbidopa, levodopa, and entacapone. Stalevo® (carbidopa, levodopa, and entacapone) is supplied as tablets in three strengths: Stalevo 50, containing 12.5 mg of carbidopa, 50 mg of levodopa, and 200 mg of entacapone; Stalevo 100, containing 25 mg of carbidopa, 100 mg of levodopa, and 200 mg of entacapone; Stalevo 150, containing 37.5 mg of carbidopa, 150 mg of levodopa, and 200 mg of entacapone. The inactive ingredients of the Stalevo tablet are cornstarch, croscarmellose sodium, glycerol 85%, hypromellose, magnesium stearate, mannitol, polysorbate 80, povidone, sucrose, red iron oxide, titanium dioxide, and yellow iron oxide.
- Starlix® (nateglinide) biconvex tablets contain 60 mg, or 120 mg, of nateglinide for oral administration. Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl methylcellulose, iron oxides (red or yellow), lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, talc, and titanium dioxide.
- Striant® is a white to off-white colored, monoconvex, tablet-like, mucoadhesive buccal system. Striant® adheres to the gum tissue above the incisors, with the flat surface facing the cheek mucosa. The active ingredient in Striant® is testosterone. Each buccal system contains 30 mg of testosterone. Other pharmacologically inactive ingredients in Striant® are anhydrous lactose NF, carbomer 934P, hypromellose USP, magnesium stearate NF, lactose monohydrate NF, polycarbophil USP, colloidal silicon dioxide NF, starch NF, and talc USP.
- SULAR® (nisoldipine) is an extended-release tablet dosage form of the dihydropyridine calcium channel blocker nisoldipine. SULAR tablets consist of an external coat and an internal core. Both coat and core contain nisoldipine, the coat as a slow-release formulation and the core as a fast-release formulation. SULAR tablets contain either 10, 20, 30 or 40 mg of nisoldipine for once-a-day oral administration. Inert ingredients in the formulation are: hydroxypropyl cellulose, lactose, cornstarch, crospovidone, microcrystalline cellulose, sodium lauryl sulfate, povidone, and magnesium stearate. The inert ingredients in the film coating are: hypromellose, polyethylene glycol, ferric oxide, and titanium dioxide.
- SYNTHROID® (levothyroxine sodium tablets, USP). Inactive ingredients: acacia, confectioner's sugar (contains cornstarch), lactose monohydrate, magnesium stearate, povidone, and talc. The following are the color additives by tablet strength: 25 FD&C Yellow No. 6 Aluminum Lake; 50 None; 75 FD&C Red No. 40 Aluminum Lake; FD&C Blue No. 2 Aluminum Lake; 88 FD&C Blue No. 1 Aluminum Lake; FD&C Yellow No. 6 Aluminum Lake; D&C Yellow No. 10 Aluminum Lake; 100 D&C Yellow No. 10 Aluminum Lake; FD&C Yellow No. 6 Aluminum Lake; 112 D&C Red No. 27 & 30 Aluminum Lake; 125 FD&C Yellow No. 6 Aluminum Lake; FD&C Red No. 40 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake; 137 FD&C Blue No. 1 Aluminum Lake; 150 FD&C Blue No. 2 Aluminum Lake; 175 FD&C Blue No. 1 Aluminum Lake, D&C Red No. 27 & 30 Aluminum Lake; 200 FD&C Red No. 40 Aluminum Lake; 300 D&C Yellow No. 10 Aluminum Lake; FD&C Yellow No. 6 Aluminum Lake; and FD&C Blue No. 1 Aluminum Lake.
- TABLOID scored tablet contains 40 mg of thioguanine and the inactive ingredients gum acacia, lactose, magnesium stearate, potato starch, and stearic acid.
- TAGAMET (cimetidine) film-coated tablet contains cimetidine as follows: 300 mg—round, debossed with the product name TAGAMET, SB and 300; 400 mg—oval Tiltab®

tablets, debossed with the product name TAGAMET, SB and 400. Inactive ingredients consist of cellulose, D&C Yellow No. 10, FD&C Blue No. 2, FD&C Red No. 40, FD&C Yellow No. 6, hypromellose, iron oxides, magnesium stearate, povidone, propylene glycol, sodium lauryl sulfate, sodium starch glycolate, starch, titanium dioxide, and trace amounts of other inactive ingredients.

- TAMBOCOR TM (flecainide acetate) is available in tablets of 50, 100 or 150 mg for oral administration. Flecainide acetate is a white crystalline substance with a pK_a of 9.3. It has an aqueous solubility of 48.4 mg/mL at 37°C. TAMBOCOR tablets also contain croscarmellose sodium, hydrogenated vegetable oil, magnesium stearate, microcrystalline cellulose, and starch.
- TARCEVA (erlotinib) is a Human Epidermal Growth Factor Receptor Type 1/Epidermal Growth Factor Receptor (HER1/EGFR) tyrosine kinase inhibitor. TARCEVA tablets are available in three dosage strengths containing erlotinib hydrochloride (27.3, 109.3, and 163.9 mg) equivalent to 25, 100, and 150 mg erlotinib and the following inactive ingredients: lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and titanium dioxide. The tablets also contain trace amounts of color additives, including FD&C Yellow #6 (25 mg only) for product identification.
- TARCEVA (erlotinib) tablets are available in three dosage strengths containing erlotinib hydrochloride (27.3, 109.3, and 163.9 mg) equivalent to 25, 100, and 150 mg erlotinib and the following inactive ingredients: lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, and titanium dioxide. The tablets also contain trace amounts of color additives, including FD&C Yellow #6 (25 mg only) for product identification.
- TARKA® (trandolapril/verapamil hydrochloride ER). The tablet strengths are trandolapril 2 mg/verapamil hydrochloride ER 180 mg, trandolapril 1 mg/verapamil hydrochloride ER 240 mg, trandolapril 2 mg/verapamil hydrochloride ER 240 mg, and trandolapril 4 mg/verapamil hydrochloride ER 240 mg. The tablets also contain the following ingredients: cornstarch, dioctyl sodium sulfosuccinate, ethanol, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, purified water, silicon dioxide, sodium alginate, sodium stearyl fumarate, synthetic iron oxides, talc, and titanium dioxide.
- TASMAR® is available as tablets containing 100 or 200 mg tolcapone. Inactive ingredients (core): lactose monohydrate, microcrystalline cellulose, dibasic calcium phosphate anhydrous, povidone K-30, sodium starch glycolate, talc, and magnesium stearate. Inactive ingredients (film coating): hydroxypropyl methylcellulose, titanium dioxide, talc, ethylcellulose, triacetin, and sodium lauryl sulfate, with the following dye systems: 100 mg of yellow and red iron oxide and 200 mg of red iron oxide.
- Tegretol, carbamazepine USP is available for oral administration as chewable tablets of 100 mg, tablets of 200 mg, XR tablets of 100, 200, and 400 mg, and as a suspension of 100 mg/5 mL (teaspoon). Inactive ingredients (tablets): Colloidal silicon dioxide, D&C Red No. 30 Aluminum Lake (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only). Inactive ingredients (suspension): Citric acid, FD&C Yellow No. 6, flavoring, polymer, potassium sorbate, propylene glycol, purified water, sorbitol, sucrose, and xanthan gum. Tegretol-XR tablets: cellulose compounds, dextrates, iron oxides, magnesium stearate, mannitol, polyethylene glycol, sodium lauryl sulfate, and titanium dioxide (200-mg tablets only).
- TENORMIN® (atenolol) is available as 25-, 50-, and 100-mg tablets for oral administration. Inactive ingredients: Magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.
- Thioridazine hydrochloride is available as tablets for oral administration containing 10, 25, 50, or 100 mg. Each tablet for oral administration contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium lauryl sulfate, titanium dioxide, and FD&C Yellow #6 Aluminum Lake.
- Thyrolar tablets (Liotrix tablets, USP) contain triiodothyronine (T3 liothyronine) sodium and tetraiodothyronine (T4 levothyroxine) sodium. The inactive ingredients are calcium phosphate, colloidal silicon dioxide, cornstarch, lactose, and magnesium stearate. The tablets also contain the following dyes: Thyrolar 1/4—FD&C Blue #1 and FD&C Red #40; Thyrolar 1/2—FD&C Red #40 and D&C Yellow #10; Thyrolar 1—FD&C Red #40; Thyrolar 2—FD&C Blue #1, FD&C Red #40, and D&C Yellow #10; Thyrolar 3—FD&C Red #40 and D&C Yellow #10. Thyrolar tablets (Liotrix tablets, USP) are available in five potencies coded as follows: 3.1 mcg/12.5 mcg, 6.25 mcg/25 mcg, 12.5 mcg/50 mcg, 25 mcg/100 mcg, and 37.5 mcg/150 mcg.
- Tinidazole is a synthetic antiprotozoal agent. Tindamax pink film-coated oral tablets contain 500 or 250 mg of tinidazole. Inactive ingredients include croscarmellose sodium, FD&C Red 40 lake, FD&C Yellow 6 lake, hypromellose, magnesium stearate, microcrystalline cellulose, polydextrose, polyethylene glycol, pregelatinized cornstarch, titanium dioxide, and triacetin.
- TRACLEER® (bosentan) is available as 62.5 and 125 mg film-coated tablets for oral administration, and contains the following excipients: cornstarch, pregelatinized starch, sodium starch glycolate, povidone, glyceryl behenate, magnesium stearate, hydroxypropyl methylcellulose, triacetin, talc, titanium dioxide, iron oxide yellow, iron oxide red, and ethylcellulose. Each TRACLEER® 62.5-mg tablet contains 64.541 mg of bosentan, equivalent to 62.5 mg of anhydrous bosentan. Each TRACLEER® 125-mg tablet contains 129.082 mg of bosentan, equivalent to 125 mg of anhydrous bosentan.
- TRANXENE T-TAB tablets contain either 3.75, 7.5, or 15 mg of clorazepate dipotassium for oral administration. Tranxene-SD and Tranxene-SD Half Strength tablets contain 22.5 and 11.25 mg of clorazepate dipotassium, respectively. Tranxene-SD and Tranxene-SD Half Strength tablets gradually release clorazepate and are designed for once-a-day administration in patients already stabilized on TRANXENE T-TAB tablets. Inactive ingredients for TRANXENE T-TAB® tablets: Colloidal silicon dioxide, FD&C Blue No. 2 (3.75 mg only), FD&C Yellow No. 6 (7.5 mg only), FD&C Red No. 3 (15 mg only), magnesium oxide, magnesium stearate, microcrystalline cellulose, potassium carbonate, potassium chloride, and talc. Inactive ingredients for TRANXENE-SD and TRANXENE-SD HALF STRENGTH tablets: Castor oil

wax, FD&C Blue No. 2 (SD Half Strength, 11.25 mg only), iron oxide (SD, 22.5 mg only), lactose, magnesium oxide, magnesium stearate, potassium carbonate, potassium chloride, and talc.

- TRECATOR TABLET. Ethionamide tablets contain 250 mg of ethionamide. The inactive ingredients present are croscarmellose sodium, FD&C Yellow #6, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, povidone, silicon dioxide, talc, and titanium dioxide.
- Triamterene capsule for oral use, with opaque red cap and body, contains triamterene, 50 or 100 mg, and is imprinted with the product name DYRENIUM, strength (50 or 100) and WPC 002 (for the 50 mg strength) and WPC 003 (for the 100 mg strength). Inactive ingredients consist of D&C Red No. 33, FD&C Yellow No. 6, gelatin NF, lactose NF, magnesium stearate NF, sodium lauryl sulfate NF, titanium dioxide USP, and silicon dioxide NF.
- TRICOR (fenofibrate tablets) is available as tablets for oral administration. Each tablet contains 48 or 145 mg of fenofibrate. Inactive ingredients: Each tablet contains hypromellose 2910 (3cps), docusate sodium, sucrose, sodium lauryl sulfate, lactose monohydrate, silicified microcrystalline cellulose, crospovidone, and magnesium stearate. In addition, individual tablets contain the following ingredients: 48-mg tablets—polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, xanthan gum, D&C Yellow #10 aluminum lake, FD&C Yellow #6/sunset yellow FCF aluminum lake, and FD&C Blue #2/indigo carmine aluminum lake. 145-mg tablets—polyvinyl alcohol, titanium dioxide, talc, soybean lecithin, and xanthan gum.
- TRIGLIDE™ (fenofibrate) tablets contains 50 or 160 mg of fenofibrate. Inactive ingredients: Each tablet also contains crospovidone, lactose monohydrate, mannitol, maltodextrin, carboxymethylcellulose sodium, egg lecithin, croscarmellose sodium, sodium lauryl sulfate, colloidal silicon dioxide, magnesium stearate, and monobasic sodium phosphate.
- Trileptal® (oxcarbazepine) is available as 150, 300, and 600 mg film-coated tablets for oral administration. Trileptal film-coated tablets contain the following inactive ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, talc, titanium dioxide, and yellow iron oxide.
- Triphasil cycle of 28 tablets consists of three different drug phases as follows: Phase 1 composed of 6 brown tablets, each containing 0.050 mg of levonorgestrel (*d*(-)-13 β-ethyl-17-α-ethinyl-17-β-hydroxygon-4-en-3-one), a totally synthetic progestogen, and 0.030 mg of ethinyl estradiol (19-nor-17(α)-pregna-1,3,5(10)-trien-20-yne-3,17-diol); phase 2 composed of 5 white tablets, each containing 0.075 mg levonorgestrel and 0.040 mg ethinyl estradiol; and phase 3 composed of 10 light-yellow tablets, each containing 0.125 mg levonorgestrel and 0.030 mg ethinyl estradiol; then followed by 7 light-green inert tablets. The inactive ingredients present are cellulose, FD&C Blue 1, iron oxides, lactose, magnesium stearate, polacrilin potassium, polyethylene glycol, titanium dioxide, and hydroxypropyl methylcellulose.
- ULTRAM® ER (tramadol hydrochloride) tablets contain 100, 200 or 300 mg of tramadol HCl in an extended-release formulation. The tablets are white in color and contain the inactive ingredients ethylcellulose, dibutyl sebacate, polyvinyl pyrrolidone, sodium stearyl fumarate, colloidal silicon dioxide, and polyvinyl alcohol.
- ULTRAM® ODT (tramadol hydrochloride) orally disintegrating tablets is supplied as orally disintegrating tablets containing 50 mg of tramadol hydrochloride for oral administration. The tablets are white in color and contain the inactive ingredients aspartame, copovidone, crospovidone, ethylcellulose, magnesium stearate, mannitol, mint flavor, and silicon dioxide.
- Uniphyl® (theophylline, anhydrous) tablets in a controlled-release system allows a 24-hour dosing interval. Each controlled-release tablet for oral administration, contains 400 or 600 mg of anhydrous theophylline. Inactive ingredients: cetostearyl alcohol, hydroxyethyl cellulose, magnesium stearate, povidone, and talc.
- Uniretic® (moexipril hydrochloride/hydrochlorothiazide) is a combination of an angiotensin-converting enzyme (ACE) inhibitor, moexipril hydrochloride, and a diuretic, hydrochlorothiazide. Uniretic® is available for oral administration in three tablet strengths. The inactive ingredients in all strengths are lactose, magnesium oxide, crospovidone, magnesium stearate, and gelatin. The film coating in all strengths contains hydroxypropyl cellulose, hypromellose, polyethylene glycol 6000, magnesium stearate, and titanium dioxide. In addition, the film coating for Uniretic® 7.5 mg/12.5 mg and Uniretic® 15 mg/25 mg contains ferric oxide.
- Univasc® (moexipril hydrochloride) is supplied as scored, coated tablets containing 7.5 and 15 mg of moexipril hydrochloride for oral administration. In addition to the active ingredient, moexipril hydrochloride, the tablet core contains the following inactive ingredients: lactose, magnesium oxide, crospovidone, magnesium stearate, and gelatin. The film coating contains hydroxypropyl cellulose, hypromellose, polyethylene glycol 6000, magnesium stearate, titanium dioxide, and ferric oxide.
- Urocit®-K is a citrate salt of potassium. Urocit®-K is supplied as wax matrix tablets containing 5 mEq (540 mg) and 10 mEq (1080 mg) of potassium citrate each, for oral administration.
- UROQID-Acid® No.2 tablet contains methenamine mandelate (500 mg) and sodium acid phosphate, monohydrate (500 mg). Inactive ingredients Calcium phosphate, hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate, starch, sugar, syloid, and talc.
- VAGIFEM® (estradiol vaginal tablets) are small, white, film-coated tablets containing 25.8 μg of estradiol hemihydrate equivalent to 25 μg of estradiol. Each tablet contains the following inactive ingredients: hypromellose, lactose monohydrate, maize starch, and magnesium stearate. The film coating contains hypromellose and polyethylene glycol. Each white tablet is 6 mm in diameter and is placed in a disposable applicator. Each tablet-filled applicator is packaged separately in a blister pack. 17(β)-estradiol hemihydrate is a white, almost white or colorless crystalline solid, chemically described as estra-1,3,5(10)-triene-3,17,diol.
- VESIcare® (solifenacin succinate) tablet contains 5 or 10 mg of solifenacin succinate and is formulated for oral administration. In addition to the active ingredient solifenacin succinate, each VESIcare tablet also contains the following inert ingredients: lactose monohydrate, cornstarch, hypromellose 2910, magnesium stearate, talc, polyethylene glycol 8000, and titanium dioxide with yellow ferric oxide (5 mg VESIcare tablet) or red ferric oxide (10 mg VESIcare tablet).
- VFEND tablets contain 50 or 200 mg of voriconazole. The inactive ingredients include lactose monohydrate,

pregelatinized starch, croscarmellose sodium, povidone, magnesium stearate and a coating containing hypromellose, titanium dioxide, lactose monohydrate, and triacetin.

- VIAGRA®, an oral tablet, is the citrate salt of sildenafil. VIAGRA (sildenafil citrate) is formulated as blue, film-coated rounded-diamond-shaped tablets equivalent to 25, 50, and 100 mg of sildenafil for oral administration. In addition to the active ingredient, sildenafil citrate, each tablet contains the following inactive ingredients: microcrystalline cellulose, anhydrous dibasic calcium phosphate, croscarmellose sodium, magnesium stearate, hypromellose, titanium dioxide, lactose, triacetin, and FD & C Blue #2 aluminum lake.
- VICODIN HP (hydrocodone bitartrate and acetaminophen) is supplied in tablet form for oral administration. Each VICODIN HP tablet contains hydrocodone bitartrate (10 mg) and acetaminophen (660 mg). In addition each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone, pregelatinized starch, and stearic acid. Meets USP Dissolution Test 2. Each VICODIN ES tablet contains hydrocodone bitartrate (7.5 mg) and acetaminophen (750 mg). In addition each tablet contains the following inactive ingredients: Colloidal silicon dioxide, pregelatinized starch, magnesium stearate, croscarmellose sodium povidone, and stearic acid. Meets USP Dissolution Test 2. Each VICODIN tablet contains hydrocodone bitartrate (5 mg) and acetaminophen (500 mg). In addition each tablet contains the following inactive ingredients: colloidal silicon dioxide, starch, croscarmellose sodium, dibasic calcium phosphate, magnesium stearate, microcrystalline cellulose, povidone, and stearic acid. Meets USP Dissolution Test 2.
- VICOPROFEN® tablet contains hydrocodone bitartrate, USP (7.5 mg), and ibuprofen, USP (200 mg). Inactive ingredients in VICOPROFEN tablets include: colloidal silicon dioxide, cornstarch, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide.
- VIRACEPT® (nelfinavir mesylate) tablets are available for oral administration as a light blue, capsule-shaped tablet with a clear film coating in 250-mg strength (as nelfinavir free base) and as a white oval tablet with a clear film coating in 625-mg strength (as nelfinavir free base). Each tablet contains the following common inactive ingredients: calcium silicate, crospovidone, magnesium stearate, hypromellose, and triacetin. In addition, the 250-mg tablet contains FD&C blue #2 powder and the 625-mg tablet contains colloidal silicon dioxide.
- Voltaren® (diclofenac sodium enteric-coated tablets). Voltaren is available as Delayed-Release (enteric-coated) tablets of 25 mg (yellow), 50 mg (light brown), and 75 mg (light pink) for oral administration. The inactive ingredients in Voltaren include hydroxypropyl methylcellulose, iron oxide, lactose, magnesium stearate, methacrylic acid copolymer, microcrystalline cellulose, polyethylene glycol, povidone, propylene glycol, sodium hydroxide, sodium starch glycolate, talc, titanium dioxide, D&C Yellow No. 10 Aluminum Lake (25-mg tablet only), and FD&C Blue No. 1 Aluminum Lake (50-mg tablet only).
- Voltaren® -XR, (diclofenac sodium extended-release tablets are available as extended-release tablets of 100 mg (light pink) for oral administration. The inactive ingredients in Voltaren-XR include cetyl alcohol, hydroxypropyl methylcellulose, iron oxide, magnesium stearate, polyethylene glycol, polysorbate, povidone, silicon dioxide, sucrose, talc, and titanium dioxide.
- VYTORIN contains ezetimibe. VYTORIN is available for oral use as tablets containing 10 mg of ezetimibe, 10 mg of simvastatin (VYTORIN 10/10), 20 mg of simvastatin (VYTORIN 10/20), 40 mg of simvastatin (VYTORIN 10/40), or 80 mg of simvastatin (VYTORIN 10/80). Each tablet contains the following inactive ingredients: butylated hydroxyanisole NF, citric acid monohydrate USP, croscarmellose sodium NF, hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, and propyl gallate NF.
- VYTORIN contains ezetimibe. VYTORIN is available for oral use as tablets containing 10 mg of ezetimibe, 10 mg of simvastatin (VYTORIN 10/10), 20 mg of simvastatin (VYTORIN 10/20), 40 mg of simvastatin (VYTORIN 10/40), or 80 mg of simvastatin (VYTORIN 10/80). Each tablet contains the following inactive ingredients: butylated hydroxyanisole NF, citric acid monohydrate USP, croscarmellose sodium NF, hydroxypropyl methylcellulose USP, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, and propyl gallate NF.
- YASMIN provides an oral contraceptive regimen consisting of 21 active film-coated tablets each containing 3.0 mg of drospirenone and 0.030 mg of ethinyl estradiol and 7 inert film-coated tablets. The inactive ingredients are lactose monohydrate NF, cornstarch NF, modified starch NF, povidone 25000 USP, magnesium stearate NF, hydroxypropyl methylcellulose USP, macrogol 6000 NF, talc USP, titanium dioxide USP, ferric oxide pigment, and yellow NF. The inert film-coated tablets contain lactose monohydrate NF, cornstarch NF, povidone 25000 USP, magnesium stearate NF, hydroxypropyl methylcellulose USP, talc USP, and titanium dioxide USP.
- Zelnorm® (tegaserod maleate) tablets contain tegaserod as the hydrogen maleate salt. Each 1.385 mg of tegaserod as the maleate is equivalent to 1 mg of tegaserod. Zelnorm is available for oral use in the following tablet formulations: 2- and 6-mg tablets (blister packs) containing 2 and 6 mg of tegaserod, respectively, and the following inactive ingredients: crospovidone, glyceryl monostearate, hypromellose, lactose monohydrate, poloxamer 188, and polyethylene glycol 4000; 6-mg tablets (bottles) containing 6 mg of tegaserod and the following inactive ingredients: crospovidone, glyceryl behenate, hypromellose, lactose monohydrate, and colloidal silicon dioxide.
- ZESTORETIC® (lisinopril and hydrochlorothiazide) combines an angiotensin converting enzyme inhibitor, lisinopril, and a diuretic, hydrochlorothiazide. ZESTORETIC is available for oral use in three tablet combinations of lisinopril with hydrochlorothiazide: ZESTORETIC 10-12.5 containing 10 mg of lisinopril and 12.5 mg of hydrochlorothiazide; ZESTORETIC 20-12.5 containing 20 mg of lisinopril and 12.5 mg of hydrochlorothiazide; and, ZESTORETIC 20-25 containing 20 mg of lisinopril and 25 mg of hydrochlorothiazide. Inactive ingredients: 10-12.5 tablets—calcium phosphate, magnesium stearate, mannitol, red ferric oxide, starch, and yellow ferric oxide. 20-12.5 tablets—calcium phosphate, magnesium stearate, mannitol, and starch. 20-25 tablets—calcium phosphate, magnesium stearate, mannitol, red ferric oxide, starch, and yellow ferric oxide.
- ZESTRIL (lisinopril) is supplied as 2.5-, 5-, 10-, 20-, 30-, and 40-mg tablets for oral administration. Inactive ingredients: 2.5-mg tablets-–calcium phosphate, magnesium stearate, mannitol, and starch. 5-, 10-, 20-, and 30-mg

tablets—calcium phosphate, magnesium stearate, mannitol, red ferric oxide, and starch. 40-mg tablets—calcium phosphate, magnesium stearate, mannitol, starch, and yellow ferric oxide.

- ZETIA (ezetimibe) is available as a tablet for oral administration containing 10 mg of ezetimibe and the following inactive ingredients: croscarmellose sodium NF, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, povidone USP, and sodium lauryl sulfate NF.
- ZETIA (ezetimibe) is available as a tablet for oral administration containing 10 mg of ezetimibe and the following inactive ingredients: croscarmellose sodium NF, lactose monohydrate NF, magnesium stearate NF, microcrystalline cellulose NF, povidone USP, and sodium lauryl sulfate NF.
- Zileuton tablets for oral administration are supplied in one dosage strength containing 600 mg of zileuton. Inactive ingredients: crospovidone, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, pregelatinized starch, propylene glycol, sodium starch glycolate, talc, and titanium dioxide.
- ZITHROMAX® tablets contain azithromycin dihydrate equivalent to 600 mg azithromycin. The tablets are supplied as white, modified oval-shaped, film-coated tablets. They also contain the following inactive ingredients: dibasic calcium phosphate anhydrous, pregelatinized starch, sodium croscarmellose, magnesium stearate, sodium lauryl sulfate and an aqueous film coat consisting of hypromellose, titanium dioxide, lactose, and triacetin.
- ZOLOFT® (sertraline hydrochloride) is supplied for oral administration as scored tablets containing sertraline hydrochloride equivalent to 25, 50, and 100 mg of sertraline and the following inactive ingredients: dibasic calcium phosphate dihydrate, D & C Yellow #10 aluminum lake (in 25-mg tablet), FD & C Blue #1 aluminum lake (in 25-mg tablet), FD & C Red #40 aluminum lake (in 25-mg tablet), FD & C Blue #2 aluminum lake (in 50-mg tablet), hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, synthetic yellow iron oxide (in 100-mg tablet), and titanium dioxide.
- ZOMIG® (zolmitriptan) tablets and ZOMIG-ZMT® (zolmitriptan) orally disintegrating tablets contain zolmitriptan, available as 2.5 mg (yellow) and 5 mg (pink) film-coated tablets for oral administration. The film-coated tablets contain anhydrous lactose NF, microcrystalline cellulose NF, sodium starch glycolate NF, magnesium stearate NF, hydroxypropyl methylcellulose USP, titanium dioxide USP, polyethylene glycol 400 NF, yellow iron oxide NF (2.5-mg tablet), red iron oxide NF (5-mg tablet), and polyethylene glycol 8000 NF. ZOMIG-ZMT® orally disintegrating tablets are available as 2.5 and 5.0 mg white uncoated tablets for oral administration. The orally disintegrating tablets contain mannitol USP, microcrystalline cellulose NF, crospovidone NF, aspartame NF, sodium bicarbonate USP, citric acid anhydrous USP, colloidal silicon dioxide NF, magnesium stearate NF, and orange flavor SN 027512.
- ZYPREXA (olanzapine) tablet contains olanzapine equivalent to 2.5 mg (8 μmol), 5 mg (16 μmol), 7.5 mg (24 μmol), 10 mg (32 μmol), 15 mg (48 μmol), or 20 mg (64 μmol). Inactive ingredients are carnauba wax, crospovidone, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, microcrystalline cellulose, and other inactive ingredients. The color coating contains titanium dioxide (all strengths), FD&C Blue No. 2 Aluminum Lake (15 mg), or synthetic red iron oxide (20 mg). The 2.5, 5.0, 7.5, and 10-mg tablets are imprinted with edible ink which contains FD&C Blue No. 2 Aluminum Lake.
- ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) contains olanzapine equivalent to 5 mg (16 μmol), 10 mg (32 μmol), 15 mg (48 μmol), or 20 mg (64 μmol). It begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid. ZYPREXA ZYDIS (olanzapine orally disintegrating tablets) also contains the following inactive ingredients: gelatin, mannitol, aspartame, sodium methyl paraben, and sodium propyl paraben.
- ZYRTEC® (tablets and syrup) is cetirizine hydrochloride. ZYRTEC tablets are formulated as white, film-coated, rounded-off rectangular shaped tablets for oral administration and are available in 5- and 10-mg strengths. Inactive ingredients are lactose, magnesium stearate, povidone, titanium dioxide, hypromellose, polyethylene glycol, and cornstarch. ZYRTEC chewable tablets are formulated as purple round tablets for oral administration and are available in 5- and 10-mg strengths. Inactive ingredients of the chewable tablets are acesulfame potassium, artificial grape flavor, betadex NF, blue dye, colloidal silicon dioxide, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, natural flavor, and red dye (carmine).
- ZYRTEC-D 12 HOUR™ (cetirizine hydrochloride (5 mg) and pseudoephedrine hydrochloride (120 mg)) extended-release tablets for oral administration contain 5 mg of cetirizine hydrochloride for immediate release and 120 mg of pseudoephedrine hydrochloride for extended release in a bilayer tablet. Tablets also contain as inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

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Pharmaceutical Science

about the book...

The largest category of pharmaceutical formulations, comprising almost two-thirds of all dosage forms, compressed solids present some of the greatest challenges to formulation scientists. ***Compressed Solid Products*** tackles these challenges head on.

Highlights from ***Compressed Solid Products, Volume One*** include:

- formulations for more than 200 of the most widely used drugs for all types of release profiles, offering formulators a rare opportunity to start with an optimal composition
- the essentials of what you need to be aware of when establishing a manufacturing process based on the formulations presented
- identification and inclusion of the most popular prescription products, a critical list for the selection of products

about the author...

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to the memory of Takeru Higuchi

Preface to the Series—Second Edition

The science and the art of pharmaceutical formulation keeps evolving as new materials, methods, and machines become readily available to produce more reliable, stable, and release-controlled formulations. At the same time, globalization of sourcing of raw and finished pharmaceuticals brings challenges to regulatory authorities and results in more frequent revisions to the current good manufacturing practices, regulatory approval dossier requirements, and the growing need for cost optimization. Since the publication of the first edition of this book, a lot has changed in all of these areas of importance to pharmaceutical manufacturers. The second edition builds on the dynamic nature of the science and art of formulations and provides an evermore useful handbook that should be highly welcomed by the industry, the regulatory authorities, as well as the teaching institutions.

The first edition of this book was a great success as it brought under one umbrella the myriad of choices available to formulators. The readers were very responsive and communicated with me frequently pointing out to the weaknesses as well as the strengths of the book. The second edition totally revised attempts to achieve these by making major changes to the text, some of which include:

1. Complete, revised errors corrected and subject matter reorganized for easy reference. Whereas this series has six volumes differentiated on the basis of the type of dosage form and a separate inclusion of the U.S. OTC products, ideally the entire collection is needed to benefit from the myriad of topics relating to formulations, regulatory compliance, and dossier preparation.
2. Total number of pages is increased from 1684 to 2726.
3. Total number of formulations is expanded by about 30% with many newly approved formulations.
4. Novel formulations are now provided for a variety of drugs; these data are collected from the massive intellectual property data and suggest toward the future trend of formulations. While some of these formulations may not have been approved in the United States or Europe, these do provide additional choices, particularly for the NDA preparation. As always, it is the responsibility of the manufacturer to assure that the intellectual property rights are not violated.
5. A significant change in this edition is the inclusion of commercial products; while most of this information is culled out from the open source such as the FOIA (http://www.fda.gov/foi/default.htm), I have made attempts to reconstruct the critical portions of it based on what I call the generally acceptable standards. The drug companies are advised to assure that any intellectual property rights are not violated and this applies to all information contained in this book. The freedom of information act (FOIA) is an extremely useful conduit for reliable information and manufacturers are strongly urged to make use of this information. Whereas this information is provided free of charge, the process of obtaining the information may be cumbersome, in which case, commercial sources of these databases can prove useful, particularly for the non-U.S. companies.
6. Also included are the new Good Manufacturing Guidelines (2007) with amendments (2008) for the United States and similar updates for European Union and WHO; it is strongly urged that the companies discontinue using all old documents as there are significant changes in the revised form, and many of them are likely to reduce the cost of GMP compliance.
7. Details on design of clean rooms is a new entry that will be of great use to sterile product manufacturers; whereas the design and flow of personnel and material flow is of critical nature, regulatory agencies view these differently and the manufacturer is advised always to comply with most stringent requirements.
8. Addition of a self-auditing template in each volume of the series. While the cGMP compliance is a complex issue and the requirements diversified across the globe, the basic compliance remains universal. I have chosen the European Union guidelines (as these are more in tune with the ICH) to prepare a self-audit module that I recommend that every manufacturer adopt as a routine to assure GMP compliance. In most instances reading the template by those responsible for compliance with keep them sensitive to the needs of GMP.
9. OTC products cross-referenced in other volumes where appropriate. This was necessary since the regulatory authorities worldwide define this class of drug differently. It is important to iterate that regardless of the prescription or the OTC status of a product, the requirements for compliance with the cGMP apply equally.
10. OTC monograph status is a new section added to the OTC volume and this should allow manufacturers to chose appropriate formulations that may not require a filing with the regulatory agencies; it is important to iterate that an approved OTC monograph includes details of formulation including the types and quantities of active drug and excipients, labeling, and presentation. To qualify the exemption, the manufacturer must comply with the monograph in its entirety. However, subtle modifications that are merely cosmetic in nature and where there is an evidence that the modification will not affect the safety and efficacy of the products can be made but require prior approval of the regulatory agencies and generally these approvals are granted.
11. Expanded discussion on critical factors in the manufacturing of formulations provided; from basic shortcuts to smart modifications now extend to all dosage forms. Pharmaceutical compounding is one of the oldest professions and whereas the art of formulations has been

relegated to more objective parameters, the art nevertheless remains. An experienced formulator, like an artist, would know what goes with what and why; he avoids the pitfalls and stays with conservative choices. These sections of the book present advice that is time tested, although it may appear random at times; this is intended for experienced formulators.

12. Expanded details on critical steps in the manufacturing processes provided but to keep the size of the book manageable, and these are included for prototype formulations. The reader is advised to browse through similar formulations to gain more insight. Where multiple formulations are provided for the same drug, it intended to show the variety of possibilities in formulating a drug and whereas it pertains to a single drug, the basic formulation practices can be extended to many drugs of same class or even of diversified classes. Readers have often requested that more details be provided in the Manufacturing Direction sections. Whereas sufficient details are provided, this is restricted to prototype formulations to keep the size of the book manageable and to reduce redundancy.
13. Addition of a listing of approved excipients and the level allowed by regulatory authorities. This new section allows formulators a clear choice on which excipients to choose; the excipients are reported in each volume pertaining to the formulation type covered. The listing is drawn from the FDA-approved entities. For the developers of an ANDA, it is critical that the level of excipients be kept within the range generally approved to avoid large expense in justifying any unapproved level. The only category for which the listing is not provided separately is the OTC volume since it contains many dosage forms and the reader is referred to dosage form–specific title of the series. The choice of excipients forms keeps increasing with many new choices that can provide many special release characteristics to the dosage forms. Choosing correct excipients is thus a tedious exercise and requires sophisticated multivariate statistical analysis. Whereas the formulator may choose any number of novel or classical components, it is important to know the levels of excipients that are generally allowed in various formulations to reduce the cost of redundant exercises; I have therefore included, as an appendix to each volume, a list of all excipients that are currently approved by the U.S. FDA along their appropriate levels. I suggest that a formulator consult this table before deciding on which level of excipient to use; it does not mean that the excipient cannot be used outside this range but it obviates the need for a validation and lengthy justification studies in the submission of NDAs.
14. Expanded section on bioequivalence submission was required to highlight the recent changes in these requirements. New entries include a comprehensive listing of bioequivalence protocols in abbreviated form as approved by the U.S. FDA; these descriptions are provided in each volume where pertinent. To receive approval for an ANDA, an applicant must generally demonstrate, among other things, equivalence of the active ingredient, dosage form, strength, route of administration and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. Bioequivalent drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 U.S.C. 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320. The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-specific BE studies, the U.S. FDA will be issuing product-specific BE recommendations (www.fda.gov/cder/ogd/index.htm). To make this vital information available, an appendix to each volume includes a summary of all currently approved products by the U.S. FDA where a recommendation on conducting bioequivalence studies is made available by the U.S. FDA. When filing an NDA or an ANDA, the filer is faced with the choice of defending the methods used to justify the bioavailability or bioequivalence data. The U.S. FDA now allows application for waiver of bioequivalence requirement; a new chapter on this topic has been added along with details of the dissolution tests, where applicable, approved for various dosage forms.
15. Dissolution testing requirements are included for all dosage forms where this testing is required by the FDA. Surrogate testing to prove efficacy and compliance is getting more acceptance at regulatory agencies; in my experience, a well-designed dissolution test is the best measure of continuous compliance. Coupled with chapters on waivers of bioequivalence testing, this information on dissolution testing should be great value to all manufacturers; it is recommended that manufacturers develop their own in-house specifications, more stringent than those allowed in these listings and the USP.
16. Best-selling products (top 200 prescription products) are identified with an asterisk and a brand name where applicable; in all instances, composition of these products is provided and formulation of generic equivalents. Despite the vast expansion of pharmaceutical sales and shifting of categories of blockbuster drugs, basic drugs affecting gastrointestinal tract, vascular system, and brain remain most widely prescribed.
17. Updated list of approved coloring agents in the United States, Canada, European Union, and Japan is included to allow manufactures to design products for worldwide distribution.
18. Tablet-coating formulations that meet worldwide requirements of color selection are included in the Volume 1 (compressed solids) and Volume 5 (OTC) because these represent the products often coated.
19. Guidelines on preparing regulatory filings are now dispersed throughout the series depending on where these guidelines are more crucial. However, the reader would, as before, need access to all volumes to benefit from the advice and guidelines provided.

As always, comments and criticism from the readers are welcomed and these can be sent to me at Niazi@pharmsci.com or Niazi@niazi.com. I would try to respond to any inquiries requiring clarification of the information enclosed in these volumes.

I would like to express deep gratitude to Sherri R. Niziolek and Michelle Schmitt-DeBonis at Informa, the publisher of

this work, for seeing an immediate value to the readers in publishing the second edition of this book and allowing me enough time to prepare this work. The diligent editing and composing staff at Informa, particularly Joseph Stubenrauch, Baljinder Kaur and others are highly appreciated. Regardless, all errors and omissions remain altogether mine.

In the first edition, I had dedicated each volume to one of my mentors; the second edition continues the dedication to these great teachers.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois, U.S.A.

Preface to the Series—First Edition

No industry in the world is more highly regulated than the pharmaceutical industry because of potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity (amortized over the cost of all molecules racing) to final regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. In the year 2004, it is anticipated that the industry will spend about $20 billion on research and development. The generic market of drugs as the new entities come off patent is one of the fastest growing segments of the pharmaceutical industry, with every major multinational company having a significant presence in this field.

Whereas many stages of new drug development are inherently constrained with time, the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced with appropriate knowledge by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the first major attempt to consolidate the available knowledge about formulations in a comprehensive, and by nature a rather voluminous, presentation.

The book is divided into six volumes, based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and OTC products. The separation of OTC products, even though they may easily fall into one of the other five categories, is made to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of product, and of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of products into these six categories.

Each volume includes a description of regulatory filing techniques for the formulations described. Also included are the current regulatory guidelines on cGMP compliance specific to the dosage form. Advice is offered on how to scale up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and cut the race to file short by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a close paradigm when it comes to selecting formulations—"not invented here" perhaps reigns in the mind of many seasoned formulations scientists subconsciously when they prefer to choose only a certain platform for development. It is expected that with the quick review of possibilities available to formulate made available in this book, scientists will benefit from the experience of others.

For the teachers of formulation sciences, this series offers a wealth of information. Whether it is a selection of a preservative system or the choice of a disintegrant, the series offers a wide choice to study and rationalize.

Many have assisted me in the development of this work that has taken years to compile, and I thank scores of my graduate students and colleagues for their help. A work of this size cannot be produced without errors, although I hope that these errors do not distract the reader from the utility of the book. I would sincerely appreciate if readers point out these mistakes for corrections in future editions.

Sarfaraz K. Niazi, Ph.D.
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Preface to the Volume—First Edition

Uncompressed solid products formulations comprise aggregates of powders, such as powders for topical application, for use as insufflations, and for extemporaneous suspensions, as well as hard gelatin capsules or any other form wherein the final form is not compressed. The rationale for this clear demarcation of formulations based on their state of aggregation is important to understand. Whereas compressed solid products require formulation components to render them compressible while allowing free flow into compression cavities, such considerations are of lesser importance for uncompressed solid products. (The flow requirement, nevertheless, stays because the powders must be forced into capsule shells or poured into bottles or other packaging forms.) Uncompressed solid products, on the other hand, offer their own set of formulation problems related to segregation of powders due to static charges, environmental contamination during the filling process, and inevitable problems in wetting and dissolution, thus leading to possible bioavailability problems in vivo. In the series of steps that determine the ultimate dissolution of the product, however, uncompressed solid products are one critical step ahead of compressed solid products—disintegration. The formulator is advised to read chapter 4 of this volume, which discusses guidelines on the waiver of bioavailability requirements. Substantial development costs can be reduced when a drug undergoes fast dissolution, and these considerations must therefore be part of any new formulation effort. The reader is also referred to Volume 1 of this series where current and proposed bioavailability guidelines are provided.

Chapter 1 addresses the fundamental issues of good manufacturing practices (GMPs). The chapter provides access addresses to all major guidelines around the world and also highlights the U.S. Food and Drug Administration (FDA) guidelines. A discussion of the most recent changes in the philosophy of establishing the GMP guidelines based on risk assessment is addressed in this chapter as well.

Chapter 2 presents a more recent discussion of how the U.S. FDA inspectors are supposed to conduct inspections; this topic is of continuous importance to all drug manufacturers. Although it is included in this volume, the guidelines apply to all dosage forms.

Chapter 3 discusses the topic of bioequivalence and bioavailability of solid products. Although this is discussed more thoroughly in Volume 1, the emphasis in chapter 3 is placed on the guidelines to request a waiver of bioavailability/bioequivalence testing; this is something of great importance to both the innovator and the generic drug manufacturer.

Chapter 4 highlights the manufacturing aspects of uncompressed drugs as well as various topics of general and specific interest.

Part II provides formulations for more than 400 pharmaceutical products. Included in part are not only the currently approved products but also several innovative products such as small proteins, instantly liquefiable powders, and nanoparticles. Formulators are strongly urged to review the methodologies described here to serve as a reference point for their own formulations. Some combination products or dosage forms are described that are not currently approved by the FDA (i.e., not included in the *Orange Book*), and they may be in the development phase or in experimental phases. As is always the case, it is the responsibility of the manufacturer to ensure that the formulations used in the production do not violate any intellectual property or proprietary practice laws. The most effective means of establishing this is through a study of the *Orange Book*, which lists the exclusivities and unexpired patents. The patent numbers provided in the *Orange Book* should then be searched for collateral patents, the FDA freedom of information (FOI) database, and other literature to ensure that the intellectual or proprietary property rights are not violated.

Whereas coating solutions are not as important as in the case of compressed solids, nevertheless, some capsules are coated and the granules that are filled in capsules for sustained or timed release are coated, utilizing nonpareil sugar beads most often. The coating solutions are described here, but the reader is further referred to Volume 1 for a detailed description of coating solutions that can be easily adapted to the product intended for formulation into a sustained release profile. Whereas some forms of powders are meant to be sterile, the sterility considerations are discussed in Volume 6.

The subject of powder technology is vast, with applications in many fields. The serious reader is referred to the journal *Advanced Powder Technology* (http://www.vsppub.com/journals/jn-AdvPowTec.html). Such advances as inhalation insulin in a powder form and the new science of nanoparticles open a new phase of pharmaceutical research and development. Nanotechnology describes the ability to create new materials from building blocks the size of an atom cluster. Nanomaterials are powders and materials optimized at the nanoscale ($10-9$ m or a billionth of a meter in size). Nanopowders consist of particles with dimensions that can be measured by X-ray crystallography to be a few hundred atoms in diameter.

The formulations are presented in this volume with a scale for each unit: per capsule or per unit dose of powder. Quantities are expressed for 1000 units. Sometimes, however, a different presentation is chosen for simplicity and clarity. It is often customary for manufacturers to scale formulae for a specific weight, such as 100 or 1000 kg to match the mixing vessel requirements. This can be done roughly by multiplying the weight of each capsule or unit powder by the quantity desired to calculate the size of the batch. The reader should be aware that the actual yield may be different because of differences in the scale and quantity due to differences in the chemical form of drugs used, excesses added, and loss of moisture during manufacturing. Further, adjustment of

quantity based on potency of raw material, where pertinent, changes the quantity requirements. Most of these products are identified in this volume by a brief description before the listing of the Bill of Materials, which may not necessarily represent the commercially available dosage form; the description includes details of the commercial product.

A distinctive feature of this volume is the identification and inclusion of the most often approved capsules and powders in the United States. It is noteworthy that in the preparation of an abbreviated new drug application (ANDA), it is important for both regulatory and scientific reasons to keep the selection of excipients as close as possible to the innovator's product. The listing provided here includes every excipient used in the innovator listing and quantitative formulae in several instances. Whereas, in most instances, sufficient details are provided to assist in the formulation of a generic equivalent with exact quantities of excipients and conditions appropriate for processing, the examples provided for other drugs of a similar type should be sufficient for an astute formulator to develop quickly these formulations. Should there be a need for assistance in finalizing the formulations, however, the reader is invited, without any obligation, to write to the author at niazi@pharmsci.com. It should be emphasized that manufacturers frequently use colored capsule shells to identify their products and often imprint them with logos or other identification marks. It is important to understand that the coloring dyes are not universally approved and, in some instances, may form the basis for a trademark. The formulator is advised to investigate this aspect carefully; nevertheless, in most formulations, the dyes used are disclosed.

Whereas the science and the art of formulations remain within the domain of experienced hands, the wide dissemination of information about drug formulation compositions and problems related to them makes it easier for one to design excellent benchmarked formulations. The Web site of the U.S. FDA (http://www.fda.gov) remains one of the best sources of information. At times, however, commercial sources of databases, particularly the details that come under the Freedom of Information Act, can be more useful (e.g., http://www.foiser-vices.com/). No endorsement is intended here for any company or resource.

I am grateful to CRC Press I LLC for taking the lead in publishing what is possibly the largest such work in the field of pharmaceutical manufacturing. It has been a distinct privilege to have known Stephen Zollo, senior editor at CRC Press, for years. Stephen has done more than any editor I have known to encourage me to complete this work on a timely basis. The editorial assistance provided by the CRC Press staff was indeed exemplary, particularly the assistance of Erika Dery, Samar Haddad, and others at CRC Press. Although much care has gone into correcting errors, any remaining errors are altogether mine. The reader is encouraged to bring any errors to my attention so that I may make corrections in future editions of this volume (niazi@pharmsci.com).

This book is dedicated to Takeru Higuchi. Higuchi was a university regents distinguished professor of pharmaceutical chemistry and chemistry at Kansas University, and the founding chair of the department of pharmaceutical chemistry. He was known for the first systematic application of chemical principles to drug design, delivery, and analysis. His scientific accomplishments earned him the informal title of "father of physical pharmacy." Higuchi died in 1987. A famous quote of Tak Higuchi is that "It is merely a matter of orderly thinking . . . and a little organization." One of his admirers notes, "His uniqueness is that he can look into the future and see things and imagine things that most of us cannot. Higuchi has the ability to identify what will be important in the future—that is his genius." I met Tak several times during my teaching career and heard a lot more about him from my colleagues and teachers who worked with him directly. (It was rumored that he wrote the entire logarithmic table when flying to Japan because he needed to solve an equation.) I learned much of my science by reading Tak's papers, which are full of insight and fresh approaches to old problems. He was also a good businessman and a wonderful role model for industry–academia partnership. His aura is inspiring and his presence overwhelming even though he is not among us anymore. People like Tak Higuchi are rare in any profession; we were just lucky to have him.

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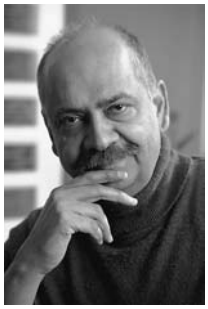
About the Author



Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 35 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents in the field of drug and dosage form delivery systems; he is also licensed to practice law before the U.S. Patent and Trademark Office. Having formulated hundreds of products from the most popular consumer entries to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science and art of formulating and regulatory filings of investigational new drugs (INDs) and new drug applications (NDAs). Dr. Niazi advises the pharmaceutical industry internationally on issues related to formulations, cGMP compliance, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (http://www.pharmsci.com). He can be contacted at Niazi@pharmsci.com

Contents

Part I

Regulatory and Manufacturing Guidelines

1

U.S. FDA Good Manufacturing Practices

I. INTRODUCTION

Good Manufacturing Practices (GMPs) is a universal concept with a dual purpose: to make pharmaceutical products both safe and consistent in their effectiveness. Remarkable changes are taking place in the basic approach to achieve these goals. The key regulations and guidelines for the manufacturing of finished pharmaceuticals (as opposed to raw material or active ingredient manufacturing) in this respect are

1. 21 Code of Federal Regulations, Parts 210 and 211 (Part 210—Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General Part 211—Current Good Manufacturing Practice for Finished Pharmaceuticals) http://www.fda.gov/cder/dmpq/cgmpregs.htm
2. The World Health Organization (WHO): Quality Assurance of Pharmaceuticals: A compendium of guidelines and related materials, Volume 2, Good Manufacturing Practices and Inspection http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html
3. The Rules Governing Medicinal Products in the European Union: Volume 4, Good Manufacturing Practices http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm
4. The European Agency for the Evaluation of Medicinal Products—International Conference on Harmonization (ICH) Guidelines http://www.emea.europa.eu/Inspections/GMPhome.html
5. Health Products and Food Branch Inspectorate of Canada. Good Manufacturing Practices Guidelines—http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/guide-ld-2002/index-eng.php
6. Therapeutic Goods Administration, Government of Australia—Australian Code for Good Manufacturing Practice http://www.tga.gov.au/docs/html/gmpcodau.htm

Though there are many common elements among the approach to GMP taken by the worldwide drug regulatory guidelines, there remains a major difference between the approvals awarded in the United States vis-a-vis Europe and the rest of the world. The U.S. Food and Drug Administration (FDA) inspection is triggered only when an application for marketing authorization has been submitted to the FDA. If the FDA chooses to inspect a facility—the so-called preapproval inspection (PAI)—the company is so advised and the approval of the pending New Drug Application (NDA) or abbreviated New Drug Application (aNDA) is delayed until the inspection is completed. The main focus of PAI is to establish if the applicant firm is capable of manufacturing a safe product, the issues relating to efficacy, dosing, and label copy being reviewed by the agency office in Washington, D.C. It is important to realize that all documents labeled as guidelines remain guidelines and the FDA inspectors are not bound by any specifications, requirements, or designs suggested in the current Good Manufacturing Practices (cGMP) documents. In almost all instances, the FDA inspector visiting a facility for the first time would take time to explain this to the technical team that receives the inspection team. "We are not bound by the CGMP guidelines because these meant to guide you and not bind us." This comes as a surprise to many who may have otherwise worked out each and every recommendation made in the guideline. In several places, the reader will find the instructions given to the inspection team on what to inspect and how to inspect it and these should be studied carefully. Since PAI is related to a specific product and not to the entire facility, the focus of inspection remains the submitted aNDA or NDA and the facility involved in the manufacturing of that specific product. Except for those systems that directly impinge on the quality of the submitted product, the FDA inspectors would generally keep out of other areas. For example, if the submitted application is a sterile product, the FDA inspection will be limited to the facility filling sterile products. Common elements of warehousing, QC, QA are however always part of any inspection.

The focus of PAI is to establish the robustness of the firm's QA systems that will allow consistent production of a safe product, meaning the product is free from contamination, complies with the listed specifications, and is packed such as to allow it to reach the consumer with sufficient shelf-life remaining. It is not unusual for the PAI team to perform a more in-depth audit of the document trail and a more superficial inspection of the physical facility. (The EDQM/EMEA and WHO inspections are mostly facility intensive.) Generally, the PAI team will ensure that the standard operating procedures (SOPs) as written by the firm are followed faithfully and that those involved in assuring the safety guarantee of the product are properly trained.

Whereas the FDA's PAI results in approval of the marketing authorization application, the facility is not declared compliant except for the product for which the inspection was made; thus it is a misnomer to call a firm, "FDA-approved." The U.S. FDA does not approve facilities, it approves products. The WHO audits can result in awarding a facility preapproval to submit for bids on WHO contracts as a GMP-certified facility.

II. U.S. FDA cGMP GUIDELINES

The U.S. FDA oversees the quality of drug products using a two-pronged approach including a review of information submitted in applications as well as an inspection of manufacturing facilities for conformance to requirements for cGMPs. These two programs have served the United States well by helping to ensure the quality of drug products available. Now, as we approach the twenty-fifth anniversary of the last major

revision to the drug cGMP regulations, the U.S. FDA has undertaken a program to overhaul the entire process of cGMP compliance so that

- the most up-to-date concepts of risk management and quality systems approaches are incorporated while continuing to ensure product quality,
- the latest scientific advances in pharmaceutical manufacturing and technology are encouraged,
- the submission review program and the inspection program operate in a coordinated and synergistic manner,
- regulation and manufacturing standards are applied consistently,
- management of the program encourages innovation in the pharmaceutical manufacturing sector,
- FDA resources are used most effectively and efficiently to address the most significant health risks.

Over the last two decades, significant changes in the environment of pharmaceutical regulation have occurred and have resulted in incremental adjustments in the FDA's regulatory approach to product quality. These changes include:

- Increased number of pharmaceutical products and a greater role of medicines in health care
- Decreased frequency of FDA manufacturing inspections as a result of fewer resources available for pharmaceutical manufacturing inspections
- The FDA's accumulation of experience with, and lessons learned from, various approaches to the regulation of product quality
- Advances in the pharmaceutical sciences and manufacturing technologies
- Application of biotechnology in drug discovery and manufacturing
- Advances in the science and management of quality
- Globalization of the pharmaceutical industry

The cumulative impact of these changes has been greater than the sum of the parts and warrants a systematic reappraisal of the FDA's approaches to product quality regulation. The following principles will guide implementation of the reappraisal:

Risk-based orientation—To provide the most effective public health protection, the FDA must match its level of effort against the magnitude of risk. Resource limitations prevent uniformly intensive coverage of all pharmaceutical products and production. Although the agency has been implementing risk-based programs, a more systematic and rigorous risk-based approach will be developed.

Science-based policies and standards—Significant advances in pharmaceutical sciences and in manufacturing technologies have occurred over the last two decades. Although this knowledge has been incorporated in an ongoing manner into the FDA's approach to product quality regulation, the fundamental nature of the changes dictates a thorough evaluation of the science base to ensure that product quality regulation not only incorporates up-to-date science, but also encourages further advances in technology. Recent science can also contribute significantly to assessment of risk.

Integrated quality systems orientation—Principles from various innovative approaches to manufacturing quality that have been developed in the past decade will be evaluated for applicability, and cGMP requirements and related preapproval requirements will be evaluated according to applicable principles. In addition, interaction of the premarket chemistry, manufacturing and control (CMC) review process and the application of cGMP requirements will be evaluated as an integrated system.

International cooperation—The globalization of pharmaceutical manufacturing requires a global approach to regulation. The FDA will collaborate with other regulatory authorities via International Conference on Harmonization and other venues.

Strong public health protection—The initiative will strengthen the public health protection achieved by the FDA's regulation of drug product manufacturing and will not interfere with strong enforcement of the existing regulatory requirements, even as we are examining and revising our approach to these programs.

To accomplish the reappraisal, the FDA will carry out the following broad actions.

- Perform an external review of the existing cGMP program and product review practices, including an evaluation of potential inconsistencies in implementation.
- Reassess and reevaluate our current scientific approach to both the product review process and the cGMP program to achieve a consistent, integrated systems approach to product quality regulation.
- Enhance the scientific approach of cGMPs to emphasize risk-based control point analysis and to facilitate the latest innovations in pharmaceutical engineering.

The following immediate steps are planned.

- Holding scientific workshops with key stakeholders
- Enhancing expertise in pharmaceutical technologies (e.g., pharmaceutical engineering and industrial pharmacy) by additional training and hiring, and by leveraging external expertise
- Encouraging innovation within the existing framework of statutory provisions and regulations by allowing certain changes in the manufacturing process without prior review/approval (e.g., comparability protocols)
- Evaluating the optimal mechanisms to effectively and efficiently communicate deficiencies to industry, including content, consistency, disclosure, and education
- Shifting the agency lead on the implementation of Part 11 to Center for Drug Evaluation and Research (CDER), with continued involvement from the other centers of the FDA and the Office of Regulatory Affairs
- Including product specialists, as needed, as a part of inspection teams
- Having centers provide a scientific and technical review of all drug cGMP warning letters
- Developing a technical dispute resolution process that integrates technical experts from the centers and addresses perceived inconsistencies between centers
- Emphasizing a risk-based approach in the work planning process
- Improving the operations of team biologics of the Center for Biological Evaluation and Research

Intermediate steps are

- using emerging science and data analysis to enhance compliance programs to target the highest risk areas,
- evaluating the feasibility of establishing dedicated cadres of pharmaceutical inspectors.

Long-term steps are

- enhancing training of agency staff on new scientific approaches and innovative pharmaceutical manufacturing technology,

- developing and publishing policies and procedures reflecting a science-based risk management approach,
- educating industry on new regulatory approaches that encourage innovation.

In conclusion, the industry must keep a close watch on these developments as new cGMP guidelines are drafted by the U.S. FDA. This is particularly important for the new start-ups wherein much of what the FDA would like to see in the future can be readily provided. Whereas it is anticipated that the FDA will loosen its noose on some of the less risky aspects of cGMP, greater emphasis will be placed on protecting patients when high-risk drugs are involved. The basic guidelines, however, are here to stay and an overview of these fundamental concepts is presented next.

A. General Provisions

Title 21 of CFR Parts 210 and 211 describes the current GMP practices; this chapter contains the guidelines current as of 2007 and their amendments current as of 2008. Section 211.1, "Scope," states:

"The regulations in this part contain the minimum current good manufacturing practice for preparation of drug products for administration to humans or animals. Pending consideration of a proposed exemption, published in the Federal Register of September 29, 1978, the requirements in this part shall not be enforced for over-the-counter (OTC) drug products if the products and all their ingredients are ordinarily marketed and consumed as human foods, and which products may also fall within the legal definition of drugs by virtue of their intended use."

Periodically, the FDA issues amendments, specific product instructions, and other labeling or manufacturing requirements for a variety of drugs. The reader is advised to consult these guidelines routinely. In light of substantial changes made to these guidelines, it is further advised that instead of comparing these guidelines with the older version, the companies discard the old guidelines and adopt the following document in their standard operating procedures.

Manufacturers who have experience in routine FDA inspections as well as special inspections know well that all of these documents are labeled as guidelines, which literally means that the FDA inspectors are not bound by these—these are merely guidelines. In every instance the purpose of inspection is to ensure that the manufacturer is capable of producing a safe product, the efficacy being already established through the filing of the NDA or aNDA.

Part 210—cGMP in Manufacturing, Processing, Packaging, or Holding of Drugs; General

210.1 Status of cGMP regulations
210.2 Applicability of cGMP regulations
210.3 Definitions

210.1 Status of cGMP regulations

a. The regulations set forth in this part and in parts 211 through 226 in the FDA guidelines contain the minimum cGMP for methods to be used in and the facilities or controls to be used for the manufacture, processing, packing, or holding of a drug to ensure that such drug meets the requirements of the act as to safety and has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess.
b. The failure to comply with any regulation set forth in this part and in parts 211 through 226 in the FDA guidelines in the manufacture, processing, packing, or holding of a drug shall render such drug to be adulterated under section 501(a)(2)(B) of the act and such drug, as well as the person who is responsible for the failure to comply, shall be subject to regulatory action.
c. Owners and operators of establishments engaged in the recovery; donor screening; testing (including donor testing); processing; storage; labeling; packaging; or distribution of human cells, tissues, and cellular and tissue-based products (HCT/Ps), as defined in 1271.3(d) of this chapter, that are drugs (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act), are subject to the donor eligibility and applicable current good tissue practice procedures set forth in part 1271 subparts C and D of this chapter, in addition to the regulations in this part and in parts 211 through 226 in the FDA guidelines. Failure to comply with any applicable regulation set forth in this part, in parts 211 through 226 in the FDA guidelines, in part 1271 subpart C of this chapter, or in part 1271 subpart D of this chapter with respect to the manufacture, processing, packing or holding of a drug, renders an HCT/P adulterated under section 501(a)(2)(B) of the act. Such HCT/P, as well as the person who is responsible for the failure to comply, is subject to regulatory action.

210.2 Applicability of cGMP regulations

a. The regulations in this part and in parts 211 through 226 in the FDA guidelines as they may pertain to a drug; in parts 600 through 680 of this chapter as they may pertain to a biological product for human use; and in part 1271 of this chapter as they are applicable to a HCT/P that is a drug (subject to review under an application submitted under section 505 of the act or under a biological product license application under section 351 of the Public Health Service Act); shall be considered to supplement, not supersede, each other, unless the regulations explicitly provide otherwise. In the event of a conflict between applicable regulations in this part and in other parts of this chapter, the regulation specifically applicable to the drug product in question shall supersede the more general.
b. If a person engages in only some operations subject to the regulations in this part, in parts 211 through 226 in the FDA guidelines, in parts 600 through 680 of this chapter, and in part 1271 of this chapter, and not in others, that person need only comply with those regulations applicable to the operations in which he or she is engaged.

210.3 Definitions

a. The definitions and interpretations contained in section 201 of the act shall be applicable to such terms when used in this part and in parts 211 through 226 in the FDA guidelines.
b. The following definitions of terms apply to this part and to parts 211 through 226 in the FDA guidelines.
    1. Act means the Federal Food, Drug, and Cosmetic Act, as amended (21 USC 301 et seq).
    2. Batch means a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture.
    3. Component means any ingredient intended for use in the manufacture of a drug product,

including those that may not appear in such drug product.

4. Drug product means a finished dosage form, for example, tablet, capsule, solution that contains an active drug ingredient generally, but not necessarily, in association with inactive ingredients. The term also includes a finished dosage form that does not contain an active ingredient but is intended to be used as a placebo.
5. Fiber means any particulate contaminant with a length at least three times greater than its width.
6. Non–fiber-releasing filter means any filter, which after any appropriate pretreatment, such as washing or flushing, will not release fibers into the component or drug product that is being filtered. All filters composed of asbestos are deemed to be fiber-releasing filters.
7. Active ingredient means any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect.
8. Inactive ingredient means any component other than an active ingredient.
9. In-process material means any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product.
10. Lot means a batch, or a specific identified portion of a batch, having uniform character and quality within specified limits; or, in the case of a drug product produced by continuous process, it is a specific identified amount produced in a unit of time or quantity in a manner that ensures its having uniform character and quality within specified limits.
11. Lot number, control number, or batch number means any distinctive combination of letters, numbers, or symbols, or any combination of them, from which the complete history of the manufacture, processing, packing, holding, and distribution of a batch or lot of drug product or other material can be determined.
12. Manufacture, processing, packing, or holding of a drug product includes packaging and labeling operations, testing, and quality control of drug products.
13. The term medicated feed means any Type B or Type C medicated feed as defined in 558.3 in the FDA guidelines. The feed contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated feeds is subject to the requirements of part 225 in the FDA guidelines.
14. The term medicated premix means a Type A medicated article as defined in 558.3 in the FDA guidelines. The article contains one or more drugs as defined in section 201(g) of the act. The manufacture of medicated premixes is subject to the requirements of part 226 in the FDA guidelines.
15. Quality control unit means any person or organizational element designated by the firm to be responsible for the duties relating to quality control.
16. Strength means
    i. the concentration of the drug substance (e.g., weight/weight, weight/volume, or unit dose/volume basis) and/or
    ii. the potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (expressed, e.g., in terms of units by reference to a standard).
17. Theoretical yield means the quantity that would be produced at any appropriate phase of manufacture, processing, or packing of a particular drug product, based upon the quantity of components to be used, in the absence of any loss or error in actual production.
18. Actual yield means the quantity that is actually produced at any appropriate phase of manufacture, processing, or packing of a particular drug product.
19. Percentage of theoretical yield means the ratio of the actual yield (at any appropriate phase of manufacture, processing, or packing of a particular drug product) to the theoretical yield (at the same phase), stated as a percentage.
20. Acceptance criteria means the product specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch (or any other convenient subgroups of manufactured units).
21. Representative sample means a sample that consists of a number of units that are drawn based on rational criteria such as random sampling and intended to ensure that the sample accurately portrays the material being sampled.
22. Gang-printed labeling means labeling derived from a sheet of material on which more than one item of labeling is printed.

Part 211—cGMP for Finished Pharmaceuticals

b. Training in cGMP shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to ensure that employees remain familiar with cGMP requirements applicable to them.
c. Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.
d. There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.

211.28 Personnel responsibilities
a. Personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform. Protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination.
b. Personnel shall practice good sanitation and health habits.
c. Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas.
d. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

211.34 Consultants: Consultants advising on the manufacture, processing, packing, or holding of drug products shall have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained. Records shall be maintained stating the name, address, and qualifications of any consultants and the type of service they provide.

Subpart C—Buildings and Facilities

211.42 Design and construction features
a. Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction, and location to facilitate cleaning, maintenance, and proper operations.
b. Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mix-ups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.
c. Operations shall be performed within specifically defined areas of adequate size. There shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mix-ups during the course of the following procedures.
    1. Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging;
    2. holding rejected components, drug product containers, closures, and labeling before disposition;
    3. storage of released components, drug product containers, closures, and labeling;
    4. storage of in-process materials;
    5. manufacturing and processing operations;
    6. packaging and labeling operations;
    7. quarantine storage before release of drug products;
    8. storage of drug products after release;
    9. control and laboratory operations;
    10. aseptic processing, which includes as appropriate:
        i. floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable;
        ii. temperature and humidity controls;
        iii. an air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar;
        iv. a system for monitoring environmental conditions;
        v. a system for cleaning and disinfecting the room and equipment to produce aseptic conditions;
        vi. a system for maintaining any equipment used to control the aseptic conditions.
d. Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.

211.44 Lighting: Adequate lighting shall be provided in all areas.

211.46 Ventilation, air filtration, air heating and cooling
a. Adequate ventilation shall be provided.
b. Equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product.
c. Air filtration systems, including prefilters and particulate matter air filters, shall be used, when appropriate, on air supplies to production areas. If air is recirculated to production areas, measures shall be taken to control recirculation of dust from production. In areas where air contamination occurs during production, there shall be adequate exhaust systems or other systems adequate to control contaminants.
d. Air-handling systems for the manufacture, processing, and packing of penicillin shall be completely separate from those for other drug products for human use.

211.48 Plumbing
- a. Potable water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product. Potable water shall meet the standards prescribed in the Environmental Protection Agency's Primary Drinking Water Regulations set forth in 40 CFR part 141. Water not meeting such standards shall not be permitted in the potable water system.
- b. Drains shall be of adequate size and, where connected directly to a sewer, shall be provided with an air break or other mechanical device to prevent backsiphonage.

211.50 Sewage and refuse: Sewage, trash, and other refuse in and from the building and immediate premises shall be disposed of in a safe and sanitary manner.

211.52 Washing and toilet facilities: Adequate washing facilities shall be provided, including hot and cold water, soap or detergent, air driers or single-service towels, and clean toilet facilities easily accessible to working areas.

211.56 Sanitation
- a. Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a clean and sanitary condition, Any such building shall be free of infestation by rodents, birds, insects, and other vermin (other than laboratory animals). Trash and organic waste matter shall be held and disposed of in a timely and sanitary manner.
- b. There shall be written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities; such written procedures shall be followed.
- c. There shall be written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents. Such written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed. Rodenticides, insecticides, and fungicides shall not be used unless registered and used in accordance with the Federal Insecticide, Fungicide, and Rodenticide Act (7 USC 135).
- d. Sanitation procedures shall apply to work performed by contractors or temporary employees as well as work performed by full-time employees during the ordinary course of operations.

211.58 Maintenance: Any building used in the manufacture, processing, packing, or holding of a drug product shall be maintained in a good state of repair.

Subpart D—Equipment

211.63 Equipment design, size, and location: Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitable location to facilitate operations for its intended use and for its cleaning and maintenance.

211.65 Equipment construction
- a. Equipment shall be constructed such that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
- b. Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures, in-process materials, or drug products so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.

211.67 Equipment cleaning and maintenance
- a. Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
- b. Written procedures shall be established and followed for cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing, or holding of a drug product. These procedures shall include, but are not necessarily limited to, the following:
  1. Assignment of responsibility for cleaning and maintaining equipment
  2. Maintenance and cleaning schedules, including, where appropriate, sanitizing schedules
  3. A description in sufficient detail of the methods, equipment, and materials used in cleaning and maintenance operations, and the methods of disassembling and reassembling equipment as necessary to ensure proper cleaning and maintenance
  4. Removal or obliteration of previous batch identification
  5. Protection of clean equipment from contamination prior to use
  6. Inspection of equipment for cleanliness immediately before use
- c. Records shall be kept of maintenance, cleaning, sanitizing, and inspection as specified in 211.180 and 211.182.

211.68 Automatic, mechanical, and electronic equipment
- a. Automatic, mechanical, or electronic equipment or other types of equipment, including computers, or related systems that will perform a function satisfactorily may be used in the manufacture, processing, packing, and holding of a drug product. If such equipment is so used, it shall be routinely calibrated, inspected, or checked according to a written program designed to ensure proper performance. Written records of those calibration checks and inspections shall be maintained.
- b. Appropriate controls shall be exercised over computer or related systems to ensure that changes in master production and control records or other records are instituted only by authorized personnel. Input to and output from the computer or related system of formulas or other records or data shall be checked for accuracy. The degree and frequency of input/output verification shall be based on the complexity and reliability of the computer or related system. A backup file of data entered into the computer or related system shall be maintained except where certain data, such as calculations performed in connection with laboratory analysis, are eliminated by computerization or other automated processes. In such instances a written record of the program shall be maintained along with appropriate validation data. Hard copy or alternative systems, such as duplicates, tapes, or microfilm, designed to ensure

that backup data are exact and complete and that it is secure from alteration, inadvertent erasures, or loss shall be maintained.

211.72 Filters: Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may not be used in the manufacture, processing, or packing of these injectable drug products unless it is not possible to manufacture such drug products without the use of such filters. If use of a fiber-releasing filter is necessary, an additional non–fiber-releasing filter of 0.22-micron maximum mean porosity (0.45 microns if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product. Use of an asbestos-containing filter, with or without subsequent use of a specific non–fiber-releasing filter, is permissible only upon submission of proof to the appropriate bureau of the FDA that use of a non–fiber-releasing filter will, or is likely to, compromise the safety or effectiveness of the injectable drug product.

Subpart E—Control of Components and Drug Product Containers and Closures

211.80 General requirements

a. There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.
b. Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.
c. Bagged or boxed components of drug product containers, or closures, shall be stored off the floor and suitably spaced to permit cleaning and inspection.
d. Each container or grouping of containers for components or drug product containers, or closures, shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).

211.82 Receipt and storage of untested components, drug product containers, and closures

a. Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.
b. Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, as appropriate, and released. Storage within the area shall conform to the requirements of 211.80.

211.84 Testing and approval or rejection of components, drug product containers, and closures

a. Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.
b. Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by 211.170.
c. Samples shall be collected in accordance with the following procedures:
    1. The containers of components selected shall be cleaned where necessary, by appropriate means.
    2. The containers shall be opened, sampled, and resealed in a manner designed to prevent contamination of their contents and contamination of other components, drug product containers, or closures.
    3. Sterile equipment and aseptic sampling techniques shall be used when necessary.
    4. If it is necessary to sample a component from the top, middle, and bottom of its container, such sample subdivisions shall not be composited for testing.
    5. Sample containers shall be identified so that the following information can be determined: name of the material sampled, the lot number, the container from which the sample was taken, the date on which the sample was taken, and the name of the person who collected the sample.
    6. Containers from which samples have been taken shall be marked to show that samples have been removed from them.
d. Samples shall be examined and tested as follows:
    1. At least one test shall be conducted to verify the identity of each component of a drug product. Specific identity tests, if they exist, shall be used.
    2. Each component shall be tested for conformity with all appropriate written specifications for purity, strength, and quality. In lieu of such testing by the manufacturer, a report of analysis may be accepted from the supplier of a component, provided that at least one specific identity test is conducted on such component by the manufacturer, and provided that the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.
    3. Containers and closures shall be tested for conformance with all appropriate written procedures. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.
    4. When appropriate, components shall be microscopically examined.
    5. Each lot of a component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination.
    6. Each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.

e. Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.

211.86 Use of approved components, drug product containers, and closures: Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

211.87 Retesting of approved components, drug product containers, and closures: Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with 211.84 as necessary, for example, after storage for long periods or after exposure to air, heat, or other conditions that might adversely affect the component, drug product container, or closure.

211.89 Rejected components, drug product containers, and closures: Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

211.94 Drug product containers and closures

a. Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.
b. Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.
c. Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to ensure that they are suitable for their intended use.
d. Standards or specifications; methods of testing; and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures.

Subpart F—Production and Process Controls

211.100 Written procedures; deviations

a. There shall be written procedures for production and process control designed to ensure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. Such procedures shall include all requirements in this subpart. These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.
b. Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance. Any deviation from the written procedures shall be recorded and justified.

211.101 Charge-in of components

Written production and control procedures shall include the following, which are designed to ensure that the drug products produced have the identity, strength, quality, and purity they purport or are represented to possess.

a. The batch shall be formulated with the intent to provide not less than 100% of the labeled or established amount of active ingredient.
b. Components for drug product manufacturing shall be weighed, measured, or subdivided as appropriate. If a component is removed from the original container to another, the new container shall be identified with the following information.
    1. Component name or item code
    2. Receiving or control number
    3. Weight or measure in new container
    4. Batch for which component was dispensed, including its product name, strength, and lot number
c. Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to ensure that
    1. the component was released by the quality control unit;
    2. the weight or measure is correct as stated in the batch production records;
    3. the containers are properly identified.
d. Each component shall be added to the batch by one person and verified by a second person.

211.103 Calculation of yield: Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall be performed by one person and independently verified by a second person.

211.105 Equipment identification

a. All compounding and storage containers, processing lines, and major equipment used during the production of a batch of a drug product shall be properly identified at all times to indicate their contents and, when necessary, the phase of processing of the batch.
b. Major equipment shall be identified by a distinctive identification number or code that shall be recorded in the batch production record to show the specific equipment used in the manufacture of each batch of a drug product. In cases where only one of a particular type of equipment exists in a manufacturing facility, the name of the equipment may be used in lieu of a distinctive identification number or code.

211.110 Sampling and testing of in-process materials and drug products

a. To ensure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate.
    1. Tablet or capsule weight variation
    2. Disintegration time

3. Adequacy of mixing to ensure uniformity and homogeneity
4. Dissolution time and rate
5. Clarity, completeness, or pH of solutions

b. Valid in-process specifications for such characteristics shall be consistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate. Examination and testing of samples shall ensure that the drug product and in-process material conform to specifications.

c. In-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, for example, at commencement or completion of significant phases or after storage for long periods.

d. Rejected in-process materials shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable.

211.111 Time limitations on production: When appropriate, time limits for the completion of each phase of production shall be established to ensure the quality of the drug product. Deviation from established time limits may be acceptable if such deviation does not compromise the quality of the drug product. Such deviation shall be justified and documented.

211.113 Control of microbiological contamination

a. Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed.

b. Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.

211.115 Reprocessing

a. Written procedures shall be established and followed prescribing a system for reprocessing batches that do not conform to standards or specifications and the steps to be taken to ensure that the reprocessed batches will conform with all established standards, specifications, and characteristics.

b. Reprocessing shall not be performed without the review and approval of the quality control unit.

Subpart G—Packaging and Labeling Control

211.122 Materials examination and usage criteria

a. There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials; such written procedures shall be followed. Labeling and packaging materials shall be representatively sampled, and examined or tested upon receipt and before use in packaging or labeling of a drug product.

b. Any labeling or packaging materials meeting appropriate written specifications may be approved and released for use. Any labeling or packaging materials that do not meet such specifications shall be rejected to prevent their use in operations for which they are unsuitable.

c. Records shall be maintained for each shipment received of each different labeling and packaging material indicating receipt, examination or testing, and whether accepted or rejected.

d. Labels and other labeling materials for each different drug product, strength, dosage form, or quantity of contents shall be stored separately with suitable identification. Access to the storage area shall be limited to authorized personnel.

e. Obsolete and outdated labels, labeling, and other packaging materials shall be destroyed.

f. Use of gang-printed labeling for different drug products, or different strengths or net contents of the same drug product, is prohibited unless the labeling from gang-printed sheets is adequately differentiated by size, shape, or color.

g. If cut labeling is used, packaging and labeling operations shall include one of the following special control procedures:

1. dedication of labeling and packaging lines to each different strength of each different drug product;
2. use of appropriate electronic or electromechanical equipment to conduct 100% examination for correct labeling during or after completion of finishing operations; or
3. use of visual inspection to conduct 100% examination for correct labeling during or after completion of finishing operations for hand-applied labeling. Such examination shall be performed by one person and independently verified by a second person.

h. Printing devices on, or associated with, manufacturing lines used to imprint labeling upon the drug product unit label or case shall be monitored to ensure that all imprinting conforms to the print specified in the batch production record.

211.125 Labeling issuance

a. Strict control shall be exercised over labeling issued for use in drug product labeling operations.

b. Labeling materials issued for a batch shall be carefully examined for identity and conformity to the labeling specified in the master or batch production records.

c. Procedures shall be used to reconcile the quantities of labeling issued, used, and returned, and shall require evaluation of discrepancies found between the quantity of drug product finished and the quantity of labeling issued when such discrepancies are outside narrow preset limits based on historical operating data. Such discrepancies shall be investigated in accordance with 211.192. Labeling reconciliation is waived for cut or roll labeling if 100% examination for correct labeling is performed in accordance with 211.122(g)(2).

d. All excess labeling bearing lot or control numbers shall be destroyed.

e. Returned labeling shall be maintained and stored in a manner to prevent mix-ups and provide proper identification.

f. Procedures shall be written describing in sufficient detail the control procedures employed for the issuance of labeling; such written procedures shall be followed.

211.130 Packaging and labeling operations

There shall be written procedures designed to ensure that correct labels, labeling, and packaging materials are used for drug products; such written procedures shall be fol-

lowed. These procedures shall incorporate the following features:

a. Prevention of mix-ups and cross-contamination by physical or spatial separation from operations on other drug products.
b. Identification and handling of filled drug product containers that are set aside and held in unlabeled condition for future labeling operations to preclude mislabeling of individual containers, lots, or portions of lots. Identification need not be applied to each individual container but shall be sufficient to determine name, strength, quantity of contents, and lot or control number of each container.
c. Identification of the drug product with a lot or control number that permits determination of the history of the manufacture and control of the batch.
d. Examination of packaging and labeling materials for suitability and correctness before packaging operations, and documentation of such examination in the batch production record.
e. Inspection of the packaging and labeling facilities immediately before use to ensure that all drug products have been removed from previous operations. Inspection shall also be made to ensure that packaging and labeling materials not suitable for subsequent operations have been removed. Results of inspection shall be documented in the batch production records.

211.132 TEP requirements for OTC human drug products

a. General. The FDA has the authority under the Federal Food, Drug, and Cosmetic Act (the act) to establish a uniform national requirement for TEP of OTC drug products that will improve the security of OTC drug packaging and help ensure the safety and effectiveness of OTC drug products. An OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale that is not packaged in a tamper-resistant package or that is not properly labeled under this section is adulterated under section 501 of the act or misbranded under section 502 of the act, or both.
b. Requirements for tamper-evident package:
    1. Each manufacturer and packer who packages an OTC drug product (except a dermatological, dentifrice, insulin, or lozenge product) for retail sale shall package the product in a tamper-evident package, if this product is accessible to the public while held for sale. A tamper-evident package is one having one or more indicators or barriers to entry, which, if breached or missing, can reasonably be expected to provide visible evidence to consumers that tampering has occurred. To reduce the likelihood of successful tampering and to increase the likelihood that consumers will discover if a product has been tampered with, the package is required to be distinctive by design or by the use of one or more indicators or barriers to entry that employ an identifying characteristic (e.g., a pattern, name, registered trademark, logo, or picture). For purposes of this section, the term "distinctive by design" means the packaging cannot be duplicated with commonly available materials or through commonly available processes. A tamper-evident package may involve an immediate container and closure system or secondary container or carton system or any combination of systems intended to provide a visual indication of package integrity. The tamper-evident feature shall be designed to and shall remain intact when handled in a reasonable manner during manufacture, distribution, and retail display.
    2. In addition to the TEP feature described in paragraph (b)(1) of this section, any two-piece, hard gelatin capsule covered by this section must be sealed using an acceptable tamper-evident technology.
c. Labeling.
    1. To alert consumers to the specific tamper-evident feature(s) used, each retail package of an OTC drug product covered by this section (except ammonia inhalant in crushable glass ampules, containers of compressed medical oxygen, or aerosol products that depend upon the power of a liquefied or compressed gas to expel the contents from the container) is required to bear a statement that
        i. identifies all tamper-evident feature(s) and any capsule sealing technologies used to comply with paragraph (b) of this section;
        ii. is prominently placed on the package; and
        iii. is so placed that it will be unaffected if the tamper-evident feature of the package is breached or missing.
    2. If the tamper-evident feature chosen to meet the requirements in paragraph (b) of this section uses an identifying characteristic, that characteristic is required to be referred to in the labeling statement. For example, the labeling statement on a bottle with a shrink band could say "for your protection, this bottle has an imprinted seal around the neck."
d. Request for exemptions from packaging and labeling requirements. A manufacturer or packer may request an exemption from the packaging and labeling requirements of this section. A request for an exemption is required to be submitted in the form of a citizen petition under 10.30 of this chapter and should be clearly identified on the envelope as a "Request for Exemption from the Tamper-Evident Packaging Rule." The petition is required to contain the following:
    1. The name of the drug product or, if the petition seeks an exemption for a drug class, the name of the drug class, and a list of products within that class
    2. The reasons that the drug product's compliance with the TEP or labeling requirements of this section is unnecessary or cannot be achieved
    3. A description of alternative steps that are available, or that the petitioner has already taken, to reduce the likelihood that the product or drug class will be the subject of malicious adulteration
    4. Other information justifying an exemption
e. OTC drug products subject to approved new drug applications. Holders of approved new drug applications for OTC drug products are required under 314.70 in the FDA guidelines to provide the agency with notification of changes in packaging and labeling to comply with the requirements of this section. Changes in packaging and labeling required by this regulation may be made before FDA approval, as provided under 314.70(c) in the FDA guidelines. Manufacturing changes by which capsules are to be sealed require prior FDA approval under 314.70(b) in the FDA guidelines.

f. Poison Prevention Packaging Act of 1970. This section does not affect any requirements for "special packaging" as defined under 310.3(l) in the FDA guidelines and required under the Poison Prevention Packaging Act of 1970.

211.134 Drug product inspection

a. Packaged and labeled products shall be examined during finishing operations to provide assurance that containers and packages in the lot have the correct label.
b. A representative sample of units shall be collected at the completion of finishing operations and shall be visually examined for correct labeling.
c. Results of these examinations shall be recorded in the batch production or control records.

211.137 Expiration dating

a. To ensure that a drug product meets applicable standards of identity, strength, quality, and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in 211.166.
b. Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in 211.166.
c. If the drug product is to be reconstituted at the time of dispensing, its labeling shall bear expiration information for both the reconstituted and un-reconstituted drug products.
d. Expiration dates shall appear on labeling in accordance with the requirements of 201.17 in the FDA guidelines.
e. Homeopathic drug products shall be exempt from the requirements of this section.
f. Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section.
g. New drug products for investigational use are exempt from the requirements of this section, provided that they meet appropriate standards or specifications as demonstrated by stability studies during their use in clinical investigations. Where new drug products for investigational use are to be reconstituted at the time of dispensing, their labeling shall bear expiration information for the reconstituted drug product.
h. Pending consideration of a proposed exemption, published in the federal register of September 29, 1978, the requirements in this section shall not be enforced for human OTC drug products if their labeling does not bear dosage limitations and they are stable for at least 3 years as supported by appropriate stability data.

Subpart H—Holding and Distribution

211.142 Warehousing procedures

Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

a. Quarantine of drug products before release by the quality control unit
b. Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected

211.150 Distribution procedures

Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

a. A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.
b. A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.

Subpart I—Laboratory Controls

211.160 General requirements

a. The establishment of any specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms required by this subpart, including any change in such specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms, shall be drafted by the appropriate organizational unit and reviewed and approved by the quality control unit. The requirements in this subpart shall be followed and shall be documented at the time of performance. Any deviation from the written specifications, standards, sampling plans, test procedures, or other laboratory control mechanisms shall be recorded and justified.
b. Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to ensure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include:
    1. Determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.
    2. Determination of conformance to written specifications and a description of sampling and testing procedures for in-process materials. Such samples shall be representative and properly identified.
    3. Determination of conformance to written descriptions of sampling procedures and appropriate specifications for drug products. Such samples shall be representative and properly identified.
    4. The calibration of instruments, apparatus, gauges, and recording devices at suitable intervals in accordance with an established written program containing specific directions, schedules, limits for accuracy and precision, and provisions for remedial action in the event accuracy and/or precision limits are not met. Instruments, apparatus, gauges, and recording devices not meeting established specifications shall not be used.

211.165 Testing and release for distribution

a. For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release. Where sterility and/or

pyrogen testing are conducted on specific batches of short-lived radiopharmaceuticals, such batches may be released prior to completion of sterility and/or pyrogen testing, provided such testing is completed as soon as possible.

b. There shall be appropriate laboratory testing, as necessary, of each batch of drug product required to be free of objectionable microorganisms.
c. Any sampling and testing plans shall be described in written procedures that shall include the method of sampling and the number of units per batch to be tested; such written procedure shall be followed.
d. Acceptance criteria for the sampling and testing conducted by the quality control unit shall be adequate to ensure that batches of drug products meet each appropriate specification and appropriate statistical quality control criteria as a condition for their approval and release. The statistical quality control criteria shall include appropriate acceptance levels and/or appropriate rejection levels.
e. The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with 211.194(a)(2).
f. Drug products failing to meet established standards or specifications and any other relevant quality control criteria shall be rejected. Reprocessing may be performed. Prior to acceptance and use, reprocessed material must meet appropriate standards, specifications, and any other relevant criteria.

211.166 Stability testing

a. There shall be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used in determining appropriate storage conditions and expiration dates. The written program shall be followed and shall include:
    1. Sample size and test intervals based on statistical criteria for each attribute examined to ensure valid estimates of stability
    2. Storage conditions for samples retained for testing
    3. Reliable, meaningful, and specific test methods
    4. Testing of the drug product in the same container-closure system as that in which the drug product is marketed
    5. Testing of drug products for reconstitution at the time of dispensing (as directed in the labeling) as well as after they are reconstituted
b. An adequate number of batches of each drug product shall be tested to determine an appropriate expiration date and a record of such data shall be maintained. Accelerated studies, combined with basic stability information on the components, drug products, and container-closure system, may be used to support tentative expiration dates provided full shelf life studies are not available and are being conducted. Where data from accelerated studies are used to project a tentative expiration date that is beyond a date supported by actual shelf life studies, there must be stability studies conducted, including drug product testing at appropriate intervals, until the tentative expiration date is verified or the appropriate expiration date determined.
c. For homeopathic drug products, the requirements of this section are as follows:
    1. There shall be a written assessment of stability based at least on testing or examination of the drug product for compatibility of the ingredients, and based on marketing experience with the drug product to indicate that there is no degradation of the product for the normal or expected period of use.
    2. Evaluation of stability shall be based on the same container-closure system in which the drug product is being marketed.
d. Allergenic extracts that are labeled "No U.S. Standard of Potency" are exempt from the requirements of this section.

211.167 Special testing requirements

a. For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed.
b. For each batch of ophthalmic ointment, there shall be appropriate testing to determine conformance to specifications regarding the presence of foreign particles and harsh or abrasive substances. The test procedures shall be in writing and shall be followed.
c. For each batch of controlled-release dosage form, there shall be appropriate laboratory testing to determine conformance to the specifications for the rate of release of each active ingredient. The test procedures shall be in writing and shall be followed.

211.170 Reserve samples

a. An appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing. The retention time is as follows:
    1. For an active ingredient in a drug product other than those described in paragraph (a)(2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient.
    2. For an active ingredient in a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for
        i. three months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is 30 days or less, or
        ii. six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days.
    3. For an active ingredient in an OTC drug product that is exempt from bearing an expiration date under 211.137, the reserve sample shall be retained for 3 years after distribution of the last lot of the drug product containing the active ingredient.
b. An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall

be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those for drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of reserve sample deterioration shall be investigated in accordance with 211.192. The results of the examination shall be recorded and maintained with other stability data on the drug product. Reserve samples of compressed medical gases need not be retained. The retention time is as follows:

1. For a drug product other than those described in paragraphs (b)(2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the drug product.
2. For a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for
   i. three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less, or
   ii. six months after the expiration date of the drug product if the expiration dating period of the drug product is more than 30 days.
3. For an OTC drug product that is exempt for bearing an expiration date under 211.137, the reserve sample must be retained for 3 years after the lot or batch of drug product is distributed.

211.173 Laboratory animals: Animals used in testing components, in-process materials, or drug products for compliance with established specifications shall be maintained and controlled in a manner that ensures their suitability for their intended use. They shall be identified, and adequate records shall be maintained showing the history of their use.

211.176 Penicillin contamination: If a reasonable possibility exists that a non–penicillin drug product has been exposed to cross-contamination with penicillin, the non–penicillin drug product shall be tested for the presence of penicillin. Such drug product shall not be marketed if detectable levels are found when tested according to procedures specified in *Procedures for Detecting and Measuring Penicillin Contamination in Drugs*, which is incorporated by reference. Copies are available from the Division of Research and Testing (HFD–470), Center for Drug Evaluation and Research, Food and Drug Administration, 5100 Paint Branch Pkwy., College Park, MD 20740 (www.fda.gov/cder/dmpq/penicillin.pdf).

Subpart J—Records and Reports

211.180 General requirements

a. Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the batch.
b. Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the last lot of drug product incorporating the component or using the container, closure, or labeling.
c. All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.
d. Records required under this part may be retained either as original records or as copies, such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available.
e. Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for
   1. a review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch;
   2. a review of complaints, recalls, returned or salvaged drug products, and investigations conducted under 211.192 for each drug product.
f. Procedures shall be established to ensure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under 211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the FDA, or any regulatory actions relating to GMP brought by the FDA.

211.182 Equipment cleaning and use log: A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.

211.184 Component, drug product container, closure, and labeling records

These records shall include the following:

a. The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in 211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known.
b. The results of any test or examination performed [including those performed as required by 211.82(a), 211.84(d), or 211.122(a)] and the conclusions derived therefrom.
c. An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure.
d. Documentation of the examination and review of labels and labeling for conformity with established specifications in accordance with 211.122(c) and 211.130(c).
e. The disposition of rejected components, drug product containers, closure, and labeling.

211.186 Master production and control records

a. To ensure uniformity from batch to batch, master production and control records for each drug product, including each batch size thereof, shall be prepared, dated, and signed (full signature, handwritten) by one person and independently checked, dated, and signed by a second person. The preparation of master production and control records shall be described in a written procedure and such written procedure shall be followed.
b. Master production and control records shall include:
    1. The name and strength of the product and a description of the dosage form
    2. The name and weight or measure of each active ingredient per dosage unit or per unit of weight or measure of the drug product and a statement of the total weight or measure of any dosage unit
    3. A complete list of components designated by names or codes sufficiently specific to indicate any special quality characteristic
    4. An accurate statement of the weight or measure of each component, using the same weight system (metric, avoirdupois, or apothecary) for each component. Reasonable variations may be permitted, however, in the amount of components necessary for the preparation in the dosage form, provided they are justified in the master production and control records
    5. A statement concerning any calculated excess of component
    6. A statement of theoretical weight or measure at appropriate phases of processing
    7. A statement of theoretical yield, including the maximum and minimum percentages of theoretical yield beyond which investigation according to 211.192 is required
    8. A description of the drug product containers, closures, and packaging materials, including a specimen or copy of each label and all other labeling signed and dated by the person or persons responsible for approval of such labeling
    9. Complete CMC instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed

211.188 Batch production and control records

Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch. These records shall include:

a. An accurate reproduction of the appropriate master production or control record, checked for accuracy, dated, and signed
b. Documentation that each significant step in the manufacture, processing, packing, or holding of the batch was accomplished, including:
    1. Dates
    2. Identity of individual major equipment and lines used
    3. Specific identification of each batch of component or in-process material used
    4. Weights and measures of components used in the course of processing
    5. In-process and laboratory control results
    6. Inspection of the packaging and labeling area before and after use
    7. A statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing
    8. Complete labeling control records, including specimens or copies of all labeling used
    9. Description of drug product containers and closures
    10. Any sampling performed
    11. Identification of the persons performing and directly supervising or checking each significant step in the operation
    12. Any investigation made according to 211.192
    13. Results of examinations made in accordance with 211.134

211.192 Production record review: All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow-up.

211.194 Laboratory records

a. Laboratory records shall include complete data derived from all tests necessary to ensure compliance with established specifications and standards, including examinations and assays as follows.
    1. A description of the sample received for testing with identification of source (that is,

location from where sample was obtained), quantity, lot number or other distinctive code, date sample was taken, and date sample was received for testing.

2. A statement of each method used in the testing of the sample. The statement shall indicate the location of data that establishes that the methods used in the testing of the sample meet proper standards of accuracy and reliability as applied to the product tested. [If the method employed is in the current revision of the *U. S. Pharmacopeia*, National Formulary, AOAC INTERNATIONAL, Book of Methods, (copies may be obtained from AOAC INTERNATIONAL, 481 North Frederick Ave., suite 500, Gaithersburg, MD 20877) or in other recognized standard references, or is detailed in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice.] The suitability of all testing methods used shall be verified under actual conditions of use.
3. A statement of the weight or measure of sample used for each test, where appropriate.
4. A complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific component, drug product container, closure, in-process material, or drug product, and lot tested.
5. A record of all calculations performed in connection with the test, including units of measure, conversion factors, and equivalency factors.
6. A statement of the results of tests and how the results compare with established standards of identity, strength, quality, and purity for the component, drug product container, closure, in-process material, or drug product tested.
7. The initials or signature of the person who performs each test and the date(s) the tests were performed.
8. The initials or signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

b. Complete records shall be maintained of any modification of an established method employed in testing. Such records shall include the reason for the modification and data to verify that the modification produced results that are at least as accurate and reliable for the material being tested as the established method.

c. Complete records shall be maintained of any testing and standardization of laboratory reference standards, reagents, and standard solutions.

d. Complete records shall be maintained of the periodic calibration of laboratory instruments, apparatus, gauges, and recording devices required by 211.160(b)(4).

e. Complete records shall be maintained of all stability testing performed in accordance with 211.166.

211.196 Distribution records: Distribution records shall contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of the drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers.

211.198 Complaint files

a. Written procedures describing the handling of all written and oral complaints regarding a drug product shall be established and followed. Such procedures shall include provisions for review by the quality control unit, of any complaint involving the possible failure of a drug product to meet any of its specifications and, for such drug products, a determination as to the need for an investigation in accordance with 211.192. Such procedures shall include provisions for review to determine whether the complaint represents a serious and unexpected adverse drug experience, which is required to be reported to the FDA in accordance with 310.305 and 514.80 of this chapter.

b. A written record of each complaint shall be maintained in a file designated for drug product complaints. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are readily available for inspection at that other facility. Written records involving a drug product shall be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, such written records shall be maintained for 3 years after distribution of the drug product.

1. The written record shall include the following information, where known: the name and strength of the drug product, lot number, name of complainant, nature of complaint, and reply to complainant.
2. Where an investigation under 211.192 is conducted, the written record shall include the findings of the investigation and follow-up. The record or copy of the record of the investigation shall be maintained at the establishment where the investigation occurred in accordance with 211.180(c).
3. Where an investigation under 211.192 is not conducted, the written record shall include the reason that an investigation was found not to be necessary and the name of the responsible person making such a determination.

Subpart K—Returned and Salvaged Drug Products

211.204 Returned drug products: Returned drug products shall be identified as such and held. If the conditions under which returned drug products have been held, stored, or shipped before or during their return, or if the condition of the drug product, its container, carton, or labeling, as a result of storage or shipping, casts doubt on the safety, identity, strength, quality, or purity of the drug product, the returned drug product shall be destroyed unless examination, testing, or other investigations prove the drug product meets appropriate standards of safety, identity, strength, quality, or purity. A drug product may be reprocessed provided the subsequent drug product meets appropriate standards,

specifications, and characteristics. Records of returned drug products shall be maintained and shall include the name and label potency of the drug product dosage form, lot number (or control number or batch number), reason for the return, quantity returned, date of disposition, and ultimate disposition of the returned drug product. If the reason for a drug product being returned implicates associated batches, an appropriate investigation shall be conducted in accordance with the requirements of 211.192. Procedures for the holding, testing, and reprocessing of returned drug products shall be in writing and shall be followed.

211.208 Drug product salvaging: Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. Whenever there is a question whether drug products have been subjected to such conditions, salvaging operations may be conducted only if there is (a) evidence from laboratory tests and assays (including animal feeding studies where applicable) that the drug products meet all applicable standards of identity, strength, quality, and purity and (b) evidence from inspection of the premises that the drug products and their associated packaging were not subjected to improper storage conditions as a result of the disaster or accident. Organoleptic examinations shall be acceptable only as supplemental evidence that the drug products meet appropriate standards of identity, strength, quality, and purity. Records including name, lot number, and disposition shall be maintained for drug products subject to this section.

III. AMENDMENTS TO PART 211

- 3. The authority citation for 21 CFR part 211 continues to read as follows:
  Authority: 21 USC 321, 351, 352, 355, 360b, 371, 374; 42 USC 216, 262, 263a, 264
- 4. Section 211.48 is amended by revising paragraph (a) to read as follows:
  211.48 Plumbing
  a. Water supplied by the plumbing system of the facility must be safe for human consumption. This water shall be supplied under continuous positive pressure in a plumbing system free of defects that could contribute contamination to any drug product.
- 5. Section 211.67 is amended by revising paragraph (a) to read as follows:
  211.67 Equipment cleaning and maintenance
  b. Equipment and utensils shall be cleaned, maintained, and sanitized and/or sterilized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements.
- 6. Section 211.68 is amended by adding paragraph (c) to read as follows:
  211.68 Automatic, mechanical, and electronic equipment
  c. Such automated equipment used for performance of operations addressed by 211.101(c) or (d), 211.103, 211.182, or 211.188(b)(11) can satisfy the requirements included in those sections for the performance of an operation by one person and checking by another person if such equipment is used in conformity with this section and one person verifies that the operations addressed in those sections are performed accurately by such equipment.
- 7. Section 211.72 is revised to read as follows:
  211.72 Filters: Filters for liquid filtration used in the manufacture, processing, or packing of injectable drug products intended for human use shall not release fibers into such products. Fiber-releasing filters may not be used in the manufacture, processing, or packing of these injectable drug products unless it is not possible to manufacture such drug products without the use of such filters. If use of a fiber-releasing filter is necessary, an additional non–fiber-releasing filter of 0.22-micron maximum mean porosity (0.45 microns if the manufacturing conditions so dictate) shall subsequently be used to reduce the content of particles in the injectable drug product.
- 8. Section 211.82 is amended by revising paragraph (b) to read as follows:
  211.82 Receipt and storage of untested components, drug product containers, and closures.
  b. Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, whichever is appropriate, and released. Storage within the area shall conform to the requirements of 211.80.
- 9. Section 211.84 is amended by revising paragraphs (c)(1), (d)(3), and (d)(6) to read as follows:
  211.84 Testing and approval or rejection of components, drug product containers, and closures
  c. ***
  1. The containers of components selected shall be cleaned when necessary in a manner to prevent introduction of contaminants into the component.
  d. ***
  3. Containers and closures shall be tested for conformity with all appropriate written specifications. In lieu of such testing by the manufacturer, a certificate of testing may be accepted from the supplier, provided that at least a visual identification is conducted on such containers/closures by the manufacturer and provided that the manufacturer establishes the reliability of the supplier's test results through appropriate validation of the supplier's test results at appropriate intervals.
  6. Each lot of a component, drug product container, or closure with potential for microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.
- 10. Section 211.94 is amended by revising paragraph (c) to read as follows:
  211.94 Drug product containers and closures
  c. Drug product containers and closures shall be clean and, where indicated by the nature of the drug sterilized and processed to remove pyrogenic properties to ensure that they are suitable for their intended use. Such depyrogenation processes shall be validated.
- 11. Section 211.101 is amended by revising paragraphs (c) and (d) to read as follows:
  211.101 Charge-in of components.

c. Weighing, measuring, or subdividing operations for components shall be adequately supervised. Each container of component dispensed to manufacturing shall be examined by a second person to ensure that
   1. the component was released by the quality control unit;
   2. the weight or measure is correct as stated in the batch production records;
   3. the containers are properly identified. If the weighing, measuring, or subdividing operations are performed by automated equipment under 211.68, only one person is needed to ensure conditions of paragraphs (c)(1), (c)(2), and (c)(3) of this section have been met.

d. Each component shall either be added to the batch by one person and verified by a second person or, if the components are added by automated equipment under 211.68, only verified by one person.

- 12. Section 211.103 is revised to read as follows:
  211.103 Calculation of yield: Actual yields and percentages of theoretical yield shall be determined at the conclusion of each appropriate phase of manufacturing, processing, packaging, or holding of the drug product. Such calculations shall either be performed by one person and independently verified by a second person, or, if the yield is calculated by automated equipment under 211.68, be independently verified by one person.
- 13. Section 211.110 is amended by revising paragraph (a) introductory text and by adding paragraph (a)(6) to read as follows:
  211.110 Sampling and testing of in-process materials and drug products
  a. To ensure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:
     6. Bioburden testing
- 14. Section 211.113 is amended by revising paragraph (b) to read as follows:
  211.113 Control of microbiological contamination.
  b. Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of all aseptic and sterilization processes.
- 15. Section 211.160 is amended by revising paragraph (b)(1) to read as follows:
  211.160 General requirements
  b. ***
     1. Determination of conformity to applicable written specifications for the acceptance of each lot within each shipment of components, drug product containers, closures, and labeling used in the manufacture, processing, packing, or holding of drug products. The specifications shall include a description of the sampling and testing procedures used. Samples shall be representative and adequately identified. Such procedures shall also require appropriate retesting of any component, drug product container, or closure that is subject to deterioration.
- 16. Section 211.182 is revised to read as follows:
  211.182 Equipment cleaning and use log: A written record of major equipment cleaning, maintenance (except routine maintenance such as lubrication and adjustments), and use shall be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. If equipment is dedicated to manufacture of one product, then individual equipment logs are not required, provided that lots or batches of such product follow in numerical order and are manufactured in numerical sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use shall be part of the batch record. The persons performing and double-checking the cleaning and maintenance (or, if the cleaning and maintenance is performed using automated equipment under 211.68, only the person verifying the cleaning and maintenance done by the automated equipment) shall date and sign or initial the log indicating that the work was performed. Entries in the log shall be in chronological order.
- 17. Section 211.188 is amended by revising paragraph (b)(11) to read as follows:
  211.188 Batch production and control records
  b. ***
     ii. Identification of the persons performing and directly supervising or checking each significant step in the operation, or if a significant step in the operation is performed by automated equipment under 211.68, the identification of the person checking the significant step performed by the automated equipment.

IV. U.S. FDA cGMP OVERVIEW CHECKLIST

1. "C" = current dynamic and evolve over time; "GMP" = Good Manufacturing Practices minimal standards
   a. Not "best" practices unless "best" is, in fact, current minimal
   b. cGMP not NDA or firm specific
2. Compliance terms and phrases related to cGMP issues
   a. Adulteration
   b. Quality controls, quality assurance, quality systems
   c. Contamination (e.g., lack of assurance of sterility)
   d. Cross-contamination (e.g., dirty manufacturing facilities)
   e. Out-of-specification (OoS) findings
   f. Equipment-related issues, calibration/maintenance
   g. Standard operating procedures (SOPs)
   h. Code of Federal Regulations (CFR), Parts 210 and 211
   i. Form FDA-483 (Inspectional Observations)
   j. Establishment Inspection Report (EIR)
   k. Collection Report (CR)
   l. Regulatory actions: warning Letters, recall, seizure, injunctions, application approvals, suspensions, revocations, and import detention Good Manufacturing Practice, or GMP
   m. Good Management Practice, or GMP
   n. Good Engineering Practice, or GEP
   o. Good Laboratory Practice, or GLP

p. Good Safety Practice, or GSP
q. Good Clinical Practice, or GCP
r. Good Distribution Practice, or GDP
s. Good Research Practice, or GRP
t. Good Review Management Practice, or GRMP
u. Good Recruitment Practice, or GxP

3. Best practice
   a. A concept of management that asserts that proper processes, checks, and testing can deliver or put out a desired outcome with fewer problems and unforeseen complications
   b. Definition of processes or methods to do something
   c. Results in achievement of assurance of quality results and consistency by following the process (the practice) if the process is followed
   d. In the modern world, the production of goods and services has become complex, dependent on integration of many different specialty activities, which include sophisticated equipment, requiring design, construction, maintenance, and operation
   e. The central axiom is best practice results in best outcome or good practice results in good outcome (product)
   f. Applied in sales, manufacturing, teaching, programming software, road construction, health care, insurance, and accounting
4. Good operating practice
   a. A strategy for management of activities to produce a desirable outcome/product
   b. Five hundred and more organizations, institutes, consultants, Web sites offering assistance
5. cGMP for pharmaceuticals
   a. Established by government
   b. Requirement of law
   c. Definition, or development
6. U.S. cGMP legal principles
   a. "Adulterated" drug due to lack of cGMPs
   b. Defined in 501(a)(2)(B) of FD&C Act: "A drug shall be deemed adulterated:. . .if the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of the Act as to safety and has that identity and strength, and meets the quality and purity characteristics, which it purports or is represented to posses."
   c. Quality built into product
      i. By "taking care" in making medicine
      ii. Can't "test" into product the quality
      iii. Controls provided by the practice
   d. Without/Inadequate cGMP
      i. Product(s) adulterated (defects need not be shown)
      ii. Firm and its management are responsible
   e. Potential problems from
      i. Noncompliance with cGMP
      ii. Superpotency or subpotency
      iii. Contamination
      iv. Safety and efficacy effects
      v. Misbranding
7. cGMP requirements apply to
   a. Finished pharmaceuticals
   b. Drug substances/APIs
   c. OTC and Rx products
   d. NDA and aNDA drug products
   e. Approved and unapproved drug products
   f. Investigational New Drug Application (IND) products administered in clinical studies (human or animal)
8. U.S. cGMP legal principles excluded from the cGMP requirement
   a. Positron emission tomography, as per FDAMA (own cGMP to be developed)
   b. Drug products compounded as per Section 503 Pharmacy Compounding (FDAMA)
9. U.S. cGMP legal principles
   a. Feasible and valuable
   b. No threshold for "percentage" in practice
   c. Doesn't have to be "predominant"
   d. Enforceable even if nobody is doing it
   e. Stronger case if someone is doing it
10. cGMP regulation scope
    a. Dosage forms for human/vet/biologics
    b. OTC, Rx, IND, NDA, medical gases
    c. Not: pharmacies, ingredients, nonclinical research
11. cGMP regulation
    a. cGMP for Finished Pharmaceuticals 21 CFR 210, 211
    b. Substantive
    c. Force and effect of law
    d. Constitute major part of (not entire) cGMP
    e. Establish "what to" do, not "how to" do
    f. Minimal standards
    g. Maximum flexibility
    h. Specific enough to address problems, for example, penicillin contamination control
    i. Technology neutral
    j. Scalable
12. cGMP guidance documents
    a. Principles
       i. Not requirements
       ii. Agency "current thinking"
       iii. Detailed, technical
       iv. Expression of "how to" meet "what to" do (requirements)
       v. Shape industry behavior
       vi. Offers routes to efficiency in meeting cGMP requirement, evaluation of compliance
    b. cGMP guidance documents (examples)
       i. General principles of process validation
       ii. Compressed medical gases
       iii. Sterile drug products produced by aseptic processing
       iv. Guideline on the preparation of investigational new drug products
       v. Investigating out-of-specification test results for pharmaceutical production
       vi. Manufacturing, processing, or holding of active pharmaceutical ingredients
13. cGMP Requirements: 21 CFR Parts 210 and 211contain the minimum cGMP regulations for the preparation of finished pharmaceuticals for administration to humans and animals and encompass
    a. Organization and personnel (e.g., quality control unit)
    b. Buildings and facilities
    c. Equipment
    d. Components and drug product containers
    e. Production and process controls
    f. Packaging and labeling controls
    g. Laboratory controls

h. Holding and distribution
i. Records and reports

14. cGMP regulations
    a. 21 CFR 210
        i. Status of the regulations
        ii. Applicability of the regulations
        iii. Definitions
        iv. Batch
        v. Lot
        vi. In-process material
        vii. Quality control unit
        viii. Representative sample
15. 21 CFR 211
    a. Subpart A—General Provisions: this is minimum cGMP
        i. Overview of cGMP requirements in the regulation
        ii. cGMP regulations
    b. Subpart B—Organization and Personnel
        i. There shall be a quality control unit
        ii. Quality control unit's responsibility to approve/reject
    c. Subpart C—Buildings and Facilities
        i. buildings shall be. . .suitable
        ii. operations to be in specifically defined areas . . . separate . . . . Or such other control systems for . . . operations as are necessary to prevent contamination or mix-ups . . . (see list, includes aseptic processing)
        iii. "separate" facilities for penicillin
        iv. building. . .shall be. . .clean and sanitary
    d. Subpart D—Equipment
        i. surfaces . . .shall not be reactive, additive, or absorptive
        ii. Equipment. . .shall be cleaned, maintained and sanitized. . .
    e. Subpart E—Control of Components, Containers, and Closures
        i. containers and closures . . .handled in a manner to prevent contamination.
        ii. Testing or examination of c/c/c's
        iii. Test to identify each component
        iv. Tests on components for conformance with specs
        v. Test c/c/c's microscopically, for adulterants, microscopically
    f. Subpart F—Production and Process Controls
        i. Written procedures for production and process control
        ii. Formulated not less than 100%
        iii. Portions of components identified, examined by a second person before dispensed for use in manufacture
        iv. Sampling and testing of in-process materials and products, some specified
        v. Time limits
        vi. Reprocessing allowed, but controlled
    g. Subpart G—Packaging and Labeling Controls
        i. Examination, approval of labels, labeling
        ii. Strict control over labeling issue, and return to stock
        iii. Written procedures, physical separation of labeling operations
        iv. Examination of materials before use
        v. Inspection of facilities immediately before
        vi. Tamper-resistant packaging (for OTC products)
        vii. Expiration dating
    h. Subpart H—Holding and Distribution
        i. Quarantine before release
        ii. Store under appropriate conditions
    i. Subpart I—Laboratory Controls
        i. Establish specs, standards, sampling plans, test procedures.
        ii. Calibration, of laboratory equipment.
        iii. Test each batch of drug product.
        iv. Adequate acceptance criteria.
        v. Validate test methods.
        vi. Conduct stability program.
    j. Subpart I—Laboratory Controls
        i. Special tests
        ii. Sterility and pyrogenicity
        iii. Ophthalmic ointments for foreign/abrasive particles
        iv. Controlled-release products for rate of release
        v. Keep reserve samples
        vi. Test non–penicillin products for penicillin when reasonable possibility of exposure to presence of penicillin
    k. Subpart J—Records and Reports
        i. Keep records, make available for inspection.
        ii. Conduct annual review of each drug product for changes to specs, control procedures.
        iii. Keep equipment clean and use log.
        iv. Keep component, container, closure, and labeling records.
        v. Have SOP for master production and control record, maintain record.
        vi. Use batch production and control records for manufacture, keep records.
        vii. Records to be reviewed/approved by quality control unit.
        viii. Complete data derived from all tests necessary to ensure compliance.
        ix. Distribution records, with lot numbers (except medical gases) complaint files.
    l. Subpart K—Returned and Salvaged Drug Products
        i. If conditions cast doubt, returned product shall be destroyed unless proved okay by test, examination, investigation.
        ii. Salvage only if evidence from tests and inspection show all standards met.
16. cGMP changes
    a. Change/Update is continuous.
    b. Establishment inspections.
    c. Industry changes/problems.
    d. Defect reports/complaints/recalls.
17. Litigation
    a. Agency application reviews
    b. Trade/Scientific literature
    c. Citizen petitions
18. Input for cGMP changes
    a. Establishment inspections
    b. Industry changes/problems
    c. Defect reports/complaints/recalls
19. cGMP initiative
    a. Opportunities
    b. Major advances in manufacturing science/technology
    c. Advances in the science of quality management (e.g., quality systems approaches)
    d. Systems-based drug inspection program
    e. Advances in application of risk analysis/management

f. Risk management approaches gaining wider acceptance in other regulatory agencies (e.g., EPA, OSHA, IRS)

20. cGMP Compliance Programs—Instructions to FDA inspectors
    a. Drug manufacturing inspections program
    b. Systems-based assessment of site
    c. PAI program
    d. Points to inspect
    e. Laboratory support
    f. Regulatory approaches
21. Systems-based approach to GMP described in CPGM 7356.002, drug process inspections
    a. Quality system
        i. Quality control unit
        ii. Responsibility and authority to review and approve all
        iii. Procedures adequate for their intended use
        iv. Batch production records
        v. Training/Qualification of personnel
        vi. Record-keeping systems
        vii. Quality control unit evaluates
        viii. Data collected to identify quality problems
        ix. Annual product reviews, complaints, OoS findings
        x. Problems to determine what corrective and preventative actions are needed
    b. Facilities system
        i. Adequate design to prevent cross-contamination or mix-up
        ii. Readily cleanable and sanitizing agents effectively used
        iii. Properly maintained
        iv. Adequate storage conditions for components
        v. Air-handling systems functioning and separate if necessary (e.g. penicillin, beta-lactams, steroids, hormones, cytotoxics)
        vi. Control system in place for implementing changes
        vii. Adequate lighting, temperature, humidity controls
    c. Equipment system
        i. Installation and operational qualification where appropriate
        ii. Adequate design, size, and location
        iii. Equipment surfaces should not be reactive, additive, or absorptive
        iv. Controls to prevent contamination
        v. Cleaning procedures and cleaning validation
        vi. Calibration and maintenance
        vii. Equipment use logs
        viii. Control system for implementing changes in the equipment
    d. Materials system
        i. Components, drug product containers, and closures.
        ii. Quarantined until tested or examined and released (or rejected).
        iii. Representative samples collected, tested, or examined (e.g., containers and closures should not be additive, reactive, or absorptive to the drug product).
        iv. At least one specific identity test is conducted on each lot of each component.
        v. A visual identification is conducted on each lot of containers and closures.
        vi. Testing or validation of supplier's test results for components, containers, and closures.
        vii. First in, first out (FIFO) use of components, containers, closures.
        viii. Water is a major component that is evaluated during most cGMP inspections.
    e. Production system
        i. Components—"charge in"
        ii. Formulation/Manufacturing at not less than 100%
        iii. Equipment properly identified—contents
        iv. Actual yields and percentage of theoretical yields
        v. Containers and closures—cleaning/ sterilization/depyrogenation
        vi. Batch production documentation—contemporaneous and complete
        vii. Time limits for completion of phases of production
        viii. In-process controls, tests, and examinations (e.g., pH, adequacy of mix, weight variation, clarity)
        ix. Environmental controls—prevent objectionable microorganisms
        x. Process validation
        xi. Computerized or automated processes—validation and security
        xii. Change control
    f. Packaging and labeling system
        i. Adequate storage controls for labels and labeling—both approved and returned after issued
        ii. Control of labels which are similar in size, shape, and color for different products
        iii. Cut labels require 100% verification
        iv. Packaging records include specimens of all labels used
        v. Control of issuance/reconciliation of labels and labeling
        vi. Examination of the labeled finished product
        vii. Physical/Spatial separation between different labeling and packaging lines
        viii. Line clearance, inspection, and documentation
        ix. Conformance to TEP packaging requirements—OTC
    g. Laboratory control system
        i. Staffing
        ii. Equipment and facilities
        iii. Calibration and maintenance of analytical instruments and equipment (e.g., system suitability checks on chromatographic systems)
        iv. Reference standards
        v. Specifications, standards, and representative sampling plans
        vi. Validation/Verification of analytical methods
        vii. Complete analytical records—includes retention of raw data
        viii. Documented investigation into any unexpected discrepancy/OoS
        ix. Reserve samples
        x. Stability testing program
    h. cGMP implementation tools
        i. Compliance policy guides.
        ii. Specific actions we do related to cGMP.
        iii. Examples: Subchapter 410—Bulk Drugs.
        iv. The regulations for finished pharmaceuticals will be applied as guidelines for bulk drugs.

v. Subchapter 420—Compendial (USP)/Test Requirements. Example: USP not required for release test.
vi. Other subchapters.
vii. Labeling and repackaging
viii. Stability/Expiration
ix. Process Validation
x. Other product-specific validation protocols

V. DRUG MASTER FILES AND CERTIFICATIONS

A Drug Master File (DMF) is a submission to the FDA that may be used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The submission of a DMF is not required by law or FDA regulation. A DMF is submitted solely at the discretion of the holder. The information contained in the DMF may be used to support an IND, an NDA, an abbreviated New Drug Application (aNDA), another DMF, an export application, or amendments and supplements to any of these.

A DMF is *not* a substitute for an IND, NDA, aNDA, or export application. It is not approved or disapproved. Technical contents of a DMF are reviewed only in connection with the review of an IND, NDA, aNDA, or an export application.

This guideline does not impose mandatory requirements [21 CFR 10.90(b)]. It does, however, offer guidance on acceptable approaches to meeting regulatory requirements. Different approaches may be followed, but the applicant is encouraged to discuss significant variations in advance with FDA reviewers to preclude spending time and effort in preparing a submission that FDA may later determine to be unacceptable.

DMFs are provided for in 21 CFR 314.420.

DMFs are generally created to allow a party other than the holder of the DMF to reference material without disclosing to that party the contents of the file. When an applicant references its own material, the applicant should reference the information contained in its own IND, NDA, or aNDA directly rather than establishing a new DMF.

A. Types of DMFs

a. *Type I*: Manufacturing Site, Facilities, Operating Procedures, and Personnel. A Type I DMF is recommended for a person outside of the United States to assist FDA in conducting on-site inspections of their manufacturing facilities. The DMF should describe the manufacturing site, equipment capabilities, and operational layout. A Type I DMF is normally not needed to describe domestic facilities, except in special cases, such as when a person is not registered and not routinely inspected. The description of the site should include acreage, actual site address, and a map showing its location with respect to the nearest city. An aerial photograph and a diagram of the site may be helpful. A diagram of major production and processing areas is helpful for understanding the operational layout. Major equipment should be described in terms of capabilities, application, and location. Make and model would not normally be needed unless the equipment is new or unique. A diagram of major corporate organizational elements, with key manufacturing, quality control, and quality assurance positions highlighted, at both the manufacturing site and corporate headquarters, is also helpful.
b. *Type II*: Drug Substance, Drug Substance Intermediate, and Material Used in Their Preparation, or Drug Product. A Type II DMF should, in general, be limited to a single drug intermediate, drug substance, drug product, or type of material used in their preparation. Summarize all significant steps in the CMCs of the drug intermediate or substance. Manufacturing procedures and controls for finished dosage forms should ordinarily be submitted in an IND, NDA, aNDA, or export application. If this information cannot be submitted in an IND, NDA, aNDA, or export application, it should be submitted in a DMF.
c. *Type III*: Packaging Material. Each packaging material should be identified by the intended use, components, composition, and controls for its release. The names of the suppliers or fabricators of the components used in preparing the packaging material and the acceptance specifications should also be given. Data supporting the acceptability of the packaging material for its intended use should also be submitted as outlined in the *Guideline for Submitting Documentation for Packaging for Human Drugs and Biologics*. Toxicological data on these materials would be included under this type of DMF, if not otherwise available by cross-reference to another document.
d. *Type IV*: Excipient, Colorant, Flavor, Essence, or Material Used in Their Preparation. Each additive should be identified and characterized by its method of manufacture, release specifications, and testing methods. Toxicological data on these materials would be included under this type of DMF, if not otherwise available by cross-reference to another document. Usually, the official compendia and FDA regulations for color additives (21 CFR Parts 70 through 82), direct food additives (21 CFR Parts 170 through 173), indirect food additives (21 CFR Parts 174 through 178), and food substances (21 CFR Parts 181 through 186) may be used as sources for release tests, specifications, and safety. Guidelines suggested for a Type II DMF may be helpful for preparing a Type IV DMF. The DMF should include any other supporting information and data that are not available by cross-reference to another document.
e. *Type V*: FDA-Accepted Reference Information. FDA discourages the use of Type V DMFs for miscellaneous information, duplicate information, or information that should be included in one of the other types of DMFs.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) ***(or Drug Substance)—***Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Airlock—An enclosed space with two or more doors, which is interposed between two or more rooms, for example, of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for use either by people or for goods and/or equipment.

API Starting Material—A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API starting materials are normally of defined chemical properties and structure.

Authorized Person—The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested, and approved for release in compliance with the laws and regulations in force in that country.

Batch (or Lot)—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. A defined quantity of starting material, packaging material, or product processed in a single process or series of processes such that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Batch Number (or Lot Number)—A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records, and corresponding certificates of analysis.

Batch Records—All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bioburden—The level and type (e.g., objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates, or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Bulk Product—Any product that has completed all processing stages up to, but not including, final packaging.

Calibration—The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Clean Area—An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Computer System—A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions. A process or operation integrated with a computer system.

Consignment (or Delivery)—The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise of one or more packages or containers and may include material belonging to more than one batch.

Contamination—The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, storage or transport.

Contract Manufacturer—A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical—Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Critical Operation—An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Cross-Contamination—Contamination of a material or product with another material or product. Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Deviation—Departure from an approved instruction or established standard.

Drug (Medicinal) Product—The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance—See Active Pharmaceutical Ingredient.

Expiry Date (or Expiration Date)—The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Finished Product—A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.

Impurity—Any component present in the intermediate or API that is not the desired entity.

Impurity Profile—A description of the identified and unidentified impurities present in an API.

In-Process Control—Checks performed during production to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate—A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Large-Volume Parenterals—Sterile solutions intended for parenteral application with a volume of 100 mL or more in one container of the finished dosage form.

Lot—See Batch.

Lot Number—See Batch Number.

Manufacture—All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Manufacturer—A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of pharmaceuticals.

Marketing authorization (Product License, Registration Certificate)—A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling, and shelf life.

Master Formula—A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master Record—A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Material—A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother Liquor—The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It may be used for further processing.

Packaging—All operations, including filling and labeling, that a bulk product has to undergo to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

Packaging Material—Any material intended to protect an intermediate or API during storage and transport. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical Product—Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Procedure—A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids—Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc).

Process Control—See In-Process Control.

Production—All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labeling and relabeling, to completion of the finished product.

Qualification—Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)—The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)—Checking or testing that specifications are met.

Quality Unit(s)—An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine—The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection or reprocessing.

Raw Material—A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reconciliation—A comparison between the theoretical quantity and the actual quantity.

Recovery—The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

Reference Standard, Primary—A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be

Reference Standard, Secondary—A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing—Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and pre-approved as part of the marketing authorization.

Retest Date—The date when a material should be reexamined to ensure that it is still suitable for use.

Reworking—Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization.

Self-Contained Area—Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well established procedures, controls and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

Signature (Signed)—See Signed.

Signed (Signature)—The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent—An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification—A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Standard Operating Procedure (SOP)—An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting Material—Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Validation—A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity or system actually leads to the expected results (see also qualification).

Validation Protocol—A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected—The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical—The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

GMP Audit Template, EU Guidelines (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm)

		Compliance 1 2 3[a]	Remarks	EU Guide
1	**PERSONNEL**			
1.1	Qualified personnel available?	☐ ☐ ☐		2.1
1.2	Organization charts available?	☐ ☐ ☐		2.2
1.3	Job descriptions available?	☐ ☐ ☐		2.2
1.4	Responsibilities clearly defined?	☐ ☐ ☐		2.2
	Key personnel			
	Responsible persons designated for			
1.5	• production?	☐ ☐ ☐		2.5
1.6	• quality control?	☐ ☐ ☐		2.6
1.7	Are they independent from each other?	☐ ☐ ☐		2.3
1.8	Are joint functions clearly defined?	☐ ☐ ☐		2.7
1.9	Are the responsible persons working full time?	☐ ☐ ☐		2.3
1.10	Have the responsible persons the appropriate formation, knowledge, and experience?	☐ ☐ ☐		2.1/2.2
1.11	Have the relevant departments enough personnel?	☐ ☐ ☐		2.1
	Training			
1.12	Continuous training programs for the production and QC staff?	☐ ☐ ☐		2.8
1.13	Initial job training for all employees?	☐ ☐ ☐		2.9
1.14	Teaching aids (videos, slides, brochures) available?	☐ ☐ ☐		2.9
1.15	External training courses for the staff?	☐ ☐ ☐		2.9
1.16	Training records?	☐ ☐ ☐		2.9
1.17	Special training in sensitive areas (sterile prod., toxic subs.)?	☐ ☐ ☐		2.10
1.18	Information for visitors to the manufacturing area?	☐ ☐ ☐		2.11
2	**HYGIENE**			
	Personnel hygiene			
	Detailed written hygiene programs for			
2.1	• clothing?	☐ ☐ ☐		2.13
2.2	• use of washrooms?	☐ ☐ ☐		2.13
2.3	• behaviour in production areas?	☐ ☐ ☐		2.13
2.4	Precautions against sick or personnel with open wounds in production?	☐ ☐ ☐		2.14
	Medical examination			
2.5	• on recruitment?	☐ ☐ ☐		2.15
2.6	• regular reexaminations?	☐ ☐ ☐		2.15

		Compliance 1 2 3[a]	Remarks	EU Guide
	Duty of notification after			
2.7	• trips to tropical countries?	☐ ☐ ☐		2.15
2.8	• cases of contagious illness in the family?	☐ ☐ ☐		2.15
2.9	Instructions for appropriate working clothes?	☐ ☐ ☐		2.16
2.10	Absence of food and drinks (chewing gum) in the working area?	☐ ☐ ☐		2.17
2.11	Measures against contact with open product (gloves)?	☐ ☐ ☐		2.18
2.12	Instructions for hand washing in production?	☐ ☐ ☐		2.19
2.13	Change of clothes when entering and leaving the production area?	☐ ☐ ☐		5.19
2.14	Change rooms and toilets easily within reach?	☐ ☐ ☐		3.31
2.15	Toilets and restrooms sufficiently separated from production areas?	☐ ☐ ☐		3.30/3.31
2.16	Workshops separate from production areas?	☐ ☐ ☐		3.32
2.17	Laboratory animal rooms totally segregated from production rooms?	☐ ☐ ☐		3.33
3	**WAREHOUSE**			
	Rooms, general			
3.1	Suitable for the intended use?	☐ ☐ ☐		3
3.2	• Adequate size?	☐ ☐ ☐		3
3.3	• Clean?	☐ ☐ ☐		3
3.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
3.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
3.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
3.7	Appropriate lighting and air conditioning?	☐ ☐ ☐		3.3
3.8	Recording of temperature and humidity?	☐ ☐ ☐		
3.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
3.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
	Type of warehousing:			
3.11	Separation of goods sufficient?	☐ ☐ ☐		3.18
3.12	Provision for different storage temperatures?	☐ ☐ ☐		3.19
3.13	Goods receiving zone weather protected?	☐ ☐ ☐		3.20
3.14	Cleaning zone for incoming goods?	☐ ☐ ☐		3.20
3.15	Separate quarantine area with controlled access?	☐ ☐ ☐		3.21
3.16	Separate, protected sampling area?	☐ ☐ ☐		3.22
	Separate and safe storage of			
3.17	• returned goods?	☐ ☐ ☐		3.23
3.18	• rejected goods?	☐ ☐ ☐		3.23
3.19	Separate and safe storage of highly active, toxic, or dangerous substances?	☐ ☐ ☐		3.24
3.20	Safe storage of narcotics?	☐ ☐ ☐		3.24
3.21	Safe storage of printed packaging materials?	☐ ☐ ☐		3.25
3.22	Security measurements against theft?	☐ ☐ ☐		3.25

			Compliance 1 2 3	Remarks	EU Guide
3.23	Smoke detectors?		☐ ☐ ☐		3.25
3.24	Fire extinguishing system?		☐ ☐ ☐		3.25
	Operations				
3.25	Reception, sampling, and labeling according to written procedures?		☐ ☐ ☐		5.2
3.26	Is a sampling plan available?		☐ ☐ ☐		suppl. 4
3.27	Cleaning of incoming containers?		☐ ☐ ☐		5.3
3.28	Investigation and recording of damaged deliveries?		☐ ☐ ☐		5.4
3.29	FIFO principle?		☐ ☐ ☐		5.7
3.30	Inventory system?		☐ ☐ ☐		5.8
3.31	The location of materials can be detected at all times?		☐ ☐ ☐		
3.32	Incoming goods: containers and seals intact?		☐ ☐ ☐		5.27
3.33	Incoming goods: conformity with bill of delivery?		☐ ☐ ☐		5.27
	Labeling of incoming containers with				
3.34	• internal name and code?		☐ ☐ ☐		5.29
3.35	• allocated batch number?		☐ ☐ ☐		5.29
3.36	• quarantine status?		☐ ☐ ☐		5.29
3.37	• expiry date or reanalysis date?		☐ ☐ ☐		5.29
3.38	Identity test for each incoming container?		☐ ☐ ☐		5.29
3.39	Are the sampled containers marked?		☐ ☐ ☐		5.30
3.40	Are reference samples taken?		☐ ☐ ☐		5.30
3.41	Safe storage of printed packaging materials?		☐ ☐ ☐		5.41
3.42	Lot tracing of all packaging materials possible?		☐ ☐ ☐		5.42
3.43	Are excessive packaging materials destroyed?		☐ ☐ ☐		5.43
	Release of starting materials by				
	Physical/Inventory checks on raw materials, packaging materials, and finished goods:				
	Item:	Stocks: Physical:	Stocks: Inventory:	Storage conditions:	
4	**DISPENSING/ASSEMBLING**				
	Rooms, general				
4.1	Suitable for the intended use?		☐ ☐ ☐		3
4.2	• Adequate size?		☐ ☐ ☐		3
4.3	• Clean?		☐ ☐ ☐		3
4.4	Located and designed to exclude external contamination?		☐ ☐ ☐		3.1
4.5	Appropriate level of maintenance?		☐ ☐ ☐		3.2

		Compliance 1 2 3[a]	Remarks	EU Guide
4.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
4.7	Appropriate lighting and air conditioning?	☐ ☐ ☐		3.3
4.8	Recording of temperature and humidity?	☐ ☐ ☐		
4.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
4.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
4.11	Segregated from production and warehouse?	☐ ☐ ☐		3.13
4.12	Separate weighing cabins?	☐ ☐ ☐		3.13
4.13	Separate AHU for each cabin?	☐ ☐ ☐		3.12
	Air pressure gradient from weighing cabin → corridor:			3.3
4.14	Dust extraction systems available?	☐ ☐ ☐		5.11
	Operations			
4.15	Balances regularly calibrated?	☐ ☐ ☐		3.41
4.16	Only pharmaceutical raw materials in this area?	☐ ☐ ☐		5.17
4.17	Check on remains from previous materials before entering of new materials into a weighing cabin?	☐ ☐ ☐		5.9/5.35
4.18	Only one material in one cabin?	☐ ☐ ☐		5.9
4.19	Are dispensed materials correct labeled?	☐ ☐ ☐		5.29
4.20	Only released products in the dispensing?	☐ ☐ ☐		5.31
4.21	Cleaning SOPs for the dispensing?	☐ ☐ ☐		4.28
4.22	Previously dispensed material recorded on weighing protocol?	☐ ☐ ☐		4.8
4.23	Safety measures against mix-ups during assembling (e.g., cage pallets)?	☐ ☐ ☐		5.32/5.34
5	**SOLIDS MANUFACTURING**			
	Field of activity:			
	• Granulation	☐		
	• Compression	☐		
	• Encapsulation	☐		
	• Film and sugar coating	☐		
	• Visual inspection (capsules, tablets, etc.)	☐		
	• Premix (human)	☐		
	Rooms, general			
5.1	Suitable for the intended use?	☐ ☐ ☐		3
5.2	• Adequate size?	☐ ☐ ☐		3
5.3	• Clean?	☐ ☐ ☐		3
5.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
5.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
5.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
5.7	Appropriate lighting and air conditioning?	☐ ☐ ☐		3.3
5.8	Recording of temperature and humidity?	☐ ☐ ☐		
5.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
5.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5

		Compliance 1 2 3[a]	Remarks	EU Guide
	Rooms, special requirements			
5.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6
5.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
5.13	Logical flow of materials?	☐ ☐ ☐		3.7
5.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
5.15	Easy cleaning possible?	☐ ☐ ☐		3.10
5.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
5.17	Appropriate air handling system?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
5.18	Appropriate dust extraction system?	☐ ☐ ☐		3.14
5.19	Appropriate lighting?	☐ ☐ ☐		3.16
5.20	Separate rest rooms?	☐ ☐ ☐		3.30
5.21	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
5.22	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
5.23	Suitable for the intended use?	☐ ☐ ☐		3.34
5.24	Well maintained?	☐ ☐ ☐		3.34
5.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
5.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
5.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
5.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
5.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
5.30	Calibration records available?	☐ ☐ ☐		3.41
5.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
5.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
5.33	Not functioning equipment in the production area (if yes: clearly marked)?	**Y N** ☐ ☐ ☐		3.44
5.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
5.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
5.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
5.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
5.38	Check of each single container of the starting materials (contents, weight, identity)?	☐ ☐ ☐		5.3
5.39	Limits for yields?	☐ ☐ ☐		5.8
5.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
5.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
5.42	Appropriate measures against generation of dust (e.g., closed systems)?	☐ ☐ ☐		5.11

		Compliance 1 2 3[a]	Remarks	EU Guide
	Correct labeling of containers, materials, equipment, and rooms with			5.12
5.43	• product name and batch no.	☐ ☐ ☐		5.12
5.44	• quarantine status?	☐ ☐ ☐		5.12
5.45	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐		5.14
5.46	Special procedures for the production of antibiotics, hormones, etc.?	☐ ☐ ☐		5.19
5.47	• Campaign production?	☐ ☐ ☐		5.19
5.48	• Special monitoring?	☐ ☐ ☐		5.19
5.49	• Validated decontamination procedure?	☐ ☐ ☐		5.19
5.50	Double check on weight?	☐ ☐ ☐		5.34
5.51	Line clearance before start of production?	☐ ☐ ☐		5.35
5.52	Investigation of deviations in yields?	☐ ☐ ☐		5.39
5.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐		5.62
5.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐		5.63
5.55	Special release procedure (QA) for those batches?	☐ ☐ ☐		5.64
5.56	Use of protective clothing (hair cover, shoes, masks, gloves)?	☐ ☐ ☐		2.16
5.57	Clothing regulation for visitors?	☐ ☐ ☐		2.11
	IPC			5.38
	Who performs IPC?			
5.58	Are IPC methods approved by QC?	☐ ☐ ☐		6.18

	Performance of IPCs	*During Start-up?* Yes No	*Frequency*	*Automatic* data *recording?* Yes No	
	Tablets/Kernels				
5.59	Individual weights	☐ ☐		☐ ☐	
5.60	Disintegration	☐ ☐		☐ ☐	
5.61	Thickness	☐ ☐		☐ ☐	
5.62	Hardness	☐ ☐		☐ ☐	
5.63	Friability/Abrasion	☐ ☐		☐ ☐	
	Sugar-/Film-coated tablets				
5.64	Weights	☐ ☐		☐ ☐	
5.65	Disintegration	☐ ☐		☐ ☐	
5.66	Residual absolute humidity (IR or)	☐ ☐		☐ ☐	
	Capsules				
5.67	Individual weights	☐ ☐		☐ ☐	
5.68	Disintegration	☐ ☐		☐ ☐	

	Validation			
5.69	Validation according to fixed procedures?	☐ ☐ ☐		5.21
5.70	New procedures released only after validation?	☐ ☐ ☐		5.22
	Validation of changes of			
5.71	• processes?	☐ ☐ ☐		5.23
5.72	• starting materials?	☐ ☐ ☐		5.23
5.73	• equipment?	☐ ☐ ☐		5.23

		Compliance 1 2 3[a]	Remarks	EU Guide
5.74	Revalidation in fixed intervals?	☐ ☐ ☐		5.24
5.75	Procedures for the retrospective validation of old procedures?	☐ ☐ ☐		
6	**LIQUIDS MANUFACTURING**			
	Operations carried out:			
	• Dispensing (if different from solid)	☐ ☐ ☐		
	• Syrups and suspensions	☐ ☐ ☐		
	• Drops	☐ ☐ ☐		
	• Ointment manufacture	☐ ☐ ☐		
	• Ointment filling	☐ ☐ ☐		
	• Ampoule solution manufacture	☐ ☐ ☐		
	• Sterile or aseptic ampoule filling	☐ ☐ ☐		
	• Sterile freeze drying	☐ ☐ ☐		
	• Sterile powder filling	☐ ☐ ☐		
	Rooms, general			
6.1	Suitable for the intended use?	☐ ☐ ☐		3
6.2	• Adequate size?	☐ ☐ ☐		3
6.3	• Clean?	☐ ☐ ☐		3
6.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
6.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
6.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
6.7	Appropriate lighting and air conditioning?	☐ ☐ ☐		3.3
6.8	Recording of temperature and humidity?	☐ ☐ ☐		
6.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
6.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
6.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6
6.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
6.13	Logical flow of materials?	☐ ☐ ☐		3.7
6.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
6.15	Easy cleaning possible?	☐ ☐ ☐		3.10
6.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
6.17	Appropriate air handling system with filtered air where open products are exposed to the environment?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
6.18	Appropriate lighting?	☐ ☐ ☐		3.16
6.19	Separate rest rooms?	☐ ☐ ☐		3.30
6.20	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
6.21	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
6.22	Suitable for the intended use?	☐ ☐ ☐		3.34
6.23	Well maintained?	☐ ☐ ☐		3.34

		Compliance 1 2 3[a]	Remarks	EU Guide
6.24	Tanks, containers, pipe work, and pumps designed for easy cleaning and sanitation (dead legs)?	☐ ☐ ☐		Suppl. 2
6.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
6.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
6.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
6.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
6.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
6.30	Calibration records available?	☐ ☐ ☐		3.41
6.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
6.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
6.33	Not functioning equipment in the production area (if yes: clearly marked)?	Y N ☐ ☐ ☐		3.44
6.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
6.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
6.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
6.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
6.38	Check of each single container of the starting materials (contents, weight, identity)?	☐ ☐ ☐		5.3
6.39	Limits for yields?	☐ ☐ ☐		5.8
6.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
6.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
	Correct labeling of containers, materials, equipment, and rooms with			5.12
6.42	• product name and batch no.	☐ ☐ ☐		5.12
6.43	• quarantine status?	☐ ☐ ☐		5.12
6.44	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐		5.14
6.45	Special procedures for the production of antibiotics, hormones, etc.?	☐ ☐ ☐		5.19
6.46	• Campaign production?	☐ ☐ ☐		5.19
6.47	• Special monitoring?	☐ ☐ ☐		5.19
6.48	• Validated decontamination procedure?	☐ ☐ ☐		5.19
6.49	Double check on weight?	☐ ☐ ☐		5.34
6.50	Line clearance before start of production?	☐ ☐ ☐		5.35
6.51	Investigation of deviations in yields?	☐ ☐ ☐		5.39
6.52	Specification of max. storage time and storage conditions if products are not immediately filled or packaged?	☐ ☐ ☐		Suppl. 9
6.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐		5.62
6.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐		5.63
6.55	Special release procedure (QA) for those batches?	☐ ☐ ☐		5.64
6.56	Use of protective clothing (hair cover, shoes, masks, gloves)?	☐ ☐ ☐		2.16
6.57	Clothing regulation for visitors?	☐ ☐ ☐		2.11

		Compliance 1 2 3[a]	Remarks	EU Guide
	Water			
6.58	Loop system for purified water?	☐ ☐ ☐		Suppl. 4
6.59	Antimicrobial treatment of purified water?	☐ ☐ ☐		Suppl. 4
6.60	Loop system for water for injection?	☐ ☐ ☐		Suppl. 4
	Storage temperature of water for injection:			Suppl. 4
6.61	Loop system constructed to avoid dead legs?	☐ ☐ ☐		Suppl. 4
6.62	Regular microbiological monitoring?	☐ ☐ ☐		Suppl. 4
6.63	Regular endotoxin control?	☐ ☐ ☐		Suppl. 4
	Special requirements for sterile and aseptic products			Suppl.
	Rooms and equipment			
6.64	Access of staff and materials to clean areas *only* through airlocks?	☐ ☐ ☐		1
6.66	Rooms classified according to the EC Guide?	☐ ☐ ☐		3
	Classification for products to be sterilized:			
6.67	• Solution preparation (EC: class C, with special precautions class D)	Class:		5
6.68	• Filling (EC: under LF in class C)	Class:		5
	Classification for aseptic products			
6.69	• Handling of starting materials that can be sterile filtered (EC: class C)	Class:		6
6.70	• Handling of starting materials that cannot be sterile filtered (EC: class A in class B)	Class:		6
6.71	Handling and filling of bulk (EC: class A in Class B)	Class:		6
6.72	All rooms easy to clean disinfect?	☐ ☐ ☐		17
6.73	Doors, windows, frames, lighting, etc. without edges?	☐ ☐ ☐		18
6.74	Suspended ceilings (if yes: sealed?)?	☐ ☐ ☐		19
6.75	Traps constructed to avoid microb. contamination?	☐ ☐ ☐		21
6.76	Appropriate constructed changing rooms?	☐ ☐ ☐		22
6.77	Measures against opening of both doors of airlocks?	☐ ☐ ☐		23
6.78	Overpressure gradient from cleanest areas to others?	☐ ☐ ☐		24
6.79	AHU validated and regularly revalidated?	☐ ☐ ☐		25
6.80	Control instruments for pressure gradient?	☐ ☐ ☐		26
6.81	Warning system for errors in air supply?	☐ ☐ ☐		26
6.82	Recording of pressure gradients?	☐ ☐ ☐		26
6.83	Do conveyor belts leave sterile areas?	☐ ☐ ☐		28
6.84	Maintenance works outside from clean areas possible?	☐ ☐ ☐		28
6.85	Cleaning and disinfection procedure after maintenance works?	☐ ☐ ☐		29
6.86	Regular revalidation of all equipment and systems?	☐ ☐ ☐		30
6.87	Water prepared, circulated, and stored to exclude microb. contamination?	☐ ☐ ☐		31
6.88	Cleaning and disinfection of rooms according to validated SOPs rooms?	☐ ☐ ☐		32
	• Disinfection methods?			
6.89	Microb. monitoring of cleaning and disinfection agents?	☐ ☐ ☐		33

		Compliance 1 2 3[a]	Remarks	EU Guide
6.90	Microb. monitoring program of production areas?	☐ ☐ ☐		35
6.91	Results recorded and considered for the release?	☐ ☐ ☐		35
	Personnel and Hygiene			
6.92	Minimal no. of personnel in clean areas?	☐ ☐ ☐		7
6.93	Special and regular training?	☐ ☐ ☐		8
6.94	Regular medical examinations?	☐ ☐ ☐		10
6.95	Appropriate clean room clothes (material, design)?	☐ ☐ ☐		12
6.96	Protective clothes worn correctly?	☐ ☐ ☐		12
6.97	Prohibition of cosmetics, jewelry, and watches?	☐ ☐ ☐		13
6.98	New clean room clothes for each working cycle?	☐ ☐ ☐		15
6.99	Appropriate washing and sterilization of clothes?	☐ ☐ ☐		16
	Operations			
6.100	Validation (media filling) in regular intervals?	☐ ☐ ☐		38
	Monitoring of water preparation system, frequency:			
6.101	• Microbiological			40
6.102	• Chemical			40
6.103	• Particles			40
6.104	• Endotoxins			40
6.105	Microbiological monitoring of starting materials?	☐ ☐ ☐		42
6.106	Max. storage times defined for sterilized equipment?	☐ ☐ ☐		45
6.107	Max. storage time defined between solution preparation and filtration?	☐ ☐ ☐		46
6.108	Material transfer to clean areas through double door autoclaves?	☐ ☐ ☐		48
	Sterilization processes			
6.109	All processes validated?	☐ ☐ ☐		50
6.110	Sterilized and not sterilized materials clearly separated?	☐ ☐ ☐		54
	Trays and boxes clearly labeled with			
6.111	• product name and code	☐ ☐ ☐		54
6.112	• batch no.	☐ ☐ ☐		54
6.113	• status: sterilized or not sterilized	☐ ☐ ☐		54
	Sterilizers:			
6.114	• Recording of temp., pressure, and time?	☐ ☐ ☐		55
6.115	• Coldest point determined?	☐ ☐ ☐		55
6.116	• Independent countercheck probe?	☐ ☐ ☐		55
6.117	• Heat-up time for each product determined?	☐ ☐ ☐		56
6.118	• Sterile cooling media?	☐ ☐ ☐		57
6.119	• Tightness tests for vacuum autoclaves?	☐ ☐ ☐		58
6.120	• Clean steam for steam autoclaves?	☐ ☐ ☐		58
6.121	• Circulated air with overpressure?	☐ ☐ ☐		61
6.122	• Recirculated air: sterile filtered?	☐ ☐ ☐		61
6.123	• Ethylene oxide autoclaves: humidity, temp., and time recorded?	☐ ☐ ☐		69
6.124	• Ethylene oxide autoclaves: use of bioindicators?	☐ ☐ ☐		70

		Compliance 1 2 3[a]	Remarks	EU Guide
	Filtration			
6.125	Double filtration?	☐ ☐ ☐		75
6.126	Integrity testing of filters immediately after use?	☐ ☐ ☐		77
6.127	Are results part of the batch protocol?	☐ ☐ ☐		77
6.128	Optical control of each single container of ampoules, vials, and infusions?	☐ ☐ ☐		82
	IPC			
6.129	Written IPC procedures and SOPs?	☐ ☐ ☐		
	Particle testing of			
6.130	• rooms	☐ ☐ ☐		
6.131	• primary packaging materials	☐ ☐ ☐		
6.132	• system of warning and action limits?	☐ ☐ ☐		
	Microbiological monitoring of			
6.133	• rooms			
6.134	• personnel			
6.135	• euipment			
6.136	Residual O_2 of ampoules, infusions, and syrups?	☐ ☐ ☐		
6.137	Endotoxin testing of water and packaging materials?	☐ ☐ ☐		
6.138	Calibration of equipment?	☐ ☐ ☐		
6.139	Regular revalidation of equipment?	☐ ☐ ☐		
7	**PACKAGING**			
	Operations carried out • blistering • foil–packaging • filling into tablet glasses • effervescent packaging • powder filling • syrup/drops filling • ointment filling	 ☐ ☐ ☐ ☐ ☐ ☐ ☐		
	Rooms			
7.1	Suitable for the intended use?	☐ ☐ ☐		3
7.2	• Adequate size?	☐ ☐ ☐		3
7.3	• Clean?	☐ ☐ ☐		3
7.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
7.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
7.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
7.7	Appropriate lighting and air conditioning?	☐ ☐ ☐		3.3
7.8	Recording of temperature and humidity?	☐ ☐ ☐		
7.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
7.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
7.11	Adequate separation of the packaging lines?	☐ ☐ ☐		3.15
	Operations			
7.12	Only *one* product per line?	☐ ☐ ☐		5.44

		Compliance 1 2 3[a]	Remarks	EU Guide
7.13	Check list for clearance before processing a new product/new batch?	☐ ☐ ☐		5.45
7.14	Adequate labeling of the lines (product name and code)?	☐ ☐ ☐		5.46
7.15	Check of all materials delivered to the line (quantity, identity, conformity with order)?	☐ ☐ ☐		5.47
7.16	Cleaning of primary packaging materials?	☐ ☐ ☐		5.48
7.17	Immediate labeling after filling?	☐ ☐ ☐		5.49
7.18	Careful check of all printing processes (code, expiry date)?	☐ ☐ ☐		5.50
7.19	Special safety measures for off-line printing?	☐ ☐ ☐		5.51
7.20	Regular checks of all control devices (code reader, counter, etc.)?	☐ ☐ ☐		5.52
7.21	Printings clear and durable?	☐ ☐ ☐		5.53
7.22	Balancing of printed packaging materials and bulk?	☐ ☐ ☐		5.56
7.23	Destruction of excessive coded packaging material after completion of an order?	☐ ☐ ☐		5.57
7.24	Are the finished products kept in quarantine until final release?	☐ ☐ ☐		5.58
7.25	Appropriate storage after release?	☐ ☐ ☐		5.60
	IPC			
7.26	Checks on identity of bulk and packaging materials?	☐ ☐ ☐		5.47
	Regular line checks on			
7.27	• aspect of the packages	☐ ☐ ☐		5.54a
7.28	• completeness	☐ ☐ ☐		5.54b
7.29	• conformity of quantity and quality of materials with packaging order	☐ ☐ ☐		5.54c
7.30	• correct imprint	☐ ☐ ☐		5.54d
7.31	• correct function of control devices	☐ ☐ ☐		5.54d
	Are the following IPC checks performed?			
7.32	• Leaking	☐ ☐ ☐		
7.33	• Release torque of screw caps	☐ ☐ ☐		
7.34	• pH, density, drop weight, viscosity, sedimentation	☐ ☐ ☐		
8	**DOCUMENTATION**			
	Specifications			
8.1	Specifications for raw/packaging materials available?	☐ ☐ ☐		4.10
	Do they include:			
8.2	• Internal name and code	☐ ☐ ☐		4.11
8.3	• Name of supplier and/or manufacturer?	☐ ☐ ☐		4.11
8.4	• Reference sample (printed pack.mat.)?	☐ ☐ ☐		4.11
8.5	• Sampling procedure?	☐ ☐ ☐		4.11
8.6	• Qualitative/Quantitative specifications with limits?	☐ ☐ ☐		4.11
8.7	• Storage conditions?	☐ ☐ ☐		4.11
8.8	• Maximum storage period?	☐ ☐ ☐		4.11
	Goods receiving?			
8.9	Written procedures for the reception of deliveries?	☐ ☐ ☐		4.19

		Compliance 1 2 3[a]	Remarks	EU Guide
	Do records receipt include:			
8.10	• Product name on labels and delivery note?	☐ ☐ ☐		4.20
8.11	• Internal name and code?	☐ ☐ ☐		4.20
8.12	• Receiving date?	☐ ☐ ☐		4.20
8.13	• Name of supplier and/or manufacturer?	☐ ☐ ☐		4.20
8.14	• Batch number of supplier?	☐ ☐ ☐		4.20
8.15	• Total quantity and number of containers?	☐ ☐ ☐		4.20
8.16	• Allocated internal batch number?	☐ ☐ ☐		4.20
8.17	SOPs for labeling, quarantine and storage conditions of all incoming goods available?	☐ ☐ ☐		4.21
	Sampling procedures (SOPs) include:			
8.18	• Authorized sampling personnel?	☐ ☐ ☐		4.22
8.19	• Methods, equipment and quantities?	☐ ☐ ☐		4.22
8.20	• Safety measures?	☐ ☐ ☐		4.22
	Master formulae			
8.21	Are master formulae for each product and batch size available?	☐ ☐ ☐		4.3
8.22	Is the master formula approved and signed by the authorized persons?	☐ ☐ ☐		4.3
	The master formula includes:			
8.23	• Product name and code?	☐ ☐ ☐		4.14a
8.24	• Description of galenical form, dosage, and batch size?	☐ ☐ ☐		4.14b
8.25	• All active ingredients with name, code, and weight?	☐ ☐ ☐		4.14c
8.26	• All excipients used during manufacture with name, code, and weight?	☐ ☐ ☐		4.14c
8.27	• Yields with limits?	☐ ☐ ☐		4.14d
	Does the working procedure include:			
8.28	• The production line?	☐ ☐ ☐		4.15a
8.29	• Equipment to be used?	☐ ☐ ☐		4.15a
8.30	• Reference to methods for cleaning, assembling, and calibration of machines?	☐ ☐ ☐		4.15b
8.31	• Detailed stepwise manufacturing prescription?	☐ ☐ ☐		4.15c
8.32	• IPCs to be performed with limits?	☐ ☐ ☐		4.15d
8.33	• Precautions to be followed?	☐ ☐ ☐		4.15e
8.34	Are batch records kept for each batch processed?	☐ ☐ ☐		4.17
	Do batch records include:			
8.35	• Protocol of line clearance?	☐ ☐ ☐		4.17
8.36	• Name of the product and batch no.?	☐ ☐ ☐		4.17a
8.37	• Date and time of start and end of production?	☐ ☐ ☐		4.17b
8.38	• Name and initials of responsible workers for each step?	☐ ☐ ☐		4.17c, d
8.39	• Batch and analytical no. and actual weight of all starting materials?	☐ ☐ ☐		4.17e
8.40	• Equipment used?	☐ ☐ ☐		4.17f
8.41	• Results of IPCs with initials of person who carries them out?	☐ ☐ ☐		4.17g
8.42	• Yields of the relevant manufacturing steps?	☐ ☐ ☐		4.17h
8.43	• Detailed notes on problems and process deviations?	☐ ☐ ☐		4.17i

		Compliance 1 2 3[a]	Remarks	EU Guide
8.44	Records on reprocessing of batches?	☐ ☐ ☐		
	Packaging instructions			
8.45	Packaging instructions for each product, package size, and presentation?	☐ ☐ ☐		4.16
	Do they include:			
8.46	• Product name?	☐ ☐ ☐		4.16a
8.47	• Description of galenical form and strength?	☐ ☐ ☐		4.16b
8.48	• Package size?	☐ ☐ ☐		4.17c
8.49	• List of all packaging materials with code for a standard batch size?	☐ ☐ ☐		4.17d
8.50	• Samples of printed packaging materials?	☐ ☐ ☐		4.17e
8.51	• Special precautions?	☐ ☐ ☐		4.17f
8.52	• Description of the process and equipment?	☐ ☐ ☐		4.17g
8.53	• IPCs to be performed with sampling instruction?	☐ ☐ ☐		4.17h
8.54	Are packaging batch records kept for each batch or part batch?	☐ ☐ ☐		4.18
	Do the packaging batch records include:			
8.55	• Protocol of line clearance?	☐ ☐ ☐		4.18
8.56	• Name of the product?	☐ ☐ ☐		4.18a
8.57	• Date and time when operations have been performed?	☐ ☐ ☐		4.18b
8.58	• Name of the responsible person?	☐ ☐ ☐		4.18c
8.59	• Initials of workers carrying out operations?	☐ ☐ ☐		4.18d
8.60	• Notes on identity checks and conformity with packaging instructions?	☐ ☐ ☐		4.18e
8.61	• Results of IPCs	☐ ☐ ☐		4.18e
8.62	• Details of operations and equipment used?	☐ ☐ ☐		4.18f
8.63	• Samples of printed packaging materials with codes (MFD, EXP, Batch no., etc.)?	☐ ☐ ☐		4.18g
8.64	• Record of problems and process deviations?	☐ ☐ ☐		4.18h
8.65	• Quantities of packaging materials delivered, used, destroyed, or returned?	☐ ☐ ☐		4.18i
8.66	• No. of packs consumed?	☐ ☐ ☐		4.18j
	Testing			
	Do the written testing procedures include:			
8.67	• Test methods?	☐ ☐ ☐		4.23
8.68	• Equipment for testing?	☐ ☐ ☐		4.23
8.69	Tests documented?	☐ ☐ ☐		4.23
	Others			
8.70	Procedures for release and rejection of materials and finished products?	☐ ☐ ☐		4.24
8.71	Final release by authorized person?	☐ ☐ ☐		4.24
8.72	Records about distribution of each batch?	☐ ☐ ☐		4.25
	Procedures and protocols about			
8.73	• validation?	☐ ☐ ☐		4.26
8.74	• setup and calibration of equipment?	☐ ☐ ☐		4.26
8.75	• maintenance, cleaning, and disinfection?	☐ ☐ ☐		4.26

		Compliance 1 2 3[a]	Remarks	EU Guide
8.76	• training records?	☐ ☐ ☐		4.26
8.77	• environmental monitoring of production areas?	☐ ☐ ☐		4.26
8.78	• pest control?	☐ ☐ ☐		4.26
8.79	• complaints?	☐ ☐ ☐		4.26
8.80	• recalls?	☐ ☐ ☐		4.26
8.81	• returned goods?	☐ ☐ ☐		4.26
8.82	Instructions for use of manufacturing and testing equipment?	☐ ☐ ☐		4.27
	Log books for major equipment incl. date and name of persons who performed			
8.83	• validation?	☐ ☐ ☐		4.28
8.84	• calibration?	☐ ☐ ☐		4.28
8.85	• maintenance, cleaning, and repair works?	☐ ☐ ☐		4.28
8.86	Chronological records of use of major equipment and manufacturing areas?	☐ ☐ ☐		4.29
9	**QUALITY CONTROL**			**6**
	General requirements			
9.1	Independent QC department available?	☐ ☐ ☐		6.1
9.2	Head of QC well-qualified and sufficiently experienced?	☐ ☐ ☐		6.1
9.3	Qualified personnel available?	☐ ☐ ☐		2.1
9.4	Organization charts available?	☐ ☐ ☐		2.2
9.5	Job descriptions available?	☐ ☐ ☐		2.2
9.6	Responsibilities clearly defined?	☐ ☐ ☐		2.2
9.7	Continuous training programs for QC staff?	☐ ☐ ☐		2.2
9.8	Initial job training for all employees?	☐ ☐ ☐		2.9
9.9	Training records?	☐ ☐ ☐		
9.10	QC personnel admitted to the production rooms for sampling?	☐ ☐ ☐		
	QC Laboratories			
9.11	Suitable for the intended use?	☐ ☐ ☐		3.26
9.12	Laboratories of adequate size?	☐ ☐ ☐		3.26
9.13	Appropriate level of maintenance?	☐ ☐ ☐		3.1
9.14	Adequate separation from the production area?	☐ ☐ ☐		3.26
9.15	Controlled access of authorized personnel only?	☐ ☐ ☐		3.5
9.16	Special laboratory to handle biological samples available?	☐ ☐ ☐		3.29
9.17	Special laboratory to handle radioactive material available?	☐ ☐ ☐		3.29
9.18	Separate recreation rooms for the personnel available?	☐ ☐ ☐		3.30
9.19	Animal laboratories present?	☐ ☐ ☐		3.33
9.20	Animal laboratories separated from other areas?	☐ ☐ ☐		3.33
9.21	Animal laboratories equipped with a separate air handling system?	☐ ☐ ☐		3.33
	QC Documentation			
9.22	Do procedures exist for self-inspection? release or rejection of products or raw material? product complaints? product recalls?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		

		Compliance 1 2 3[a]	Remarks	EU Guide
	local stability testing?	☐ ☐ ☐		
	storage of reference samples?	☐ ☐ ☐		
	validation of analytical procedures?	☐ ☐ ☐		
9.23	Specifications available for	☐ ☐ ☐		6.7
	raw materials?	☐ ☐ ☐		
	bulk products?	☐ ☐ ☐		
	packaging materials?	☐ ☐ ☐		
9.24	Analytical procedures for every product?	☐ ☐ ☐		
9.25	Are Basel methods followed?	☐ ☐ ☐		
9.26	Validation of locally developed test methods?	☐ ☐ ☐		
9.27	Sampling procedures available for			6.7
	raw materials?	☐ ☐ ☐		
	bulk products?	☐ ☐ ☐		
	packaging materials?	☐ ☐ ☐		
9.28	Suppliers' certificates available?	☐ ☐ ☐		6.7
9.29	Calibration program for analytical instruments installed?	☐ ☐ ☐		6.7
9.30	Maintenance program for analytical instruments?	☐ ☐ ☐		6.7
9.31	Retention system for QC records?	☐ ☐ ☐		6.8
9.32	Batch documents stored for expiry + 1 year or 5 years (EEC 75/319, article 22) minimum?	☐ ☐ ☐		6.8
9.33	Are original data like notebooks stored in addition to the batch documents?	☐ ☐ ☐		6.10
9.34	Can the original data be traced back easily and quickly from the analytical report number or batch number?	☐ ☐ ☐		6.10
9.35	Are trend analyses being performed for			6.9
	analytical results?	☐ ☐ ☐		
	yields?	☐ ☐ ☐		
	environmental monitoring data?	☐ ☐ ☐		
	Sampling			
9.36	Written procedures for taking samples?	☐ ☐ ☐		6.11
9.37	Do procedures define			
	method of sampling?	☐ ☐ ☐		
	necessary equipment?	☐ ☐ ☐		
	quantity of the sample?	☐ ☐ ☐		
	subdivision of the sample?	☐ ☐ ☐		
	sample container?	☐ ☐ ☐		
	labeling of samples?	☐ ☐ ☐		
	storage conditions?	☐ ☐ ☐		
	cleaning and storage of sampling equipment?	☐ ☐ ☐		
	identification of containers sampled	☐ ☐ ☐		
9.38	Are samples representative for the batch they are taken from (sampling plan)?	☐ ☐ ☐		6.12
9.39	Are critical steps being surveillanced and validated by additional sampling (e.g., beginning or end of a process)?	☐ ☐ ☐		6.12
9.40	Sample containers labeled with			6.13
	name of the content	☐ ☐ ☐		
	batch number	☐ ☐ ☐		
	date of sampling	☐ ☐ ☐		
	batch containers sampled	☐ ☐ ☐		
9.41	Are samples taken by QC/QA?	☐ ☐ ☐		

		Compliance 1 2 3[a]	Remarks	EU Guide
9.42	Reference samples retained for validity plus 1 year?	☐ ☐ ☐		6.14
9.43	Storage of reference samples under the recommended storage conditions?	☐ ☐ ☐		6.14
9.44	Finished products stored in the final packaging?	☐ ☐ ☐		6.14
9.45	Quantity of the reference sample makes 1 (better 2) complete reanalysis possible?	☐ ☐ ☐		6.14
9.46	Sample room secure?	☐ ☐ ☐		
9.47	Sample room neatly organized and not overcrowded?	☐ ☐ ☐		
	Testing			
9.48	Are the applied analytical methods validated?	☐ ☐ ☐		6.15
9.49	Analytical methods in compliance with the registration?	☐ ☐ ☐		6.16
9.50	Are all results recorded and checked for correctness?	☐ ☐ ☐		6.16
9.51	Are all calculations checked?	☐ ☐ ☐		6.16
9.52	Do the testing protocols contain			6.17
	name and galenical form of material?	☐ ☐ ☐		
	batch number?	☐ ☐ ☐		
	supplier if applicable?	☐ ☐ ☐		
	specification reference?	☐ ☐ ☐		
	method reference?	☐ ☐ ☐		
	analytical results?	☐ ☐ ☐		
	reference to analytical certificates?	☐ ☐ ☐		
	date of the analysis?	☐ ☐ ☐		
	name of the analyst?	☐ ☐ ☐		
	name of the person verifying the data?	☐ ☐ ☐		
	statement of release or rejection?	☐ ☐ ☐		
	date and signature of the release person?	☐ ☐ ☐		
9.53	Are all IPC methods in production approved by QC?	☐ ☐ ☐		6.18
9.54	Are written methods available for the preparation of reagents and volumetric solutions?	☐ ☐ ☐		6.19
9.55	Is a record maintained of standardization of volumetric solutions?	☐ ☐ ☐		6.2
9.56	Are reagents for prolonged use labeled with			6.20
	date of the preparation?	☐ ☐ ☐		
	sign of the preparator?	☐ ☐ ☐		
9.57	Are unstable reagents labeled with			6.20
	expiry date?	☐ ☐ ☐		
	storage conditions?	☐ ☐ ☐		
9.58	Are volumetric solutions labeled with			6.20
	the last date of standardization?	☐ ☐ ☐		
	last current factor?	☐ ☐ ☐		
9.59	Are reference standards labeled with			6.21
	name and potency	☐ ☐ ☐		
	suppliers' reference	☐ ☐ ☐		
	date of receipt	☐ ☐ ☐		
	date of expiry	☐ ☐ ☐		
9.60	Are reference standards stored properly and under the control of a designated person?	☐ ☐ ☐		
9.61	Are animals used for testing of components, materials, or products			
	quarantined before use?	☐ ☐ ☐		
	checked for suitability?	☐ ☐ ☐		
	Are records maintained showing the history of their use?	☐ ☐ ☐		

		Compliance 1 2 3[a]	Remarks	EU Guide
10	**COMPLAINTS AND PRODUCT RECALLS**			**8**
	Complaints			8.1
10.1	Does a written complaint procedure exist?	☐ ☐ ☐		8.2
10.2	Are product complaints carefully reviewed?	☐ ☐ ☐		8.1
10.3	Is a person designated to handle complaints and to decide on measures to be taken?	☐ ☐ ☐		8.1
10.4	Is each complaint concerning a product recorded with all original details?	☐ ☐ ☐		8.3
10.5	Are product complaints thoroughly investigated?	☐ ☐ ☐		8.3
10.6	Is a responsible person of QC involved in the study?	☐ ☐ ☐		8.3
10.7	Is it considered that other batches might be concerned as well?	☐ ☐ ☐		8.4
10.8	Are decisions and measures as a result recorded?	☐ ☐ ☐		8.5
10.9	Is this record added to the corresponding batch documents?	☐ ☐ ☐		8.5
10.10	Are the complaint records regularly revised with respect to specific or recurring problems?	☐ ☐ ☐		8.6
10.11	Are the authorities informed of serious quality problems with a product?	☐ ☐ ☐		8.7
	Recalls			8.8
10.12	Does a written recall procedure exist?	☐ ☐ ☐		8.9
10.13	Is a person nominated responsible for the execution and coordination of a recall?	☐ ☐ ☐		8.8
10.14	Responsible person independent of the marketing and sales organization?	☐ ☐ ☐		8.8
10.15	Are the competent authorities informed of an imminent recall?	☐ ☐ ☐		8.11
10.16	Does the person responsible for a recall have access to the distribution records?	☐ ☐ ☐		8.12
10.17	Do the distribution records contain sufficient information on customers with addresses? phone numbers inside or outside working hours? batches and amounts delivered? medical samples?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		8.12
10.18	Are recalled products stored separately in a secure area?	☐ ☐ ☐		8.13
10.19	Is a final record made including a reconciliation between the delivered and recovered quantities?	☐ ☐ ☐		8.14
10.20	Is the effectiveness of the arrangements for recalls checked critically from time to time?	☐ ☐ ☐		8.15
11	**SELF-INSPECTION**			**9**
11.1	Does a self-inspection procedure exist which defines frequency and program?	☐ ☐ ☐		9.1
11.2	Are self-inspections carried out to check compliance with GMP rules?	☐ ☐ ☐		9.1
11.3	Are self-inspections conducted in an independent and detailed way? by designated competent persons from the company or external experts?	 ☐ ☐ ☐ ☐ ☐ ☐		9.2
11.4	Are self-inspections recorded?	☐ ☐ ☐		9.3

		Compliance 1 2 3[a]	Remarks	EU Guide
11.5	Do reports contain the observations made during a self-inspection? proposals for corrective measures?	 ☐ ☐ ☐ ☐ ☐ ☐		9.3
11.6	Are actions subsequently taken recorded?	☐ ☐ ☐		9.3
12	**CONTRACT MANUFACTURE AND ANALYSIS**			**7**
12.1	Written contract between contract giver and contract acceptor available?	☐ ☐ ☐		7.1
12.2	Are responsibilities and duties clearly defined?	☐ ☐ ☐		7
12.3	All arrangements in accordance with the marketing authorization of the product concerned?	☐ ☐ ☐		7.2
	The contract giver			
12.4	Competence of the acceptor to carry out the work successful and according to GMP assessed?	☐ ☐ ☐		7.3
12.5	Acceptor provided with all the informations necessary to carry out the contract work?	☐ ☐ ☐		7.4
12.6	Acceptor informed of safety aspects?	☐ ☐ ☐		7.4
12.7	Conformance of products supplied by the acceptor ensured?	☐ ☐ ☐		7.5
12.8	Product released by a qualified person on the acceptor's side?	☐ ☐ ☐		7.5
	The contract acceptor			
12.9	Does the acceptor have adequate premises and equipment? knowledge and experience? competent personnel? a manufacturing authorization?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.6
12.10	Does the acceptor ensure that all products or materials delivered to him are suitable?	☐ ☐ ☐		7.7
12.11	There must be no work passed to a third party without the permission of the giver.	☐ ☐ ☐		7.8
12.12	If a third party is involved it must have the necessary manufacturing and analytical information.	☐ ☐ ☐		7.8
	The contract			
12.13	Does the written contract specify the responsibilities?	☐ ☐ ☐		7.10
12.14	Have technical aspects been drawn up by competent persons?	☐ ☐ ☐		7.10
12.15	Release of material and check for compliance with the marketing authorization defined?	☐ ☐ ☐		7.11
12.16	Is defined who is responsible for purchasing of materials? IPC controls testing and release of materials? manufacturing and quality control? sampling? storage of batch documentation?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.12
12.17	Are manufacturing, analytical, and distribution records available to the contract giver?	☐ ☐ ☐		7.13
12.18	Contract permits the giver to visit the facilities of the acceptor?	☐ ☐ ☐		7.14
12.19	In the case of contract analysis: Does the contract acceptor understand that he is subject to inspection by the competent authorities?	☐ ☐ ☐		7.15

		Compliance 1 2 3[a]	Remarks	EU Guide
13	**AUDIT OF SUPPLIERS**			**2.7**
13.1	Supplier audits performed for			
	excipients?	☐ ☐ ☐		
	active substances?	☐ ☐ ☐		
	packaging material?	☐ ☐ ☐		

[a] 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

3

Guideline on the Common Technical Document for the Registration of Pharmaceuticals for Human Use

The International Conference on Harmonization (www.ich.org) has developed a universal format for the registration of pharmaceutical products in the member country states. It took decades to agree on the nature, structure, and substance of this document—it is called Common Technical Document (CTD). This chapter provides an overview of the technical details and data required to complete this filing and to appreciate the great complexity involved in organizing this document. A common format for the technical documentation will significantly reduce the time and resources needed to compile applications for registration of human pharmaceuticals and will ease the preparation of electronic submissions. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements. In addition, exchange of regulatory information between Regulatory Authorities will be simplified. Whether a firm plans to file this document or not, preparing this for every product manufactured helps in cGMP compliance. Provided in this chapter are details regarding the agreed upon common format for the preparation of a well-structured CTD for applications that will be submitted to regulatory authorities.

BACKGROUND

Through the ICH process, considerable harmonization has been achieved among the three regions in the technical requirements for the registration of pharmaceuticals for human use. However, until now, there has been no harmonization of the organization of the registration documents. Each region has its own requirements for the organization of the technical reports in the submission and for the preparation of the summaries and tables. In Japan, the applicants must prepare the GAIYO, which organizes and presents a summary of the technical information. In Europe, expert reports and tabulated summaries are required, and written summaries are recommended. The U.S. FDA has guidance regarding the format and content of the New Drug Application. To avoid the need to generate and compile different registration dossiers, this guideline describes a format for the CTD that will be acceptable in all three regions.

SCOPE OF THE GUIDELINE

This guideline primarily addresses the organization of the information to be presented in registration applications for new pharmaceuticals (including biotechnology-derived products). No reference is provided here to suggest what studies are required, it merely indicates an appropriate format for the data that have been acquired. Applicants should not modify the overall organization of the CTD as outlined in the guideline. However, in the nonclinical and clinical summaries, applicants can modify individual formats if needed to provide the best possible presentation of the technical information, in order to facilitate the understanding and evaluation of the results.

GENERAL PRINCIPLES

Throughout the CTD, the display of information should be unambiguous and transparent, in order to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper (EU and Japan) and 8.5 × 11″ paper (United States). The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font, is recommended for narrative text. Every page should be numbered, according to the granularity document. Acronyms and abbreviations should be defined the first time they are used in each module. References should be cited in accordance with the current edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, International Committee of Medical Journal Editors (ICMJE).

ORGANIZATION OF THE COMMON TECHNICAL DOCUMENT

The CTD is organized into five modules. Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions. Conformance with this guideline should ensure that these four modules are provided in a format acceptable to the regulatory authorities.

Module 1. Administrative Information and Prescribing Information

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

Module 2. Common Technical Document Summaries

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacological class, mode of action, and proposed clinical use. In general, the Introduction should not exceed one page.

Module 2 should contain seven sections in the following order:

- CTD Table of Contents
- CTD Introduction
- Quality Overall Summary

- Nonclinical Overview
- Clinical Overview
- Nonclinical Written and Tabulated Summaries
- Clinical Summary

The organization of these summaries is described in Guidelines for M4Q, M4S, and M4E.

Module 3. Quality

Information on Quality should be presented in the structured format described in Guideline M4Q.

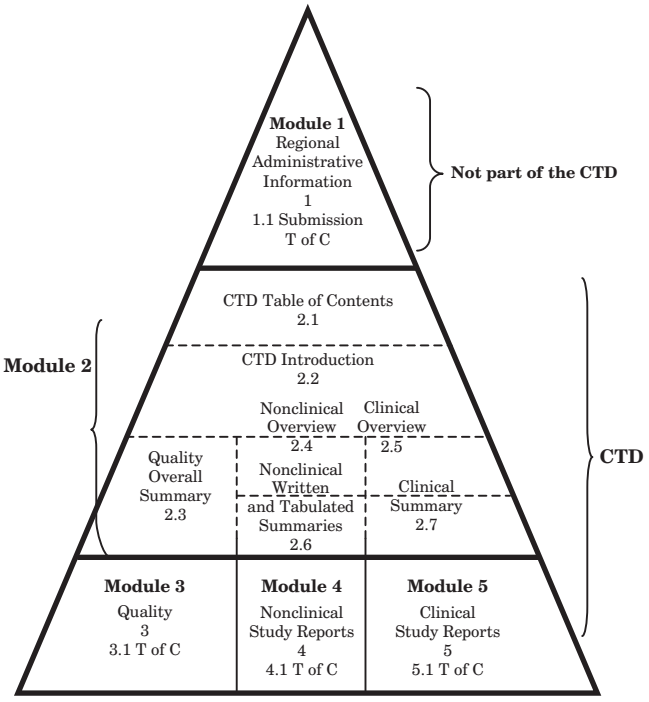
Module 4. Nonclinical Study Reports

The nonclinical study reports should be presented in the order described in Guideline M4S.

Module 5. Clinical Study Reports

The human study reports and related information should be presented in the order described in Guideline M4E.

The overall organization of the CTD is presented on the following pages.



Diagrammatic Representation of the Organization of the ICH CTD Common Technical Document

ORGANIZATION OF THE COMMON TECHNICAL DOCUMENT FOR THE REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

Module 1: Administrative Information and Prescribing Information
- 1.1 Table of Contents of the Submission Including Module 1
- 1.2 Documents Specific to Each Region (e. g., Application Forms, Prescribing Information)

Module 2: Common Technical Document Summaries
- 2.1 Common Technical Document Table of Contents (Modules 2–5)
- 2.2 CTD Introduction
- 2.3 Quality Overall Summary
- 2.4 Nonclinical Overview
- 2.5 Clinical Overview
- 2.6 Nonclinical Written and Tabulated Summaries
  - Pharmacology
  - Pharmacokineticals
  - Toxicology
- 2.7 Clinical Summary
  - Biopharmaceutical Studies and Associated Analytical Methods
  - Clinical Pharmacology Studies
  - Clinical Efficacy
  - Clinical Safety
  - Literature References
  - Synopses of Individual Studies

Module 3: Quality
- 3.1 Table of Contents of Module 3
- 3.2 Body of Data
- 3.3 Literature References

Module 4: Nonclinical Study Reports
- 4.1 Table of Contents of Module 4
- 4.2 Study Reports
- 4.3 Literature References

Module 5: Clinical Study Reports
- 5.1 Table of Contents of Module 5
- 5.2 Tabular Listing of All Clinical Studies
- 5.3 Clinical Study Reports
- 5.4 Literature References

Granularity of Document

The CTD specifies many section headings and numbers. This section provides answer to the following questions:

Could guidance be provided for all modules on headings in relation to document location and the section headings within those documents?

Could guidance also be provided on where in the CTD and eCTD multiple documents can be located in the hierarchy?

As a consequence of this definition, could guidance be given on how documents should be paginated and on what the module Table of Contents should therefore include?

Definition of a Document

A document is defined for a paper submission as a set of pages, numbered sequentially and divided from other documents by a tab (see Document Pagination and Segregation section of this Annex). A document can be equated to a file for an electronic submission. The granularity of the paper and electronic submissions should be equivalent, although if a paper submission is updated to be an electronic submission, some changes in granularity could be introduced to facilitate on-going lifecycle management. In an electronic submission, a new file starts at the same point at which in a paper submission, a tab divides the documents.

In deciding whether one or more documents or files are appropriate, it should be considered that once a particular approach has been adopted, the same approach should be used throughout the life of the dossier since it is the intention that replacement documents/files be provided when information is changed.

The following tables describe the levels in the CTD/eCTD hierarchy at which documents/files should be placed and whether single or multiple documents are appropriate at each point. This describes all sections of a CTD/eCTD but for individual submissions all sections might not be applicable.

Module 2

Module 2	2.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD	
	2.2		
		Introduction	
	2.3 Note 1	2.3.S Note 2	2.3.S.1
			2.3.S.2
			2.3.S.3
			2.3.S.4
			2.3.S.5
			2.3.S.6
			2.3.S.7
		2.3.P Note 3	2.3.P.1
			2.3.P.2
			2.3.P.3
			2.3.P.4
			2.3.P.5
			2.3.P.6
			2.3.P.7
			2.3.P.8
		2.3.A	2.3.A.1
			2.3.A.2
			2.3.A.3
		2.3.R	
	2.4		
	2.5		
	2.6	2.6.1	
		2.6.2	
		2.6.3	
		2.6.4	
		2.6.5	
		2.6.6	
		2.6.7	
	2.7	2.7.1	
		2.7.2	
		2.7.3 Note 4	
		2.7.4	
		2.7.5	
		2.7.6	
Key			
Documents rolled up to this level are not considered appropriate			
One document may be submitted at this level			

Note 1: Optionality of granularity for the Quality Overall Summary is provided in order to accommodate different levels of complexity of products. The applicant can choose the level at which the QOS is managed.
Note 2: One document should be submitted for each drug substance.
Note 3: For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate part "P" document.
Note 4: One document for each indication should be submitted, although closely related indications can be within a single document.

Module 3

Module 3 [Note 1]	3.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD		
	3.2	3.2.S [Note 2]	3.2.S.1	3.2.S.1.1
				3.2.S.1.2
				3.2.S.1.3
			3.2.S.2	3.2.S.2.1
				3.2.S.2.2
				3.2.S.2.3
				3.2.S.2.4
				3.2.S.2.5
				3.2.S.2.6
			3.2.S.3	3.2.S.3.1
				3.2.S.3.2
			3.2.S.4	3.2.S.4.1
				3.2.S.4.2
				3.2.S.4.3
				3.2.S.4.4
				3.2.S.4.5
			3.2.S.5	
			3.2.S.6	
			3.2.S.7	3.2.S.7.1
				3.2.S.7.2
				3.2.S.7.3
		3.2.P [Note 3]	3.2.P.1	
			3.2.P.2	3.2.P.2.1 [Note 4]
				3.2.P.2.2 [Note 4]
				3.2.P.2.3
				3.2.P.2.4
				3.2.P.2.5
				3.2.P.2.6
			3.2.P.3	3.2.P.3.1
				3.2.P.3.2
				3.2.P.3.3

				3.2.P.3.4
				3.2.P.3.5
			3.2.P.4	3.2.P.4.1
				3.2.P.4.2
				3.2.P.4.3
				3.2.P.4.4
				3.2.P.4.5
				3.2.P.4.6
			3.2.P.5	3.2.P.5.1
				3.2.P.5.2
				3.2.P.5.3
				3.2.P.5.4
				3.2.P.5.5
				3.2.P.5.6
			3.2.P.6	
			3.2.P.7	
			3.2.P.8	3.2.P.8.1
				3.2.P.8.2
				3.2.P.8.3
		3.2.A	3.2.A.1	
			3.2.A.2	
			3.2.A.3	
		3.2.R	Note 5	
	3.3	One file		
		per reference Note 6		
Key				
Documents rolled up to this level are not considered appropriate				
One or multiple documents can be submitted at this level				

Note 1: In choosing the level of granularity for this module, the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided in the CTD and eCTD.
Note 2: For a drug product containing more than one drug substance, the information requested for part "S" should be provided in its entirety for each drug substance.
Note 3: For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate part "P," as appropriate.
Note 4: The lower level of headings included in CTD-Q at this point are unlikely to be individual documents or files.
Note 5: Refer to regional guidances.
Note 6: Literature references should be listed in the tables of contents.

Module 4

Module 4	4.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD			
	4.2	4.2.1	4.2.1.1	Studies Note 1	
			4.2.1.2	Studies Note 1	
			4.2.1.3	Studies Note 1	
			4.2.1.4	Studies Note 1	
		4.2.2	4.2.2.1	Studies Note 1	
			4.2.2.2	Studies Note 1	
			4.2.2.3	Studies Note 1	
			4.2.2.4	Studies Note 1	
			4.2.2.5	Studies Note 1	
			4.2.2.6	Studies Note 1	
			4.2.2.7	Studies Note 1	
		4.2.3	4.2.3.1	Studies Note 1	
			4.2.3.2	Studies Note 1	
			4.2.3.	4.2.3.3.1	Studies Note 1
				4.2.3.3.2	Studies Note 1
			4.2.3.4	4.2.3.4.1	Studies Note 1
				4.2.3.4.2	Studies Note 1
				4.2.3.4.3	Studies Note 1
			4.2.3.5	4.2.3.5.1	Studies Note 1
				4.2.3.5.2	Studies Note 1
				4.2.3.5.3	Studies Note 1
				4.2.3.5.4	Studies Note 1
			4.2.3.6	Studies Note 1	
			4.2.3.7	4.2.3.7.1	Studies Note 1
				4.2.3.7.2	Studies Note 1
				4.2.3.7.3	Studies Note 1
				4.2.3.7.4	Studies Note 1
				4.2.3.7.5	Studies Note 1
				4.2.3.7.6	Studies Note 1
				4.2.3.7.7	Studies Note 1
	4.3	One file per			
		reference Note 2			
Key					
Documents rolled up to this level are not considered appropriate					
One or multiple documents can be submitted at this level					

Note 1: Typically, a single document should be provided for each study report included in Module 4. However, where the study report is large (e.g., a carcinogenicity study), the applicant can choose to submit the report as more than one document. In this case, the text portion of the report should be one document and the appendices can be one or more documents. In choosing the level of granularity for these reports, the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided.

Note 2: Literature references should be listed in the tables of contents.

Module 5

Module 5	5.1	The TOC is only called for in the paper version of the CTD; there is no entry needed for the eCTD		
	5.2			
	5.3	5.3.1	5.3.1.1	Studies Note 1
			5.3.1.2	Studies Note 1
			5.3.1.3	Studies Note 1
			5.3.1.4	Studies Note 1
		5.3.2	5.3.2.1	Studies Note 1
			5.3.2.2	Studies Note 1
			5.3.2.3	Studies Note 1
		5.3.3	5.3.3.1	Studies Note 1
			5.3.3.2	Studies Note 1
			5.3.3.3	Studies Note 1
			5.3.3.4	Studies Note 1
			5.3.3.5	Studies Note 1
		5.3.4	5.3.4.1	Studies Note 1
			5.3.4.2	Studies Note 1
		5.3.5 Note 2	5.3.5.1	Studies Note 1
			5.3.5.2	Studies Note 1
			5.3.5.3	Studies Note 1
			5.3.5.4	Studies Note 1
		5.3.6		
		5.3.7	Studies Note 1	
	5.4	One file per reference Note 3		
Key				
Documents rolled up to this level are not considered appropriate				
One document can be submitted at this level				
One or multiple documents can be submitted at this level				

Note 1: The applicants should ordinarily provide the study reports as multiple documents (a synopsis, a main body of the study report and appropriate appendices). Appendices should be organized in accordance with the ICH E3 guideline, which describes the content and format of the clinical study report. In choosing the level of granularity for reports the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided.

Note 2: For applications in support of more than one indication, this section should be repeated for each indication.

Note 3: Literature references should be listed in the tables of content.

Document Pagination and Segregation

Every document should be numbered starting at page one, except for individual literature references, where the existing journal page numbering is considered sufficient. Applicants need not display the number as "1 of *n*," where *n* is the total number of pages in the document. Additionally, all pages of a document should include a unique header or footer that briefly identifies its subject matter. In a paper-based drug submission, a similar identifier should be used on a tab that precedes the document, to facilitate finding that document within the dossier. An abbreviation of the full section number and title can be used.

If a section contains more than one document, a specific Table of Contents for that section can be included to identify the chronology and titles of the documents contained therein, for example,

- Tab with "3.2.S.4.2 Analytical Procedures"
  - Table of Contents, listing the title of Procedure A, Procedure B, Procedure C
- Tab with "3.2.S.4.2 "Procedure A";
  - Procedure A (i.e., document, page 1–*n*)
- Tab with "3.2.S.4.2 "Procedure B";
  - Procedure B (i.e., document, page 1–*n*)
- Tab with "3.2.S.4.2 "Procedure C";
  - Procedure C (i.e., document, page 1–*n*)

If a section contains only a single document (e.g., 3.2.S.1.1 Nomenclature), only a tab identified by "3.2.S.1.1 Nomenclature" should precede the document.

Section Numbering Within Documents

In order to avoid fifth-, sixth-level subheading numbering (e.g., 2.6.6.3.2.1) within a document, the applicant can use a shortened numbering string. In this case, the document number and the name (e.g., 2.6.6 Toxicology Written Summary) should appear in page headers or footers and then section numbering within the document can be used, for example, 1, 1.1, 2, 3, 3.1, 3.2 etc. Use of the full numbering string (e.g., 2.6.6.3.2.1) is also considered acceptable.

Table of Contents Formatting

Module 2

The 2.1 CTD Table of Contents should go down to the third (e.g., 2.3.S) or fourth (e.g., 2.3.S.1) level, depending on how a document is defined for the Quality Overall Summary. (See Definition of a Document for Module 2.)

Module 3

The Table of Contents provided under section 3.1 should cover the high-level section numbering, the associated section heading, and the volume number in the order that they appear in the drug submission. This Table of Contents would be used to identify the contents of Module 3 as defined in the M4Q guideline. It should go down to the fifth level only (e.g., 3.2.P.2.1). Note that additional subsections and subheadings are defined in the M4Q guideline beyond this level (e.g., under 3.2.P.2) and this formatting should be used within the dossier, despite not being included in the 3.1 Table of Contents. The lower level Table of Contents described under Document Pagination and Segregation should be excluded from the 3.1 Table of Contents.

At the applicant's discretion, a Table of Contents can also be included for a particular section that contains multiple documents, in order to identify the chronology and the document subject matter. If there is a desire to introduce additional headers or subsection numbering beyond those which are defined in the M4Q guideline, these should only be included within a document and should be created neither as a separate document nor as a new subsection. In this case, a specific Table of Contents for that document can be included to identify the chronology and titles of the subsections contained therein. These documents and subsections should not appear in the 3.1 Table of Contents.

Furthermore, additional attachments or appendices should not be incorporated into this formatting, except as a document under a section where multiple documents might be provided. In this case, a cross-reference should be made within the relevant section to the attached or appended document. If there is a desire to append or attach additional information to a section that is comprised of only one document, this information should be incorporated within that document.

All Table of Contents title entries should either correspond to heading names and section numbering as defined in the M4Q guideline or to identifiers appearing on tabs (for a paper-based drug submission only), preferably by their full title, which should easily identify any abbreviated title that might be used on the corresponding tab. The Table of Contents should not specify any page numbers.

Literature References should be listed in a Table of Contents specific for this section.

Module 4

The Table of Contents for Module 4 should include all of the numerical items listed in the CTD guideline in order to identify all of the important components of the application (e.g., 4.2.3.5.1 Fertility and Early Embryonic Development) and should continue down to at least the level of the study report. Thus, each study report should be identified in the table of contents. The sections of a study report could be identified in the Module 4 Table of Contents of the dossier or only in the Table of Contents of the individual study report.

Illustration of part of the Module 4 Table of Contents

4.2.3.2	Repeat-Dose Toxicity
Study aa-aaa:	30 day repeat dose toxicity study with drug C in rat
Study bb-bbb:	6 month repeat dose toxicity study with drug C in rat
Study cc-ccc:	30 day repeat dose toxicity study with drug C in dog
Study dd-ddd:	6 month repeat dose toxicity study with drug C in dog
4.2.3.3	Genotoxicity
4.2.3.3.1	In vitro
Study ee-eee:	Ames test with drug C etc.

Module 5

The Table of Contents for Module 5 should include all of the numerical items listed in the CTD guideline in order to identify all of the important components of the application (e.g., 5.3.5.1.1 Placebo-Controlled Trials) and should continue down to at least the level of the clinical study report. Thus, each clinical study report should be identified in the table of contents. The sections of a clinical study report (E3) could be identified in the Module 5 Table of Contents of the dossier or

only in the Table of Contents of the individual clinical study report.

Illustration of part of the Module 5 Table of Contents

5.3.5	Indication Z—Reports of Efficacy and Safety Studies
5.3.5.1	Indication Z—Study Reports of Controlled Clinical Trials Pertinent to the Claimed Indication
5.3.5.1.1	Indication Z—Placebo-Controlled Trials
Study xx-xxx:	A double-blind, placebo-controlled trial of drug A in indication Z
Study yy-yyy:	A double blind. . .
5.3.5.1.2	Indication Z—Active Controlled Trials
Study zz-zzz:	A double blind, active controlled trial of drug A versus drug C in indication Z
5.3.5	Indication Q—Reports of Efficacy and Safety Studies
5.3.5.1	Indication Q—Study Reports of Controlled Clinical Trials Pertinent to the Claimed Indication etc.

Organization of Module 3

MODULE 2: COMMON TECHNICAL DOCUMENT SUMMARIES

2.3: QUALITY OVERALL SUMMARY

The Quality overall summary (QOS) is a summary that follows the scope and the outline of the body of data in Module 3. The QOS should not include information, data, or justification that was not already included in Module 3 or in other parts of the CTD.

The QOS should include sufficient information from each section to provide the quality reviewer with an overview of Module 3. The QOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g., qualification of impurities via toxicological studies discussed under the CTD-S module), including cross-referencing to volume and page number in other Modules.

This QOS normally should not exceed 40 pages of text, excluding tables and figures. For biotech products and products manufactured using more complex processes, the document could be longer but normally should not exceed 80 pages of text (excluding tables and figures).

The *italicized* text below indicates where tables, figures, or other items can be imported directly from Module 3.

INTRODUCTION

The introduction should include proprietary name, nonproprietary name, or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s).

2.3.S DRUG SUBSTANCE (NAME, MANUFACTURER)

2.3.S.1 General Information (Name, Manufacturer)

Information from 3.2.S.1 should be included.

2.3.S.2 Manufacture (Name, Manufacturer)

Information from 3.2.S.2 should include

- information on the manufacturer;
- a brief description of the manufacturing process (including, e.g., reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality;
- a flow diagram, as provided in section 3.2.S.2.2;
- a description of the source and starting material and raw materials of biological origin used in the manufacture of the drug substance, as described in 3.2.S.2.3;
- a discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in 3.2.S.2.4;
- a description of process validation and/or evaluation, as described in 3.2.S.2.5; and
- a brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6. The QOS should also cross-refer to the nonclinical and clinical studies that used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier.

2.3.S.3 Characterization (Name, Manufacturer)

For NCE:

A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1, should be included. When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

For Biotech:

A description of the desired product and product-related substances and a summary of general properties, characteristic features, and characterization data (e.g., primary and higher order structure and biological activity), as described in 3.2.S.3.1, should be included.

For NCE and Biotech:

The QOS should summarize the data on potential and actual impurities arising from the synthesis, manufacture, and/or degradation, and should summarize the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarize the impurity levels in batches of the drug substance used in the nonclinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. The QOS should state how the proposed impurity limits are qualified.

A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate should be included.

2.3.S.4 Control of Drug Substance (Name, Manufacturer)

A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included.

Specification from 3.2.S.4.1 should be provided.

A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.

2.3.S.5 Reference Standards or Materials (Name, Manufacturer)
Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

2.3.S.6 Container Closure System (Name, Manufacturer)
A brief description and discussion of the information, from 3.2.S.6 should be included.

2.3.S.7 Stability (Name, Manufacturer)
This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date, or shelf life, where relevant, as described in 3.2.S.7.1.

The postapproval stability protocol, as described in 3.2.S.7.2, should be included.

A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

2.3.P DRUG PRODUCT (NAME, DOSAGE FORM)

2.3.P.1 Description and Composition of the Drug Product (Name, Dosage Form)
Information from 3.2.P.1 should be provided.
Composition from 3.2.P.1 should be provided.

2.3.P.2 Pharmaceutical Development (Name, Dosage Form)
A discussion of the information and data from 3.2.P.2 should be presented.
A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

2.3.P.3 Manufacture (Name, Dosage Form)
Information from 3.2.P.3 should include

information on the manufacturer;
a brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality;
a flow diagram, as provided under 3.2.P.3.3; and
a brief description of the process validation and/or evaluation, as described in 3.2.P.3.5.

2.3.P.4 Control of Excipients (Name, Dosage Form)
A brief summary on the quality of excipients, as described in 3.2.P.4, should be included.

2.3.P.5 Control of Drug Product (Name, Dosage Form)
A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterization of impurities should be provided.
Specification(s) from 3.2.P.5.1 should be provided.
A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

2.3.P.6 Reference Standards or Materials (Name, Dosage Form)
Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.

2.3.P.7 Container Closure System (Name, Dosage Form)
A brief description and discussion of the information in 3.2.P.7 should be included.

2.3.P.8 Stability (Name, Dosage Form)
A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf life and, if applicable, in-use storage conditions and shelf life should be given.

A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included.

The postapproval stability protocol, as described in 3.2.P.8.2, should be provided.

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment (Name, Manufacturer)
Biotech:
A summary of facility information described under 3.2.A.1 should be included.

2.3.A.2 Adventitious Agents Safety Evaluation (Name, Dosage Form, Manufacturer)
A discussion on measures implemented to control endogenous and adventitious agents in production should be included.

A tabulated summary of the reduction factors for viral clearance from 3.2.A.2, should be provided.

2.3.A.3 Excipients

2.3.R REGIONAL INFORMATION

A brief description of the information specific for the region, as provided under "3.2.R" should be included, where appropriate.

Module 3: Quality

SCOPE OF THE GUIDELINE

This document is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products as defined in the scope of the ICH Guidelines Q 6A ("NCE") and ICH Guideline Q 6B ("Biotech"). This format may also be appropriate for certain other categories of products. To determine the applicability of this format for a particular type of product, applicants should consult with the appropriate regulatory authorities.

The text following the section titles is intended to be explanatory and illustrative only. The content of these sections should include relevant information described in existing ICH guidelines, but harmonized content is not available for all sections. The "Body of Data" in this guideline merely indicates where the information should be located. Neither the type nor the extent of specific supporting data has been addressed in this guideline, and both may depend upon regional guidance.

The section titles of part 3.2.R (Regional Information) represent examples of typical topics of information that are not common to all ICH regions. Hence, the information to be provided in these sections should be based on the relevant regional guidelines.

3.1 TABLE OF CONTENTS OF MODULE 3

A Table of Contents for the filed application should be provided.

3.2 BODY OF DATA

3.2.S DRUG SUBSTANCE (NAME, MANUFACTURER)

3.2.S.1 General Information (Name, Manufacturer)

3.2.S.1.1 Nomenclature (Name, Manufacturer)

Information on the nomenclature of the drug substance should be provided. For example,

- recommended International Nonproprietary Name (INN);
- compendial name, if relevant;
- chemical name(s);
- company or laboratory code;
- other nonproprietary name(s), for example, national name, United States adopted name (USAN), Japanese accepted name (JAN), British approved name (BAN); and
- chemical abstracts service (CAS) registry number.

3.2.S.1.2 Structure (Name, Manufacturer)

NCE:

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

Biotech:

The schematic amino acid sequence indicating glycosylation sites or other posttranslational modifications and relative molecular mass should be provided, as appropriate.

3.2.S.1.3 General Properties (Name, Manufacturer)

A list should provide physicochemical and other relevant properties of the drug substance, including biological activity for biotech.

Reference ICH Guidelines: Q6A and Q6B.

3.2.S.2 Manufacture (Name, Manufacturer)

3.2.S.2.1 Manufacturer(s) (Name, Manufacturer)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

3.2.S.2.2 Description of Manufacturing Process and Process Controls (Name, Manufacturer)

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example,

NCE:

A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment, and operating conditions (e.g., temperature, pressure, pH, time).

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2.S.2.5.

Biotech:

Information should be provided on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage, and shipping conditions.

Batch(es) and scale definition

An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided.

Cell culture and harvest

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g., cells contained in one or more vials(s) of the Working Cell Bank up to the last harvesting operation. The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature, should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in 3.2.S.2.4) should be identified.

A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; culture media and other additives (details provided in 3.2.S.2.3); major equipment (details provided in 3.2.A.1); and process controls, including in-process tests and operational parameters, process steps, equipment, and intermediates with acceptance criteria (details provided in 3.2.S.2.4). Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided. (Details on shipping and storage provided in 3.2.S.2.4.)

Purification and modification reactions

A flow diagram should be provided that illustrates the purification steps (i.e., unit operations) from the crude harvest(s) up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (e.g., volumes, pH, critical processing time, holding times, temperatures and elution profiles and selection of fraction, storage of intermediate, if applicable) should be included. Critical steps for which specifications are established as mentioned in 3.2.S.2.4 should be identified.

A description of each process step (as identified in the flow diagram) should be provided. The description should include information on, for example, scale, buffers and other reagents (details provided in 3.2.S.2.3, major equipment (details provided in 3.2.A.1), and materials. For materials such as membranes and chromatography resins, information for conditions of use and reuse also should be provided. (Equipment details in 3.2.A.1; validation studies for the reuse and regeneration of columns and membranes in 3.2.S.2.5.) The description should include process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment, and intermediates. (Details in 3.2.S.2.4.)

Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. (Details should be given in 3.2.S.2.5.)

Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided (details on shipping and storage provided in 3.2.S.2.4).

Filling, storage, and transportation (shipping)
A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided. (Details in 3.2.S.2.4.) The container closure system(s) used for storage of the drug substance (details in 3.2.S.6) and storage and shipping conditions for the drug substance should be described.

Reference ICH Guidelines: Q5A, Q5B, and Q6B.

3.2.S.2.3 Control of Materials (Name, Manufacturer)
Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials (including biologically sourced materials, for example, media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically sourced materials, this can include information regarding the source, manufacture, and characterization. (Details in 3.2.A.2 for both NCE and Biotech.)

Reference ICH Guidelines: Q6A and Q6B.

Biotech:
Control of source and starting materials of biological origin
Summaries of viral safety information for biologically sourced materials should be provided. (Details in 3.2.A.2.)

Source, history, and generation of the cell substrate
Information on the source of the cell substrate and analysis of the expression construct used to genetically modify cells and incorporated in the initial cell clone used to develop the Master Cell Bank should be provided as described in Q5B and Q5D.

Cell banking system, characterization, and testing
Information on the cell banking system, quality control activities, and cell line stability during production and storage [including procedures used to generate the Master and Working Cell Bank(s)] should be provided as described in Q5B and Q5D.

Reference ICH Guidelines: Q5A, Q5B, Q5C, and Q5D.

3.2.S.2.4 Controls of Critical Steps and Intermediates (Name, Manufacturer)
Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Reference ICH Guidelines: Q6A and Q6B.

Additionally for Biotech: Stability data supporting storage conditions should be provided.

Reference ICH Guideline: Q5C.

3.2.S.2.5 Process Validation and/or Evaluation (Name, Manufacturer)
Process validation and/or evaluation studies for aseptic processing and sterilization should be included.

Biotech:
Sufficient information should be provided on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification).

The plan for conducting the study should be described and the results, analysis, and conclusions from the executed study or studies should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., 3.2.S.2.4, 3.2.S.4.3) or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in 3.2.A.2.

3.2.S.2.6 Manufacturing Process Development (Name, Manufacturer)
NCE:
A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

Reference ICH Guideline: Q3A.

Biotech:
The developmental history of the manufacturing process, as described in 3.2.S.2.2, should be provided. The description of change(s) made to the manufacture of drug substance batches used in support of the marketing application (e.g., nonclinical or clinical studies) should include, for example, changes to the process or to critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, should be provided.

The significance of the change should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches should be provided to determine the impact on quality of the drug substance (see Q6B for additional guidance).A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. Cross-reference to the location of these studies in other modules of the submission should be included.

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

Reference ICH Guideline: Q6B.

3.2.S.3 Characterization (Name, Manufacturer)

3.2.S.3.1 Elucidation of Structure and Other Characteristics (Name, Manufacturer)

NCE:

Confirmation of structure based on, for example, synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs should also be included.

Reference ICH Guideline: Q6A.

Biotech:

For desired product and product-related substances, details should be provided on primary, secondary, and higher-order structure, posttranslational forms (e.g., glycoforms), biological activity, purity, and immunochemical properties, when relevant.

Reference ICH Guideline: Q6B.

3.2.S.3.2 Impurities (Name, Manufacturer)

Information on impurities should be provided.

Reference ICH Guidelines: Q3A, Q3C, Q5C, Q6A, and Q6B.

3.2.S.4 Control of Drug Substance (Name, Manufacturer)

3.2.S.4.1 Specification (Name, Manufacturer)

The specification for the drug substance should be provided.

Reference ICH Guidelines: Q6A and Q6B.

3.2.S.4.2 Analytical Procedures (Name, Manufacturer)

The analytical procedures used for testing the drug substance should be provided.

Reference ICH Guidelines: Q2A and Q6B.

3.2.S.4.3 Validation of Analytical Procedures (Name, Manufacturer)

Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance, should be provided.

Reference ICH Guidelines: Q2A, Q2B, and Q6B.

3.2.S.4.4 Batch Analyses (Name, Manufacturer)

Description of batches and results of batch analyses should be provided.

Reference ICH Guidelines: Q3A, Q3C, Q6A, and Q6B.

3.2.S.4.5 Justification of Specification (Name, Manufacturer)

Justification for the drug substance specification should be provided.

Reference ICH Guidelines: Q3A, Q3C, Q6A, and Q6B.

3.2.S.5 Reference Standards or Materials (Name, Manufacturer)

Information on the reference standards or reference materials used for testing of the drug substance should be provided.

Reference ICH Guidelines: Q6A and Q6B.

3.2.S.6 Container Closure System (Name, Manufacturer)

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Noncompendial methods (with validation) should be included, where appropriate.

For nonfunctional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the drug substance, including sorption to container and leaching, and/or safety of materials of construction.

3.2.S.7 Stability (Name, Manufacturer)

3.2.S.7.1 Stability Summary and Conclusions (Name, Manufacturer)

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf life, as appropriate.

Reference ICH Guidelines: Q1A, Q1B, and Q5C.

3.2.S.7.2 Postapproval Stability Protocol and Stability Commitment (Name, Manufacturer)

The postapproval stability protocol and stability commitment should be provided.

Reference ICH Guidelines: Q1A and Q5C.

3.2.S.7.3 Stability Data (Name, Manufacturer)

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Reference ICH Guidelines: Q1A, Q1B, Q2A, Q2B, and Q5C.

3.2.P DRUG PRODUCT (NAME, DOSAGE FORM)

3.2.P.1 Description and Composition of the Drug Product (name, dosage form)

A description of the drug product and its composition should be provided. The information provided should include, for example:

- description of the dosage form;
- composition, that is list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications);
- description of accompanying reconstitution diluent(s); and
- type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

Reference ICH Guidelines: Q6A and Q6B.

3.2.P.2 Pharmaceutical Development (Name, Dosage Form)

The pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and

describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance, and drug product quality. Supportive data and results from specific studies or published literature can be included within or attached to the pharmaceutical development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

Reference ICH Guidelines: Q6A and Q6B.

3.2.P.2.1 Components of the Drug Product (Name, Dosage Form)

3.2.P.2.1.1 Drug substance (name, dosage form)

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g., water content, solubility, particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed.

For combination products, the compatibility of drug substances with each other should be discussed.

3.2.P.2.1.2 Excipients (name, dosage form)

The choice of excipients listed in 3.2.P.1, their concentration, their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

3.2.P.2.2 Drug Product (Name, Dosage Form)

3.2.P.2.2.1 Formulation development (name, dosage form)

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e., composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies [e.g., bioequivalence (BE)] should be discussed when appropriate.

3.2.P.2.2.2 Overages (name, dosage form)

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

3.2.P.2.2.3 Physicochemical and biological properties (name, dosage form)

Parameters relevant to the performance of the drug product, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheologic properties, biological activity or potency, and/or immunological activity, should be addressed.

3.2.P.2.3 Manufacturing Process Development (Name, Dosage Form)

The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Differences between the manufacturing process(es) used to produce pivotal clinical batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

3.2.P.2.4 Container Closure System (Name, Dosage form)

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping), and use of the drug product should be discussed. This discussion should consider, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the drug product).

3.2.P.2.5 Microbiological Attributes (Name, Dosage Form)

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for nonsterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

3.2.P.2.6 Compatibility (Name, Dosage Form)

The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.

3.2.P.3 Manufacture (Name, Dosage Form)

3.2.P.3.1 Manufacturer(s) (Name, Dosage Form)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

3.2.P.3.2 Batch Formula (Name, Dosage Form)

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.

3.2.P.3.3 Description of Manufacturing Process and Process Controls (Name, Dosage Form)

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests, or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging, that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogenizer) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in section 3.2.P.3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.2.P.3.3).

Additionally for Biotech, see 3.2.A.1 for facilities, if appropriate.

Reference ICH Guideline: Q6B.

3.2.P.3.4 Controls of Critical Steps and Intermediates (Name, Dosage Form)
Critical steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps identified in 3.2.P.3.3 of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Reference ICH Guidelines: Q2A, Q2B, Q6A, and Q6B.

3.2.P.3.5 Process Validation and/or Evaluation (Name, Dosage Form)
Description, documentation, and results of the validation and/or evaluation studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilization process or aseptic processing or filling). Viral safety evaluation should be provided in 3.2.A.2, if necessary.

Reference ICH Guideline: Q6B.

3.2.P.4 Control of Excipients (Name, Dosage Form)

3.2.P.4.1 Specifications (Name, Dosage Form)
The specifications for excipients should be provided.

Reference ICH Guideline: Q6A and Q6B.

3.2.P.4.2 Analytical Procedures (Name, Dosage Form)
The analytical procedures used for testing the excipients should be provided, where appropriate.

Reference ICH Guidelines: Q2A and Q6B.

3.2.P.4.3 Validation of Analytical Procedures (Name, Dosage Form)
Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Reference ICH Guidelines: Q2A, Q2B, and Q6B.

3.2.P.4.4 Justification of Specifications (Name, Dosage Form)
Justification for the proposed excipient specifications should be provided, where appropriate.

Reference ICH Guidelines: Q3C and Q6B.

3.2.P.4.5 Excipients of Human or Animal Origin (Name, Dosage Form)
For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources; specifications; description of the testing performed; viral safety data.) (Details in 3.2.A.2.)

Reference ICH Guidelines: Q5A, Q5D, and Q6B.

3.2.P.4.6 Novel Excipients (Name, Dosage Form)
For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterization, and controls, with cross-references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format. (Details in 3.2.A.3.)

3.2.P.5 Control of Drug Product (Name, Dosage Form)

3.2.P.5.1 Specification(s) (Name, Dosage Form)
The specification(s) for the drug product should be provided.

Reference ICH Guidelines: Q3B, Q6A, and Q6B.

3.2.P.5.2 Analytical Procedures (Name, Dosage Form)
The analytical procedures used for testing the drug product should be provided.

Reference ICH Guidelines: Q2A and Q6B.

3.2.P.5.3 Validation of Analytical Procedures (Name, Dosage Form)
Analytical validation information, including experimental data, for the analytical procedures used for testing the drug product, should be provided.

Reference ICH Guidelines: Q2A, Q2B, and Q6B.

3.2.P.5.4 Batch Analyses (Name, Dosage Form)
A description of batches and results of batch analyses should be provided.

Reference ICH Guidelines: Q3B, Q3C, Q6A, and Q6B.

3.2.P.5.5 Characterization of Impurities (Name, Dosage Form)
Information on the characterization of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities".

Reference ICH Guidelines: Q3B, Q5C, Q6A, and Q6B.

3.2.P.5.6 Justification of Specification(s) (Name, Dosage Form)
Justification for the proposed drug product specification(s) should be provided.

Reference ICH Guidelines: Q3B, Q6A, and Q6B.

3.2.P.6 Reference Standards or Materials (Name, Dosage Form)

Information on the reference standards or reference materials used for testing of the drug product should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials".

Reference ICH Guidelines: Q6A and Q6B.

3.2.P.7 Container Closure System (Name, Dosage Form)

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification. The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Noncompendial methods (with validation) should be included where appropriate.

For nonfunctional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in 3.2.P.2.

3.2.P.8 Stability (Name, Dosage Form)

3.2.P.8.1 Stability Summary and Conclusion (Name, Dosage Form)
The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf life, and, if applicable, in-use storage conditions and shelf life.

Reference ICH Guidelines: Q1A, Q1B, Q3B and Q5C, Q6A.

3.2.P.8.2 Postapproval Stability Protocol and Stability Commitment (name, dosage form)
The postapproval stability protocol and stability commitment should be provided.

Reference ICH Guidelines: Q1A and Q5C.

3.2.P.8.3 Stability Data (Name, Dosage Form)
Results of the stability studies should be presented in an appropriate format (e.g., tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Information on characterization of impurities is located in 3.2.P.5.5.

Reference ICH Guidelines: Q1A, Q1B, Q2A, Q2B, and Q5C.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment (Name, Manufacturer)

Biotech:

A diagram should be provided illustrating the manufacturing flow, including movement of raw materials, personnel, waste, and intermediate(s) in and out of the manufacturing areas. Information should be presented with respect to adjacent areas or rooms that may be of concern for maintaining integrity of the product.

Information on all developmental or approved products manufactured or manipulated in the same areas as the applicant's product should be included.

A summary description of product-contact equipment, and its use (dedicated or multiuse) should be provided. Information on preparation, cleaning, sterilization, and storage of specified equipment and materials should be included, as appropriate.

Information should be included on procedures (e.g., cleaning and production scheduling) and design features of the facility (e.g., area classifications) to prevent contamination or cross-contamination of areas and equipment, where operations for the preparation of cell banks and product manufacturing are performed.

3.2.A.2 Adventitious Agents Safety Evaluation (Name, Dosage Form, Manufacturer)

Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

For nonviral adventitious agents:

Detailed information should be provided on the avoidance and control of nonviral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process, and agent.

Reference ICH Guidelines: Q5A, Q5D, and Q6B.

For viral adventitious agents:

Detailed information from viral safety evaluation studies should be provided in this section. Viral evaluation studies should demonstrate that the materials used in production are considered safe, and that the approaches used to test, evaluate, and eliminate the potential risks during manufacturing are suitable. The applicant should refer to Q5A, Q5D, and Q6B for further guidance.

Materials of biological origin

Information essential to evaluate the virologic safety of materials of animal or human origin (e.g., biological fluids, tissue, organ, cell lines) should be provided. (See related information in 3.2.S.2.3, and 3.2.P.4.5.) For cell lines, information on the selection, testing, and safety assessment for potential viral contamination of the cells and viral qualification of cell banks should also be provided. (See related information in 3.2.S.2.3.)

Testing at appropriate stages of production

The selection of virologic tests that are conducted during manufacturing (e.g., cell substrate, unprocessed bulk, or postviral clearance testing) should be justified. The type of test, sensitivity and specificity of the test, if applicable, and frequency of testing should be included. Test results to confirm, at an appropriate stage of manufacture, that the product is free from viral contamination should be provided. (See related information in 3.2.S.2.4 and 3.2.P.3.4.)

Viral testing of unprocessed bulk

In accordance with Q5A and Q6B, results for viral testing of unprocessed bulk should be included.

Viral clearance studies

In accordance with Q5A, the rationale and action plan for assessing viral clearance and the results and evaluation of the viral clearance studies should be provided. Data can include those that demonstrate the validity of the scaled-down model compared to the commercial scale process; the adequacy of viral inactivation or removal procedures for manufacturing equipment and materials; and manufacturing steps that are capable of removing or inactivating viruses. (See related information in 3.2.S.2.5 and 3.2.P.3.5.)

Reference ICH Guidelines: Q5A, Q5D, and Q6B.

3.2.A.3 Excipients

3.2.R REGIONAL INFORMATION

Any additional drug substance and/or drug product information specific to each region should be provided in section R of the application. Applicants should consult the appropriate regional guidelines and/or regulatory authorities for additional guidance.

Some examples are as follows:

- **Executed batch records (USA only)**
- **Method validation package (USA only)**
- **Comparability protocols (USA only)**
- **Process validation scheme for the drug product (EU only)**

Where validation is still to be completed, a summary of the studies intended to be conducted should be provided.

- **Medical device (EU only)**

3.3 LITERATURE REFERENCES

Key literature referenced should be provided, if applicable.

Organization of Module 4

Nonclinical Overview and Nonclinical Summaries of Module 2

Module 2: Common Technical Document Summaries

General Principles of Nonclinical Overview and Summaries

This guideline provides recommendations for the harmonization of the Nonclinical Overview, Nonclinical Written Summary, and Nonclinical Tabulated Summaries.

The primary purpose of the Nonclinical Written and Tabulated Summaries should be to provide a comprehensive factual synopsis of the nonclinical data. The interpretation of the data, the clinical relevance of the findings, cross-linking with the quality aspects of the pharmaceutical, and the implications of the nonclinical findings for the safe use of the pharmaceutical (i.e., as applicable to labeling) should be addressed in the overview.

2.4 NONCLINICAL OVERVIEW

The Nonclinical Overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overview should not exceed about 30 pages.

General Aspects

The Nonclinical Overview should present an integrated and critical assessment of the pharmacological, PK, and toxicological evaluation of the pharmaceutical. Where relevant guidelines on the conduct of studies exist, these should be taken into consideration, and any deviation from these guidelines should be discussed and justified. The nonclinical testing strategy should be discussed and justified. There should be comment on the GLP status of the studies submitted. Any association between nonclinical findings and the quality characteristics of the human pharmaceutical, the results of clinical trials, or effects seen with related products should be indicated, as appropriate.

Except for biotechnology-derived products, an assessment of the impurities and degradants present in the drug substance and product should be included along with what is known of their potential pharmacological and toxicological effects. This assessment should form part of the justification for proposed impurity limits in the drug substance and product, and be appropriately cross-referenced to the quality documentation. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the nonclinical studies and the product to be marketed should be discussed. For biotechnology-derived products, comparability of material used in nonclinical studies, clinical studies, and proposed for marketing should be assessed. If a drug product includes a novel excipient, an assessment of the information regarding its safety should be provided.

Relevant scientific literature and the properties of related products should be taken into account. If detailed references to published scientific literature are to be used in place of studies conducted by the applicant, this should be supported by an appropriate justification that reviews the design of the studies and any deviations from available guidelines. In addition, the availability of information on the quality of batches of drug substance used in these referenced studies should be discussed.

The Nonclinical Overview should contain appropriate reference citations to the Tabulated Summaries, in the following format: (Table X.X, Study/Report Number).

Content and Structural Format

The Nonclinical Overview should be presented in the following sequence:

Overview of the Nonclinical Testing Strategy
Pharmacology
Pharmacokinetics
Toxicology
Integrated Overview and Conclusions
List of Literature References

Studies conducted to establish the pharmacodynamic (PD) effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise.

The assessment of the PK, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the PK models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (e.g., impact of the disease states, changes in physiology, antiproduct antibodies, cross-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Interspecies comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, Cmax, and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

The onset, severity, and duration of the toxic effects, their dose-dependency and degree of reversibility (or irreversibility), and species- or gender-related differences should be evaluated and important features discussed, particularly with regard to the following:

- pharmacodynamics;
- toxic signs;
- causes of death;
- pathologic findings;
- genotoxic activity—the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds;
- carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data;
- the carcinogenic risk to humans—if epidemiologic data are available, they should be taken into account;
- fertility, embryofetal development, pre-and postnatal toxicity;
- studies in juvenile animals;
- the consequences of use before and during pregnancy, during lactation, and during pediatric development;
- local tolerance; and
- other toxicity studies/studies to clarify special problems.

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a

certain effect/phenomenon are brought together. Extrapolation of the data from animals to humans should be considered in relation to the following:

- Animal species used.
- Numbers of animals used.
- Routes of administration employed.
- Dosages used.
- Duration of treatment or of the study.
- Systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in humans at the maximum recommended human dose. Tables or figures summarizing this information are recommended.
- The effect of the drug substance observed in nonclinical studies in relation to that expected or observed in humans.

If alternatives to whole animal experiments are employed, their scientific validity should be discussed.

The Integrated Overview and Conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, PKs, and toxicology results into account, the implications of the nonclinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labeling).

2.6 NONCLINICAL WRITTEN AND TABULATED SUMMARIES

Nonclinical Written Summaries

Introduction

This guideline is intended to assist authors in the preparation of nonclinical pharmacology, PKs, and toxicology written summaries in an acceptable format. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The sequence and content of the Nonclinical Written Summary sections are described below. It should be emphasized that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results.

Whenever appropriate, age- and gender-related effects should be discussed. Relevant findings with stereoisomers and/or metabolites should be included, as appropriate. Consistent use of units throughout the summaries will facilitate their review.A table for converting units might also be useful.

In the Discussion and Conclusion sections, information should be integrated across studies and across species, and exposure in the test animals should be related to exposure in humans given the maximum intended doses.

General Presentation Issues

Order of presentation of information within sections

When available, in vitro studies should precede in vivo studies.

Where multiple studies of the same type need to be summarized within the PKs and toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).

Species should be ordered as follows:

- Mouse
- Rat
- Hamster
- Other rodent
- Rabbit
- Dog
- Nonhuman primate
- Other nonrodent mammal
- Nonmammals.

Routes of administration should be ordered as follows:

- The intended route for human use
- Oral
- Intravenous
- Intramuscular
- Intraperitoneal
- Subcutaneous
- Inhalation
- Topical
- Others

Use of Tables and Figures

Although the Nonclinical Written Summaries are envisaged to be composed mainly of text, some information contained within them might be more effectively and/or concisely communicated through the use of appropriate tables or figures. Examples of formats that might be included in the Written Summaries are shown in Appendix A.

To allow authors flexibility in defining the optimal structure for the Written Summaries, tables and figures should preferably be included within the text. Alternatively, they could be grouped together at the end of each of the Nonclinical Written Summaries.

Throughout the text, reference citations to the Tabulated Summaries should be included, in the following format: (Table X.X, Study/Report Number).

Length of Nonclinical Written Summaries

Although there is no formal limit to the length of the Nonclinical Written Summaries, it is recommended that the total length of the three Nonclinical Written Summaries in general not exceed 100 to 150 pages.

Sequence of Written Summaries and Tabulated Summaries

The following order is recommended:

- Introduction
- Written Summary of Pharmacology
- Tabulated Summary of Pharmacology
- Written Summary of Pharmacokinetics
- Tabulated Summary of Pharmacokinetcs
- Written Summary of Toxicology
- Tabulated Summary of Toxicology

Content of Nonclinical Written and Tabulated Summaries

2.6.1 Introduction

The aim of this section should be to introduce the reviewer to the pharmaceutical and to its proposed clinical use. The following key elements should be covered:

- Brief information concerning the pharmaceutical's structure (preferably, a structure diagram should be provided) and pharmacological properties.

- Information concerning the pharmaceutical's proposed clinical indication, dose, and duration of use.

2.6.2 Pharmacology Written Summary

Within the Pharmacology Written Summary, the data should be presented in the following sequence:

- Brief Summary
- Primary Pharmacodynamics
- Secondary Pharmacodynamics
- Safety Pharmacology
- Pharmacodynamic Drug Interactions
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

2.6.2.1 Brief Summary

The principal findings from the pharmacology studies should be briefly summarized in approximately two to three pages. This section should begin with a brief description of the content of the pharmacological data package, pointing out any notable aspects such as the inclusion/exclusion of particular data (e.g., lack of an animal model).

2.6.2.2 Primary Pharmacodynamics

Studies on primary pharmacodynamics should be summarized and evaluated. Where possible, it would be helpful to relate the pharmacology of the drug to available data (in terms of selectivity, safety, potency, etc.) on other drugs in the class.

2.6.2.3 Secondary Pharmacodynamics

Studies on secondary pharmacodynamics should be summarized by organ system, where appropriate, and evaluated in this section.

2.6.2.4 Safety Pharmacology

Safety pharmacology studies should be summarized and evaluated in this section. In some cases, secondary PD studies can contribute to the safety evaluation when they predict or assess potential adverse effect(s) in humans. In such cases, these secondary PD studies should be considered along with safety pharmacology studies.

2.6.2.5 Pharmacodynamic Drug Interactions

If they have been performed, PD drug interaction studies should be briefly summarized in this section.

2.6.2.6 Discussion and Conclusions

This section provides an opportunity to discuss the pharmacological evaluation and to consider the significance of any issues that arise.

2.6.2.7 Tables and Figures

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

2.6.3 Pharmacology Tabulated Summary (See Appendix B)

2.6.4 Pharmacokinetics Written Summary

The sequence of the Pharmacokinetics Written Summary should be as follows:

- Brief Summary
- Methods of Analysis
- Absorption
- Distribution
- Metabolism
- Excretion
- Pharmacokinetic Drug Interactions
- Other Pharmacokinetic Studies
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

2.6.4.1 Brief Summary

The principal findings from the PKs studies should be briefly summarized in approximately two to three pages. This section should begin with a description of the scope of the PK evaluation, emphasizing, for example, whether the species and strains examined were those used in the pharmacology and toxicology evaluations, and whether the formulations used were similar or identical.

2.6.4.2 Methods of Analysis

This section should contain a brief summary of the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure. If possible, validation data for the analytical method and stability of biological samples should be discussed in this section. The potential impact of different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.

2.6.4.3 Absorption

The following data should be summarized in this section:

- Absorption (extent and rate of absorption, in vivo and in situ studies)
- Kinetic parameters, bioequivalence, and/or bioavailability (serum/plasma/blood PK studies)

2.6.4.4 Distribution

The following data should be summarized in this section:

- Tissue distribution studies
- Protein binding and distribution in blood cells
- Placental transfer studies

2.6.4.5 Metabolism (Interspecies Comparison)

The following data should be summarized in this section:

- Chemical structures and quantities of metabolites in biological samples
- Possible metabolic pathways
- Presystemic metabolism (GI/hepatic first-pass effects)
- In vitro metabolism including P450 studies
- Enzyme induction and inhibition

2.6.4.6 Excretion

The following data should be summarized in this section:

- Routes and extent of excretion
- Excretion in milk

2.6.4.7 Pharmacokinetic Drug Interactions

If they have been performed, nonclinical pharmacokinetic drug-interaction studies (in vitro and/or in vivo) should be briefly summarized in this section.

2.6.4.8 Other Pharmacokinetic Studies

If studies have been performed in nonclinical models of disease (e.g., renally impaired animals), they should be summarized in this section.

2.6.4.9 Discussion and Conclusions

This section provides an opportunity to discuss the PK evaluation and to consider the significance of any issues that arise.

2.6.4.10 Tables and Figures

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, there is the option of including tables and figures at the end of the summary.

2.6.5 Pharmacokinetics Tabulated Summary (See Appendix B)

2.6.6 Toxicology Written Summary

The sequence of the Toxicology Written Summary should be as follows:

- Brief Summary
- Single-Dose Toxicity
- Repeat-Dose Toxicity
- Genotoxicity
- Carcinogenicity
- Reproductive and Developmental Toxicity
- Studies in Juvenile Animals
- Local Tolerance
- Other Toxicity Studies
- Discussion and Conclusions
- Tables and Figures (either here or included in text)

2.6.6.1 Brief Summary

The principal findings from the toxicology studies should be briefly summarized in a few pages (generally not more than six). In this section, the extent of the toxicological evaluation can be indicated by the use of a table listing the principal toxicological studies (results should not be presented in this table), for example:

TOXICOLOGY PROGRAM

Study Type and Duration	Route of Administration	Species	Compound Administered[a]
Single-dose toxicity	po and IV	Rat and mouse	Parent drug
Single-dose toxicity	po and IV	Rat and mouse	Metabolite X
Repeat-dose toxicity			
1 mo	po	Rat and dog	Parent drug
6 mo	po	Rat	Parent drug
9 mo	po	Dog	Parent drug

[a]This column required only if metabolite(s) are investigated.

The scope of the toxicological evaluation should be described in relation to the proposed clinical use. A comment on the GLP status of the studies should be included.

2.6.6.2 Single-Dose Toxicity

The single-dose data should be very briefly summarized, in order by species, by route. In some instances, it may be helpful to provide the data in the form of a table.

2.6.6.3 Repeat-Dose Toxicity (Including Supportive Toxicokinetics Evaluation)

Studies should be summarized in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings (e.g., nature and severity of target organ toxicity, dose (exposure)/response relationships, no observed adverse effect levels, etc.). Nonpivotal studies can be summarized in less detail (pivotal studies are the definitive GLP studies specified by ICH Guideline M3).

2.6.6.4 Genotoxicity

Studies should be briefly summarized in the following order:

- in vitro nonmammalian cell system;
- in vitro mammalian cell system;
- in vivo mammalian system (including supportive toxicokinetics evaluation); and
- other systems.

2.6.6.5 Carcinogenicity (Including Supportive Toxicokinetics Evaluations)

A brief rationale should explain why the studies were chosen and the basis for high-dose selection. Individual studies should be summarized in the following order:

- Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- Other studies

2.6.6.6 Reproductive and Developmental Toxicity (Including Range-Finding Studies and Supportive Toxicokinetics Evaluations)

Studies should be summarized in the following order, giving brief details of the methodology and highlighting important findings:

- Fertility and early embryonic development
- Embryo–fetal development
- Prenatal and postnatal development, including maternal function
- Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted

If modified study designs are used, the subheadings should be modified accordingly.

2.6.6.7 Local Tolerance

If local tolerance studies have been performed, they should be summarized in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings.

2.6.6.8 Other Toxicity Studies (If Available)

If other studies have been performed, they should be summarized. When appropriate, the rationale for conducting the studies should be provided.

- Antigenicity
- Immunotoxicity
- Mechanistic studies (if not reported elsewhere)
- Dependence
- Studies on metabolites
- Studies on impurities
- Other studies

2.6.6.9 Discussion and Conclusions
This section should provide an opportunity to discuss the toxicological evaluation and the significance of any issues that arise. Tables or figures summarizing this information are recommended.

2.6.6.10 Tables and Figures
Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

2.6.7 Toxicology Tabulated Summary (See Appendix B)

Nonclinical Tabulated Summaries
It is recommended that summary tables for the nonclinical information in the CTD be provided in the format outlined in this guideline. Applicants can modify the format if needed to provide the best possible presentation of the information and to facilitate the understanding and evaluation of the results.

This guideline is not intended to indicate what studies are requested, but solely to advise how to tabulate study results if a study is performed. Applicants might need to add some items to or delete some items from the cited format where appropriate. One tabular format can contain results from several studies. Alternatively, it may be appropriate to cite the data resulting from one study in several tabular formats.

The recommended formats for the tables in the Nonclinical Tabulated Summaries are provided in Appendices B and C, which follow. Appendix B contains templates for use in preparation of the tables. The templates are annotated (in italics) to provide guidance on their preparation. (The italicized information should be deleted when the tables are prepared.) Appendix C provides examples of the summary tables. The purpose of the examples is to provide additional guidance on the suggested content and format of the Tabulated Summaries. However, it is the responsibility of the applicant to decide on the best possible presentation of the data for each product. Authors should keep in mind that, in some regions, a review of the Tabulated Summaries (in conjunction with the Written Summaries) represents the primary review of the nonclinical information. Presentation of the data in the formats provided as templates and examples should ensure that a sufficient level of detail is available to the reviewer and should provide concise overviews of related information.

When a juvenile animal study has been conducted, it should be tabulated using the template appropriate for the type of study.

The order of presentation given for the Nonclinical Written Summaries should be followed for the preparation of the tables for the Nonclinical Tabulated Summaries.

Module 4: Nonclinical Study Reports

This guideline presents an agreed format for the organization of the nonclinical reports in the CTD for applications that will be submitted to Regulatory Authorities. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The appropriate location for individual–animal data is in the study report or as an appendix to the study report.

4.1 Table of Contents of Module 4

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the CTD.

4.2 Study Reports

The study reports should be presented in the following order:

4.2.1 Pharmacology
- 4.2.1.1 Primary pharmacodynamics
- 4.2.1.2 Secondary pharmacodynamics
- 4.2.1.3 Safety pharmacology
- 4.2.1.4 Pharmacodynamic drug interactions

4.2.2 Pharmacokinetics
- 4.2.2.1 Analytical methods and validation reports (if separate reports are available)
- 4.2.2.2 Absorption
- 4.2.2.3 Distribution
- 4.2.2.4 Metabolism
- 4.2.2.5 Excretion
- 4.2.2.6 Pharmacokinetic drug interactions (nonclinical)
- 4.2.2.7 Other pharmacokinetic studies

4.2.3 Toxicology
- 4.2.3.1 Single-dose toxicity (in order by species, by route)
- 4.2.3.2 Repeat-dose toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)
- 4.2.3.3 Genotoxicity
- 4.2.3.3.1 In vitro
- 4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)
- 4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)
- 4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- 4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
- 4.2.3.4.3 Other studies
- 4.2.3.5 Reproductive and developmental toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following subheadings should be modified accordingly)
- 4.2.3.5.1 Fertility and early embryonic development
- 4.2.3.5.2 Embryo–fetal development
- 4.2.3.5.3 Prenatal and postnatal development (including maternal function)
- 4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.
- 4.2.3.6 Local tolerance
- 4.2.3.7 Other toxicity studies (if available)
- 4.2.3.7.1 Antigenicity
- 4.2.3.7.2 Immunotoxicity
- 4.2.3.7.3 Mechanistic studies (if not included elsewhere)
- 4.2.3.7.4 Dependence
- 4.2.3.7.5 Metabolites
- 4.2.3.7.6 Impurities
- 4.2.3.7.7 Other

4.3 Literature References

Appendix A
Tables and Figures for Written Summaries

Appendix B
The Nonclinical Tabulated Summaries—Templates

The Nonclinical Tabulated Summaries—Templates

2.6.3 Pharmacology
- 2.6.3.1 Pharmacology: Overview
- 2.6.3.2 Primary Pharmacodynamics[a]
- 2.6.3.3 Secondary Pharmacodynamics[a]
- 2.6.3.4 Safety Pharmacology
- 2.6.3.5 Pharmacodynamic Drug Interactions[a]

2.6.5 Pharmacokinetics
- 2.6.5.1 Pharmacokinetics: Overview
- 2.6.5.2 Analytical Methods and Validation Reports[a]
- 2.6.5.3 Pharmacokinetics: Absorption After a Single Dose
- 2.6.5.4 Pharmacokinetics: Absorption After Repeated Doses
- 2.6.5.5 Pharmacokinetics: Organ Distribution
- 2.6.5.6 Pharmacokinetics: Plasma Protein Binding
- 2.6.5.7 Pharmacokinetics: Study in Pregnant or Nursing Animals
- 2.6.5.8 Pharmacokinetics: Other Distribution Study
- 2.6.5.9 Pharmacokinetics: Metabolism In Vivo
- 2.6.5.10 Pharmacokinetics: Metabolism In Vitro
- 2.6.5.11 Pharmacokinetics: Possible Metabolic Pathways
- 2.6.5.12 Pharmacokinetics: Induction/Inhibition of Drug-Metabolizing Enzymes
- 2.6.5.13 Pharmacokinetics: Excretion
- 2.6.5.14 Pharmacokinetics: Excretion into Bile
- 2.6.5.15 Pharmacokinetics: Drug–Drug Interactions
- 2.6.5.16 Pharmacokinetics: Other

2.6.7 Toxicology
- 2.6.7.1 Toxicology: Overview
- 2.6.7.2 Toxicokinetics: Overview of Toxicokinetics Studies
- 2.6.7.3 Toxicokinetics: Overview of Toxicokinetics Data
- 2.6.7.4 Toxicology: Drug Substance
- 2.6.7.5 Single-Dose Toxicity
- 2.6.7.6 Repeat-Dose Toxicity: Nonpivotal Studies
- 2.6.7.7 Repeat-Dose Toxicity: Pivotal Studies
- 2.6.7.8 Genotoxicity: In Vitro
- 2.6.7.9 Genotoxicity: In Vivo
- 2.6.7.10 Carcinogenicity
- 2.6.7.11 Reproductive and Developmental Toxicity: Nonpivotal Studies
- 2.6.7.12 Reproductive and Developmental Toxicity—Fertility and Early Embryonic Development to Implantation (Pivotal)
- 2.6.7.13 Reproductive and Developmental Toxicity—Effects on Embryo–Fetal Development (Pivotal)
- 2.6.7.14 Reproductive and Developmental Toxicity—Effects on Pre- and Postnatal Development, Including Maternal Function (Pivotal)
- 2.6.7.15 Studies in Juvenile Animals[b]
- 2.6.7.16 Local Tolerance
- 2.6.7.17 Other Toxicity Studies

[a]: Tabulated Summary is optional. It is preferable to include text tables and figures with the Nonclinical Written Summary.
[b]: When a juvenile animal study has been conducted, it should be tabulated using the template appropriate for the type of study and located in Section 2.6.7.15.

Module 5: Clinical Study Reports

Clinical Overview and Clinical Summary of Module 2

MODULE 2: COMMON TECHNICAL DOCUMENT SUMMARIES

2.5: CLINICAL OVERVIEW

Preamble

The Clinical Overview is intended to provide a critical analysis of the clinical data in the CTD. The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them. Specifically, the Clinical Summary should provide a detailed factual summarization of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information (e.g., pertinent animal data or product quality issues that may have clinical implications).

The Clinical Overview is primarily intended for use by regulatory agencies in the review of the clinical section of a marketing application. It should also be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application. The Clinical Overview should present the strengths and limitations of the development program and study results, analyze the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.

In order to achieve these objectives the Clinical Overview should

- describe and explain the overall approach to the clinical development of a medicinal product, including critical study design decisions;
- assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance;
- provide a brief overview of the clinical findings, including important limitations (e.g., lack of comparisons with an especially relevant active comparator, or absence of information on some patient populations, on pertinent end points, or on use in combination therapy);
- provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will optimize benefits and manage risks;
- address particular efficacy or safety issues encountered in development, and how they have been evaluated and resolved;

- explore unresolved issues, explain why they should not be considered as barriers to approval, and describe plans to resolve them; and
- explain the basis for important or unusual aspects of the prescribing information.

The Clinical Overview should generally be a relatively short document (approximately 30 pages). The length, however, will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged for brevity and to facilitate understanding. It is not intended that material presented fully elsewhere be repeated in the Clinical Overview; cross-referencing to more detailed presentations provided in the Clinical Summary or in Module 5 is encouraged.

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Detailed Discussion of Content of the Clinical Overview Sections

2.5.1 Product Development Rationale

The discussion of the rationale for the development of the medicinal product should

- identify the pharmacological class of the medicinal product;
- describe the particular clinical/pathophysiologic condition that the medicinal product is intended to treat, prevent, or diagnose (the targeted indication);
- briefly summarize the scientific background that supported the investigation of the medicinal product for the indication(s) that was (were) studied;
- briefly describe the clinical development program of the medicinal product, including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the program. Briefly describe plans for the use of foreign clinical data (ICH E5);
- note and explain concordance or lack of concordance with current standard research approaches regarding the design, conduct, and analysis of the studies. Pertinent published literature should be referenced. Regulatory guidance and advice (at least from the region(s) where the Clinical Overview is being submitted) should be identified, with discussion of how that advice was implemented. Formal advice documents (e.g., official meeting minutes, official guidance, letters from regulatory authorities) should be referenced, with copies included in the references section of Module 5.

2.5.2 Overview of Biopharmaceuticals

The purpose of this section is to present a critical analysis of any important issues related to bioavailability that might affect efficacy and/or safety of the to-be-marketed formulation(s) (e.g., dosage form/strength proportionality, differences between the to-be-marketed formulation and the formulation(s) used in clinical trials, and influence of food on exposure).

2.5.3 Overview of Clinical Pharmacology

The purpose of this section is to present a critical analysis of the PK, PD, and related in vitro data in the CTD. The analysis should consider all relevant data and explain why and how the data support the conclusions drawn. It should emphasize unusual results and known or potential problems, or note the lack thereof. This section should address:

- PKs, for example, comparative PK in healthy subjects, patients, and special populations; PK related to intrinsic factors (e.g., age, sex, race, renal, and hepatic impairment) and to extrinsic factors (e.g., smoking, concomitant drugs, diet); rate and extent of absorption; distribution, including binding with plasma proteins; specific metabolic pathways, including effects of possible genetic polymorphism and the formation of active and inactive metabolites; excretion; time-dependent changes in PKs; stereochemistry issues; clinically relevant PK interactions with other medicinal products or other substances.
- Pharmacodynamics, for example, information on mechanism of action, such as receptor binding; onset and/or offset of action; relationship of favorable and unfavorable PD effects to dose or plasma concentration (i.e., PK/PD relationships); PD support for the proposed dose and dosing interval; clinically relevant PD interactions with other medicinal products or substances; and possible genetic differences in response.
- Interpretation of the results and implications of immunogenicity studies, clinical microbiology studies, or other drug class specific PD studies summarized in section 2.7.2.4 of the Clinical Summary.

2.5.4 Overview of Efficacy

The purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. Those studies deemed relevant for evaluation of efficacy should be identified, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided. Prematurely terminated studies should be noted and their impact considered.

The following issues should generally be considered:

- Relevant features of the patient populations, including demographic features, disease stage, any other potentially important covariates, any important patient populations excluded from critical studies, and participation of children and elderly (ICH E11 and E7). Differences between the studied population(s) and the population that would be expected to receive the medicinal product after marketing should be discussed.
- Implications of the study design(s), including selection of patients, duration of studies, and choice of end points and control group(s). Particular attention should be given to end points for which there is limited experience. Use of surrogate end points should be justified. Validation of any scales used should be discussed.
- For noninferiority trials used to demonstrate efficacy, the evidence supporting a determination that the trial had assay sensitivity and justifying the choice of noninferiority margin (ICH E10).
- Statistical methods and any issues that could affect the interpretation of the study results (e.g., important

modifications to the study design, including endpoint assessments and planned analyses, as they were specified in the original protocol; support for any unplanned analyses; procedures for handling missing data; and corrections for multiple end points).
- Similarities and differences in results among studies, or in different patient sub-groups within studies, and their effect upon the interpretation of the efficacy data.
- Observed relationships between efficacy, dose, and dosage regimen for each indication, in both the overall population and in the different patient subgroups (ICH E4).
- Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).
- For products intended for long-term use, efficacy findings pertinent to the maintenance of long-term efficacy and the establishment of long-term dosage. Development of tolerance should be considered.
- Data suggesting that treatment results can be improved through plasma concentration monitoring, if any, and documentation for an optimal plasma concentration range.
- The clinical relevance of the magnitude of the observed effects.
- If surrogate end points are relied upon, the nature and magnitude of expected clinical benefit and the basis for these expectations.
- Efficacy in special populations. If efficacy is claimed with inadequate clinical data in the population, support should be provided for extrapolating efficacy from effects in the general population.

2.5.5 Overview of Safety

The purpose of this section is to provide a concise critical analysis of the safety data, noting how results support and justify proposed prescribing information.A critical analysis of safety should consider:

- Adverse effects characteristic of the pharmacological class. Approaches taken to monitor for similar effects should be described.
- Special approaches to monitoring for particular adverse events (e.g., ophthalmic, QT interval prolongation).
- Relevant animal toxicology and product quality information. Findings that affect or could affect the evaluation of safety in clinical use should be considered.
- The nature of the patient population and the extent of exposure, both for test drug and control treatments. Limitations of the safety database, for example, related to inclusion/exclusion criteria and study subject demographics, should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed.
- Common and nonserious adverse events, with reference to the tabular presentations of events with the test drug and with control agents in the Clinical Summary. The discussion should be brief, focusing on events of relatively high frequency, those with an incidence higher than placebo, and those that are known to occur in active controls or other members of the therapeutic class. Events that are substantially more or less common or problematic (considering the duration and degree of the observed events) with the test drug than with active controls are of particular interest.
- Serious adverse events (relevant tabulations should be cross-referenced from the Clinical Summary). This section should discuss the absolute number and frequency of serious adverse events, including deaths, and other significant adverse events (e.g., events leading to discontinuation or dose modification), and should discuss the results obtained for test drug versus control treatments. Any conclusions regarding causal relationship (or lack of this) to the product should be provided. Laboratory findings reflecting actual or possible serious medical effects should be considered.
- Similarities and differences in results among studies, and their effect upon the interpretation of the safety data.
- Any differences in rates of adverse events in population subgroups, such as those defined by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic metabolism.
- Relation of adverse events to dose, dose regimen, and treatment duration.
- Long-term safety (E1a).
- Methods to prevent, mitigate, or manage adverse events.
- Reactions due to overdose, the potential for dependence, rebound phenomena and abuse, or lack of data on these issues.
- Worldwide marketing experience. The following should be briefly discussed:
  - the extent of the worldwide experience,
  - any new or different safety issues identified, and
  - any regulatory actions related to safety.
- Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).

2.5.6 Benefits and Risks Conclusions

The purpose of this section is to integrate all of the conclusions reached in the previous sections about the biopharmaceuticals, clinical pharmacology, efficacy, and safety of the medicinal product and to provide an overall appraisal of the benefits and risks of its use in clinical practice. Also, implications of any deviations from regulatory advice or guidelines and any important limitations of the available data should be discussed here. This assessment should address critical aspects of the proposed Prescribing Information. This section should also consider the risks and benefits of the medicinal product as they compare to available alternative treatments or to no treatment in illnesses, where no treatment may be a medically acceptable option; and should clarify the expected place of the medicinal product in the armamentarium of treatments for the proposed indication. If there are risks to individuals other than those who will receive the drug, these risks should be discussed (e.g., risks of emergence of drug-resistant bacterial strains with widespread use of an antibiotic for minor illnesses). The analyses provided in previous sections should not be reiterated here. This section often can be quite abbreviated when no special concerns have arisen and the drug is a member of a familiar pharmacological class.

This analysis of benefits and risks is generally expected to be very brief but it should identify the most important conclusions and issues concerning each of the following points:

- The efficacy of the medicinal product for each proposed indication.
- Significant safety findings and any measures that may enhance safety.
- Dose–response and dose–toxicity relationships, optimal dose ranges, and dosage regimens.
- Efficacy and safety in subpopulations, for example, those defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphisms.

- Data in children in different age groups, if applicable, and any plans for a development program in children.
- Any risks to the patient of known and potential interactions, including food–drug interactions and drug–drug interactions, and recommendations for product use.
- Any potential effect of the medicinal product that might affect ability to drive or operate heavy machinery.

Examples of issues and concerns that could warrant a more detailed discussion of benefits and risks might include the following:

- The drug is for treatment of a nonfatal disease but has known or potential serious toxicity, such as a strong signal of carcinogenicity, teratogenicity, proarrhythmic potential (effect on QT interval), or suggestion of hepatotoxicity.
- The proposed use is based on a surrogate end point and there is a well-documented important toxicity.
- Safe and/or effective use of the drug requires potentially difficult selection or management approaches that require special physician expertise or patient training.

2.5.7 Literature References

A list of references used, stated in accordance with the current edition of the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, International Committee of Medical Journal Editors (ICMJE), or the system used in "Chemical Abstracts" should be provided. Copies of all references cited in the Clinical Overview should be provided in section 5.4 of Module 5.

2.7: CLINICAL SUMMARY

Preamble

The Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the CTD. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses, or other cross-study analyses for which full reports have been included in Module 5; and postmarketing data for products that have been marketed in other regions. The comparisons and analyses of results across studies provided in this document should focus on factual observations. In contrast, the CTD Clinical Overview document should provide critical analysis of the clinical study program and its results, including discussion and interpretation of the clinical findings and discussion of the place of the test drug in the armamentarium.

The length of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will usually be in the range of 50 to 400 pages.

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2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods

2.7.1.1 Background and Overview

This section should provide the reviewer with an overall view of the formulation development process, the in vitro and in vivo dosage form performance, and the general approach and rationale used in developing the BA, comparative BA, BE, and in vitro dissolution profile database. Reference should be made to any guidelines or literature used in planning and conducting the studies. This section should also provide the reviewer with an overview of the analytical methods used, with emphasis on the performance characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality control (e.g., accuracy and precision). This section should not include detailed information about individual studies.

2.7.1.2 Summary of Results of Individual Studies

A tabular listing of all biopharmaceutical studies should generally be provided (see 2.7.1.4 Appendix), together with narrative descriptions of relevant features and outcomes of each of the individual studies that provided important in vitro or in vivo data and information relevant to BA and BE. The narrative descriptions should be brief, for example, similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. These narratives may be abstracted from the ICH E3 synopsis. References or electronic links to the full report of each study should be included in the narratives.

2.7.1.3 Comparison and Analyses of Results across Studies

This section should provide a factual summary of all in vitro dissolution, BA, and comparative BA studies carried out with the drug substance or drug product, with particular attention to differences in results across studies. This overview should typically summarize the findings in text and tables (see 2.7.1.4 Appendix) and should consider the following:

- Evidence of the effects of formulation and manufacturing changes on in vitro dissolution and BA and conclusions regarding BE. When manufacturing or formulation changes are made for products containing complex drug substances (e.g., a protein), PK studies comparing the product before and after the changes may be performed to ensure that the PK characteristics have not changed as a result of product changes. Although such studies are sometimes referred to as BE studies, they generally do not focus on assessing release of drug substance from drug product. Nonetheless, such studies should be reported in this section. Note also that PK studies alone may not be sufficient to assure similarity between such drug products. In many situations, PD studies or clinical trials may be necessary. Additionally, depending on the circumstances, antigenicity data may also be needed. Results of these other types of studies, when they are needed, should be reported in the appropriate places in the dossier.
- Evidence of the extent of food effects on BA and conclusions regarding BE with respect to meal type or timing of the meal (where appropriate).
- Evidence of correlations between in vitro dissolution and BA, including the effects of pH on dissolution, and conclusions regarding dissolution specifications.
- Comparative BA, including BE conclusions, for different dosage form strengths.
- Comparative BA of the clinical study formulations (for clinical studies providing substantial evidence of efficacy) and the formulations to be marketed.
- The source and magnitude of observed inter- and intrasubject variability for each formulation in a comparative BA study.

2.7.1.4 Appendix

Tables and figures should be embedded in the text of the appropriate sections when they enhance the readability of the

document. Lengthy tables can be provided in the appendix at the end of the section.

Tables 2.7.1.1 and 2.7.1.2 are provided as examples of tabular formats for reporting information and results related to bioavailability and in vitro dissolution studies respectively. These examples give results as well as identifying the type and design of the study. Tables prepared for reporting the results of BE studies could also include the mean ratios (test/reference) for Cmax and AUC and their 90% confidence interval, or the currently recommended metrics for BE assessments.

These tables are not intended to be templates, but only to illustrate the type of information that should be considered by an applicant in designing the tables for biopharmaceutical studies. Applicants should also decide whether information and results from these studies are best presented in tables, text, or figures in order to aid clarity. If, for example, results are best presented in text and figures, tables might be used simply to list the studies.

2.7.2 Summary of Clinical Pharmacology Studies

2.7.2.1 Background and Overview

This section should provide the reviewer with an overall view of the clinical pharmacology studies. These studies include clinical studies performed to evaluate human PK, and PD, and in vitro studies performed with human cells, tissues, or related materials (hereinafter referred to as human biomaterials) that are pertinent to PK processes. For vaccine products, this section should provide the reviewer with immune response data that support the selection of dose, dosage schedule, and formulation of the final product. Where appropriate, relevant data that are summarized in sections 2.7.1, 2.7.3, and 2.7.4 can also be referenced to provide a comprehensive view of the approach and rationale for the development of the PK, , PK/PD, and human biomaterial database. This section should not include detailed information about individual studies.

This section should begin with a brief overview of the human biomaterial studies that were conducted and that were intended to help in the interpretation of PK or PD data. Studies of permeability (e.g., intestinal absorption, blood–brain barrier passage), protein binding, hepatic metabolism, and metabolic-based drug–drug interactions are particularly relevant. This should be followed by a brief overview of the clinical studies that were carried out to characterize PK and PD of the medicinal product, including studies of PK/PD relationships in healthy subjects and patients, and relevant effects of intrinsic and extrinsic factors on PK and PK/PD relationships (In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors that may result in different responses to a drug in different populations are categorized as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively). Critical aspects of study design and data analysis should be noted, for example, the choice of the single or multiple doses used, the study population, choice of the intrinsic or extrinsic factors that were studied, the choice of PD end points, and whether a traditional approach or a population approach was used to collect and analyze data to assess PK or PD.

2.7.2.2 Summary of Results of Individual Studies

A tabular listing of all clinical pharmacology studies should generally be provided (see 2.7.2.5 Appendix), together with a narrative description of the relevant features and outcomes of each of the critical individual studies that provided in vitro or in vivo data and information relevant to PK, PD and PK/PD relationships. The narrative descriptions should be brief, for example, similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies. References or electronic links to the full report of each study should be included in the narratives.

Summaries of dose–response or concentration–response (PK/PD) studies with PD end points should generally be included in this section. In some cases, however, when well-controlled dose-response PD or PK/PD studies provide important evidence of efficacy or safety, they should be placed in 2.7.3 or 2.7.4 as appropriate and referenced, but not summarized, here.

2.7.2.3 Comparison and Analyses of Results across Studies

This section should use the results of all in vitro human biomaterial studies and PK, PD, and PK/PD studies to characterize the PK, PD, and PK/PD relationships of the drug. Results related to the inter- and intraindividual variability in these data and the intrinsic and extrinsic factors affecting these PK relationships should be discussed.

This section (typically with the use of text and tables) should provide a factual presentation of all data across studies pertinent to the following:

- In vitro drug metabolism and in vitro drug–drug interaction studies and their clinical implications.
- Human PK studies, including the best estimates of standard parameters and sources of variability. The focus should be on evidence supporting dose and dose individualization in the target patient population and in special populations, for example, paediatric or geriatric patients, or patients with renal or hepatic impairment.
- Comparison between single and repeated-dose PK.
- Population PK analyses, such as results based on sparse sampling across studies that address interindividual variations in the PK or PD of the active drug substances that may be due to extrinsic or intrinsic factors.
- Dose–response or concentration–response relationships. This discussion should highlight evidence to support the selection of dosages and dose intervals studied in the important clinical trials. In addition, information that supports the dosage instructions in the proposed labeling should be discussed in section 2.7.3.4.
- Major inconsistencies in the human biomaterial, PK, or PD database.
- PK studies that were performed to determine whether foreign clinical data could be extrapolated to the new region (see ICH E5). The result of the studies and analysis of the similarity of the PK data between regions or races should be summarized in this section. Such studies that use PD biomarkers (but do not evaluate clinical efficacy) may similarly be summarized here. An independent subsection can be created to summarize these kinds of data.

2.7.2.4 Special Studies

This section should include studies that provide special types of data relevant to specific types of medicinal products. For immunogenicity studies and other studies in which data may correlate with PK, PD, safety, and/or efficacy data, explanations of such correlations should be summarized here. Any

observed or potential effects on PK, PD, safety, and/or efficacy should be considered in other appropriate sections of the Clinical Summary as well, with cross-referencing to this section. Human studies that address a specific safety issue should not be reported here, but instead should be reported in the Summary of Clinical Safety (section 2.7.4).

Example 1: Immunogenicity
For protein products and other products to which specific immunological reactions have been measured, data regarding immunogenicity should be summarized in this section. For vaccines or other products intended to induce specific immune reactions, immunogenicity data should be described in the efficacy section 2.7.3. Assays used should be briefly described and information about their performance (e.g., sensitivity, specificity, reliability, validity) should be summarized; the location in the application of detailed information should be cross-referenced.

Data regarding the incidence, titre, timing of onset, and duration of antibody responses should be summarized for each type of antibody assay used (e.g., IgG by ELISA, neutralization). Relationships of antibody formation to underlying disease, concomitant medication, dose, duration, regimen, and formulation should be explored and summarized. For drugs intended to be given as chronic, continuous therapy, any data on the impact of interruptions of therapy on antigenicity should be analyzed and summarized.

It is particularly important to summarize analyses of potential clinically relevant correlates of immunogenicity, for example, to determine the extent to which the presence of antibodies of a particular type or titer appears to correlate with alterations of PK, changes in PD, loss of efficacy, loss of adverse event profile, or development of adverse events. Particular attention should be paid to events that might be immunologically mediated (e.g., serum sickness) and events that might result from binding of cross-reactive endogenous substances by antibodies to the administered drug.

Example 2: Clinical microbiology
For antimicrobial or antiviral medicinal products, in vitro studies to characterize the spectrum of activity are an important part of the program of studies relevant to clinical efficacy. Clinical efficacy studies that include characterization of the susceptibility of the clinical isolates as a part of the efficacy determination should be included in section 2.7.3, Summary of Clinical Efficacy. However, studies that evaluate such findings as the pattern of in vitro susceptibility of strains of bacteria from different parts of the world (not in the context of clinical efficacy study) would be included here.

2.7.2.5 Appendix
Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the section.

Table 2.7.2.1 is provided as an example of a tabular format for reporting information and results related to PK drug–drug interaction studies. Similar tables could be prepared for PK/PD studies, dose–response studies, studies of effects on human biomaterials, and population PK studies. This table is not intended to be a template, but only to illustrate the type of information that should be considered by sponsors in designing their own tables. Applicants should also decide whether information and results from clinical pharmacology studies are best presented in tables, text, or figures in order to aid clarity. If, for example, results are best presented in text and figures, the tables might simply list the studies.

In designing tables, if any, for various types of other clinical pharmacology studies such as those listed below, applicants should consider including the following types of information. These examples are for illustrative purposes only and the sponsor should decide which information needs to be presented.

- Metabolism studies using human biomaterials: biomaterials used (e.g., microsomes, hepatocytes), probe drugs, enzymatic pathways and% contribution, and relevant kinetic parameters (e.g., V_{max}, Km).
- In vitro studies of drug–drug interactions using human biomaterials: for studies of other drugs inhibiting the new drug, the metabolite(s) inhibited, enzymatic pathways affected, range of inhibitor concentrations used, IC_{50} and K_i values and proposed mechanism of inhibition should be included. For studies of the new drug inhibiting other drugs, the drugs and metabolites inhibited should be included, along with the information mentioned above.
- Population PK studies: covariates studied, number and type of subjects or patients studied, summary statistical parameters and final estimates of mean (± standard deviation) PK parameters.

2.7.3 Summary of Clinical Efficacy

A separate section 2.7.3 should be provided for each indication, although closely related indications can be considered together. When more than one section 2.7.3 is submitted, the sections should be labeled 2.7.3 pneumonia, 2.7.3 URI, etc.

2.7.3.1 Background and Overview of Clinical Efficacy
This section should describe the program of controlled studies and other pertinent studies in the application that evaluated efficacy specific to the indication(s) sought. Any results of these studies that are pertinent to evaluation of safety should be discussed in section 2.7.4, Summary of Clinical Safety.

The section should begin with a brief overview of the design of the controlled studies that were conducted to evaluate efficacy. These studies include dose–response, comparative efficacy, long-term efficacy, and efficacy studies in population subsets. Critical features of study design should be discussed, for example, randomization, blinding, choices of control treatment, choice of patient population, unusual design features such as crossover or randomized withdrawal designs, use of run-in periods, other methods of "enrichment," study end points, study duration, and prespecified plans for analysis of the study results. Although this section is intended to focus on clinical investigations, nonclinical data, and clinical pharmacology data may also be referenced as appropriate to provide a comprehensive summary of human experience related to efficacy. This section should not include detailed information about individual studies.

2.7.3.2 Summary of Results of Individual Studies
A tabular listing of all studies that provided (or were designed to provide) information relevant to product efficacy should generally be provided (see the section 2.7.3.6 Appendix), together with narrative descriptions for important studies. The narrative descriptions should be brief, for example, similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any

important differences among the studies. For studies that also contributed significantly to the safety analysis, study narratives should include information about the extent of exposure of study subjects to the test drug or control agent, and how safety data were collected. These narratives can be abstracted from the synopses of the clinical study reports (ICH E3). References or electronic links to the full report of each study should be included in the narratives.

Narratives of any bridging studies using clinical end points, that is, certain studies intended to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5), should be included in this section. An analysis of the results of such studies, together with other information (e.g., PK and PD data) that addresses the ability to extrapolate the efficacy and safety results of foreign studies, should be performed if necessary. The conclusions of such an analysis should be noted at the start of section 2.7.3.3.2, Comparison of Efficacy Results of All Studies, and the full report of the analysis should be provided in Module 5.

2.7.3.3 Comparison and Analyses of Results across Studies
Using text, figures, and tables as appropriate (see the section 2.7.3.6 Appendix), the subsections of 2.7.3.3 should summarize all available data that characterize the efficacy of the drug. This summary should include analyses of all data, irrespective of their support for the overall conclusion and should, therefore, discuss the extent to which the results of the relevant studies do or do not reinforce each other. Any major inconsistencies in the data regarding efficacy should be addressed and any areas needing further exploration should be identified.

The section will generally utilize two kinds of analysis: comparison of results of individual studies, and analysis of data combined from various studies. Details of analysis that are too extensive to be reported in a summary document should be presented in a separate report, to be placed in Module 5, section 5.3.5.3.

This section should also cross-reference important evidence from section 2.7.2, such as data that support the dosage and administration section of the labeling. These data include dosage and dose interval recommended, evidence pertinent to individualization of dosage and need for modifications of dosage for specific subgroups (e.g., paediatric or geriatric subjects, or subjects with hepatic or renal impairment), and data relevant to dose–response or concentration–response (PK/PD) relationships.

2.7.3.3.1 Study Populations
The demographic and other baseline characteristics of patients across all efficacy studies should be described. The following should be included:

- The characteristics of the disease (e.g., severity, duration) and prior treatment in the study subjects, and study inclusion/exclusion criteria.
- Differences in baseline characteristics of the study populations in different studies or groups of studies.
- Any differences between populations included in critical efficacy analyses and the overall patient population that would be expected to receive the drug when it is marketed should be noted.
- Assessment of the number of patients who dropped out of the studies, time of withdrawal (a defined study day or visit during treatment or follow up period), and reasons for discontinuation.

Tabular presentations that combine and compare study populations across studies may be useful.

2.7.3.3.2 Comparison of Efficacy Results of all Studies
The results of any bridging studies using clinical end points,that is, certain studies used to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5), should be summarized in this section. An analysis of the similarity of efficacy in subjects between regions, as well as any other information that may support extrapolation of the efficacy data to the new region, should be summarized here. An independent subsection can be created to summarize these kinds of data.

The results from all studies designed to evaluate the drug's efficacy should be summarized and compared, including studies with inconclusive or negative results. Important differences in study design such as end points, control group, study duration, statistical methods, patient population, and dose should be identified.

Comparisons of results across studies should focus on prespecified primary end points. However, when the primary end points involved different variables or time points in different efficacy studies, it may be useful to provide cross-study comparisons of important data elements that were obtained in all studies. If results over time are important, results of studies may be displayed in a figure that illustrates the change over time in each study.

Confidence intervals for treatment effects should be given to aid in the interpretation of point estimates. If differences are shown between placebo and test drugs in the change from baseline, the baseline values and the magnitude of effect in all treatment groups, including placebo and active controls (if used), should generally be presented in the table or in text accompanying a figure. If the objective of an active control trial was to show equivalence or non-inferiority, the difference or the ratio of outcomes between treatments should be given with the confidence interval. The results should be evaluated by using the predefined criteria for defining equivalence or noninferiority and the rationale for the criteria and support for the determination that the study (studies) had assay sensitivity should be provided (see ICH E10).

Important differences in outcomes between studies with a similar design should be delineated and discussed. Cross-study comparisons of factors that may have contributed to differences in outcomes should be described.

If a meta-analysis of the clinical studies is performed, it should be clear whether this analysis is conducted according to a predefined protocol or is a post hoc exercise. Any differences in trial designs or populations, or in efficacy measurements between trials should be described to allow assessment of the relevance and validity of the results and conclusions (see ICH E9).A detailed description of the methodology and results of the meta-analysis should generally be submitted in a separate report (section 5.3.5.3 of Module 5).

2.7.3.3.3 Comparison of Results in Subpopulations
The results of individual studies or overview analyses of efficacy in specific populations should be summarized in this section. The purpose of these comparisons should be to show whether the claimed treatment effects are observed consistently across all relevant subpopulations, especially those where there are special reasons for concern. The comparisons may highlight apparent variations in efficacy that require further investigation and discussion. The limitations of such analyses, however, should be recognized (ICH E9), and it is important to note that their purpose is neither to provide

the basis for specific claims, nor to attempt to improve the evidence of efficacy in situations where the overall results are disappointing.

Given the limited sample sizes in individual studies, analyses across multiple studies should be performed to evaluate effects of major demographic factors (age, sex, and race) and of other predefined or relevant intrinsic and extrinsic factors (e.g., disease severity, prior treatment, concomitant illness, concomitant drugs, alcohol, tobacco, and body weight) on efficacy. Factors of special interest may arise from general concerns (e.g., the elderly) or from specific issues that are related to the pharmacology of the drug or that have arisen during earlier drug development. Efficacy in the paediatric population should be routinely analyzed in applications for a proposed indication that occurs in children. Depending on the data set, if extensive, detailed efficacy analyses are performed, they can be placed in Module 5, with the results of those analyses reported here.

2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations

This section should provide an integrated summary and analysis of all data that pertain to the dose–response or blood level–response relationships of effectiveness (including dose–blood level relationships), and thus have contributed to dose selection and choice of dose interval. Relevant data from nonclinical studies may be referenced, and relevant data from PK studies, other clinical pharmacology studies, and controlled and uncontrolled clinical studies should be summarized to illustrate these dose–response or blood level–response relationships. For PK and PD studies from which data have been summarized in section 2.7.2.2, it may be appropriate to draw upon those data in this summary while cross-referencing the summaries in section 2.7.2.2, without repeating those summaries.

While the interpretation of how these data support specific dosing recommendations should be supplied in the Clinical Overview document, the individual study results and any cross-study analyses that will be used to support the dosing recommendations (including the recommended starting and maximal doses, the method of dose titration, and any other instructions regarding individualization of dosage) should be summarized here. Any identified deviations from relatively simple dose–response or blood-level response relationships due to nonlinearity of PKs, delayed effects, tolerance, enzyme induction, etc. should be described.

Any evidence of differences in dose–response relationships that result from a patient's age, sex, race, disease, or other factors should be described. Any evidence of different PK or PD responses should also be discussed, or discussions in section 2.7.2 can be cross-referenced. The ways in which such differences were looked for, even if no differences were found, should be described (e.g., specific studies in subpopulations, analysis of efficacy results by subgroup, or blood level determinations of the test drug).

2.7.3.5 Persistence of Efficacy and/or Tolerance Effects

Available information on persistence of efficacy over time should be summarized. The number of patients for whom long-term efficacy data are available, and the length of exposure, should be provided. Any evidence of tolerance (loss of therapeutic effects over time) should be noted. Examination of any apparent relationships between dose changes over time and long-term efficacy may be useful.

The primary focus should be on controlled studies specifically designed to collect long-term efficacy data, and such studies should be clearly differentiated from other, less rigorous, studies such as open extension studies. This distinction also applies to specific studies designed for evaluation of tolerance and withdrawal effects. Data concerning withdrawal or rebound effects pertinent to product safety should be presented in the safety section (see section 2.7.4).

In long-term efficacy trials, the effect of premature discontinuation of therapy or switching to other therapies upon the assessment of the results should be considered. These issues might also be important for short-term trials and should be addressed when discussing the results of these trials, if appropriate.

2.7.3.6 Appendix

Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the section.

Tables should identify all studies pertinent to the evaluation of efficacy (including studies that were terminated or are not yet completed, studies that failed to show effectiveness for any reason, studies available only as publications, studies reported in full technical reports (ICH E3), and studies described in abbreviated reports); and should provide the most important results of those studies. Note, however, that unplanned interim analyses on ongoing studies are generally not needed or encouraged. When more than one section 2.7.3 is provided for an application with more than one indication, usually each section should have its own appendix with tables.

Illustrative tables for an antihypertensive drug are provided, but these examples will not be relevant to every application. In general, applications will require tables and/or figures that are developed specifically for the particular drug class and the studies that were carried out.

Table 2.7.3.1 Description of Clinical Efficacy and Safety Studies

Table 2.7.3.2 Results of Efficacy Studies

2.7.4 Summary of Clinical Safety

This section should be a summary of data relevant to safety in the intended patient population, integrating the results of individual clinical study reports as well as other relevant reports, for example, the integrated analyses of safety that are routinely submitted in some regions.

The display of safety-related data can be considered at three levels (ICH E3):

- The extent of exposure (dose, duration, number of patients, type of patients) should be examined to determine the degree to which safety can be assessed from the database.
- The more common adverse events and changes in laboratory tests should be identified and classified, and their occurrence should be summarized.
- Serious adverse events (defined in ICH E2A) and other significant adverse events (defined in ICH E3) should be identified and their occurrence should be summarized. These events should be examined for frequency over time, particularly for drugs that may be used chronically.

The safety profile of the drug, described on the basis of analysis of all clinical safety data, should be outlined in a detailed, clear, and objective manner, with use of tables and figures.

2.7.4.1 Exposure to the Drug

2.7.4.1.1 Overall Safety Evaluation Plan and Narratives of Safety Studies

The overall safety evaluation plan should be described briefly, including special considerations and observations concerning the nonclinical data, any relevant pharmacological class effects, and the sources of the safety data (controlled trials, open studies, etc).A tabular listing of all clinical studies that provided safety data, grouped appropriately, should generally be provided (see the section 2.7.4.7 Appendix). In addition to studies that evaluated efficacy and safety, and uncontrolled studies that generate safety information, this section includes studies that consider special safety issues. Examples would include studies to compare particular adverse event rates for two therapies, to assess safety in particular demographic subsets, to evaluate withdrawal or rebound phenomena, or to evaluate particular adverse events (e.g., sedation, sexual function, effects on driving, absence of a class adverse effect). Studies in indications for which approval is not being sought in the current application and ongoing studies would also be included here if they contribute to the safety analysis.

Narrative descriptions of these studies should be provided here, except that narrative descriptions for studies that contributed both efficacy and safety data should be included in section 2.7.3.2 and cross-referenced here. The narratives should provide enough detail to allow the reviewer to understand the exposure of study subjects to the test drug or control agent, and how safety data were collected (including the methods used and the extent of safety monitoring of the subjects enrolled in the individual studies). If some studies are not analyzed separately but are grouped for safety analysis, that should be noted, and a single narrative description can be provided.

2.7.4.1.2 Overall Extent of Exposure

A table (see example provided in the section 2.7.4.7 Appendix) and appropriate text should be generated to summarize the overall extent of drug exposure from all phases of the clinical study development program. The table should indicate the numbers of subjects exposed in studies of different types and at various doses, routes, and durations. If a large number of different doses and/or durations of exposure were used, these can be grouped in a manner appropriate for the drug. Thus, for any dose or range of doses, duration of exposure can be summarized by the number of subjects exposed for specific periods of time, such as 1 day or less, 2 days to 1 week, 1 week to 1 month, 1 month to 6 months, 6 months to 1 year, more than 1 year (ICH E3). In some applications, it may be important to identify diagnostic subgroups and/or groups receiving specific concomitant therapies deemed particularly relevant to safety assessment in the intended use.

The dose levels used for each subject in this presentation could be the maximum dose received by that subject, the dose with longest exposure, and/or the mean daily dose, as appropriate. In some cases, cumulative dose may be pertinent. Dosage may be given as the actual daily dose or on a mg/kg or mg/m^2 basis, as appropriate. If available, drug concentration data (e.g., concentration at the time of an adverse event, maximum plasma concentration, area under curve) may be helpful in individual subjects for correlation with adverse events or changes in laboratory variables.

It is assumed that all subjects, who were enrolled and received at least one dose of the treatment are included in the safety analysis; if that is not so, an explanation should be provided.

2.7.4.1.3 Demographic and Other Characteristics of Study Population

A summary table should provide the reader with an overview of the demographic characteristics (Table 2.7.4.2) of the population that was exposed to the therapeutic agent during its development. Choice of age ranges used should take into account considerations discussed in ICH E7 (Studies in Support of Special Populations: Geriatrics) and ICH E11 (Clinical Investigation of Medicinal Products in the Paediatric Population). If the relative exposure of demographic groups in the controlled trials differed from overall exposure, it may be useful to provide separate tables.

In addition, one or more tables should show the relevant characteristics of the study population, and the numbers of subjects with special characteristics. Such characteristics could include

- Severity of disease
- Hospitalization
- Impaired renal function
- Concomitant illnesses
- Concomitant use of particular medications
- Geographical location

If these characteristics are distributed differently in controlled trials versus the overall database, it will generally be useful to present tables on both groupings.

The text accompanying the table(s) should mention any imbalance(s) between the drug and placebo and/or comparator regarding any of the above demographic characteristics, particularly if they could lead to differences in safety outcomes.

If certain subjects were excluded from studies (concomitant illness, severity of illness, concomitant medications), this fact should be noted.

Separate demographic tables should be provided for every indication, although closely related indications can be considered together, if study subject characteristics are such that risks are believed to be the same.

2.7.4.2 Adverse Events

2.7.4.2.1 Analysis of Adverse Events

Data on the frequency of adverse events should be described in text and tables. Text should appear in the appropriate subsections of section 2.7.4.2.1 and the tables that are not embedded in the text should be placed in the section 2.7.4.7 Appendix.

All adverse events occurring or worsening after treatment have begun ("treatment emergent signs and symptoms," those adverse events not seen at baseline and those that worsened even if present at baseline) should be summarized in tables listing each event, the number of subjects in whom the event occurred and the frequency of occurrence in subjects treated with the drug under investigation, with comparator drugs, and with placebo. Such tables could also present results for each dose and could be modified to show, for example, adverse event rates by severity, by time from onset of therapy, or by assessment of causality.

When most of the relevant safety data are derived from a small number of studies (e.g., one or two studies), or when very different study subject populations were enrolled in the studies that were performed, presentation of data by study will often be appropriate. When the relevant exposure data is not concentrated in a small number of studies, however, grouping the studies and pooling the results to improve precision of estimates and sensitivity to differences should generally be considered.

While often useful, pooling of safety data across studies should be approached with caution because in some cases interpretation can be difficult, and it can obscure real differences. In cases where differences are apparent, it is more appropriate to present the data by study. The following issues should be considered:

- It is most appropriate to combine data from studies that are of similar design, for example, similar in dose, duration, methods of determining adverse events, and population.
- If the incidence for a particular adverse event differs substantially across the individual studies in a pool, the pooled estimate is less informative.
- Any study with an unusual adverse event pattern should be presented separately.
- The appropriate extent of analysis depends on the seriousness of the adverse event and the strength of evidence of drug causation. Differences in rates of drug-related, serious events or events leading to discontinuation or dosage change deserve more investigation, whereas rates of other adverse events do not merit elaborate analysis.
- Examination of which subjects experience extreme laboratory value abnormalities ("outliers") may be useful in identifying subgroups of individuals who are at particular risk for certain adverse events.

Groups of studies that could be used in pooled safety analyses include

- All controlled studies or subsets of controlled studies, such as all placebo-controlled studies, studies with any positive control, studies with a particular positive control, or studies of particular indications (and thus carried out in different populations). These groupings are considered the best source of information about the more common adverse events and can distinguish drug-related events from spontaneous events. Rates in control and treatment groups should be compared.
- All studies, excluding short-term studies in healthy subjects. This grouping is most useful for evaluating rarer events.
- All studies using a particular dose route or regimen, or a particular concomitant therapy.
- Studies in which adverse event reports are elicited by checklist or direct questioning, or studies in which events are volunteered.
- Pools of studies by region.

It is almost always useful to carry out the first two groupings; the others chosen would vary from drug to drug and should be influenced by inspection of individual study results. Whatever methods are used, it should be recognized that, as for results of single studies, any numerical rate is often only a rough approximation of reality.

When a decision is made to pool data from several studies, the rationale for selecting the method used for pooling should be described. It is common to combine the numerator events and the denominators for the selected studies. Other methods for pooling results across studies are available, for example, weighting data from studies on the basis of study size or inversely to their variance.

If substantial differences are seen between clinical trials in the rates of adverse events, these differences should be noted and possible reasons should be discussed (e.g., relevant differences in study populations, in dose administration, or in methods of collecting adverse event data).

Adverse events should be described as shown in the individual study report (ICH E3). In combining data from many studies, it is important to use standardized terms to describe events and collect synonymous terms under a single preferred term. This can be done with a standard dictionary, and the MedDRA terminology (ICH M1 guideline) should be used. Until MedDRA can be fully implemented, other dictionaries can be used, but should be specified. Frequencies should be presented for preferred terms and for appropriately defined groupings. Examination of which adverse events led to change in therapy (discontinuation of drug use, change in dose, need for added therapy) can help in assessing the clinical importance of adverse events. These rates can be added to the adverse event rate tables, or can be presented in separate tables. Overall discontinuation rates by study may be useful, but it is also important to specify the particular adverse events leading to discontinuation in a separate table. The preferred terms should be grouped by body system and arranged by decreasing frequency.

2.7.4.2.1.1 Common Adverse Events

Tabular displays of adverse event rates (see the section 2.7.4.7 Appendix) should be used to compare rates in treatment and control groups. For this analysis, it may be helpful to combine the event severity categories and the causality categories, if they are used, leading to a simpler side-by-side comparison of treatment groups. It should be noted that while causality categories may be reported, if used, the presentation of the data should include total adverse events (whether deemed related or unrelated to treatment); evaluations of causality are inherently subjective and may exclude unexpected adverse events that are in fact treatment related. Additionally, comparisons of rates of adverse events between treatment and control groups in individual trials should be summarized here. It is often useful to tabulate rates in selected trials (see example table 2.7.4.4, in the section 2.7.4.7 Appendix).

It is usually useful to examine more closely the more common adverse events that seem to be drug related (e.g., those that show that a dose response and/or a clear difference between drug and placebo rates) for relationship to relevant factors, including

– dosage;
– mg/kg or mg/m^2 dose;
– dose regimen;
– duration of treatment;
– total dose;
– demographic characteristics such as age, sex, race;
– concomitant medication use;
– other baseline features such as renal status;
– efficacy outcomes; and
– drug concentration, where available.

It may also be useful to summarize the results of examination of time of onset and duration for these drug-related events.

Rigorous statistical evaluations of the possible relationship of specific adverse events to each of the above factors are often unnecessary. It may be apparent from initial display and inspection of the data that there is no evidence of a significant relationship to demographic or other baseline features. In that case, no further analysis of these particular factors is needed. Further, it is not necessary that all such analyses be presented in this report. When the safety analyses are too extensive to be presented in detail in this report, they may be presented in a separate report in Module 5, section 5.3.5.3, and summarized here.

Under certain circumstances, life table or similar analyses may be more informative than reporting of crude adverse event rates.

2.7.4.2.1.2 Deaths
A table in the section 2.7.4.7 Appendix should list all deaths occurring while on study (including deaths that occurred shortly following treatment termination, for example, within 30 days or as specified in the study protocol, as well as all other deaths that occurred later but may have resulted from a process that began during studies). Only deaths that are clearly disease-related per protocol definitions and not related to the investigational product, either in studies of conditions with high mortality such as advanced cancer or in studies where mortality from disease is a primary study end point, should be excepted from this listing (it is assumed, however, that these deaths would still be reported in the individual ICH E3 study reports). Even these deaths should be examined for any unexpected patterns between study arms, and further analyzed if unexplained differences are observed. Deaths should be examined individually and analyzed on the basis of rates in individual trials and appropriate pools of trials, considering both total mortality and cause-specific deaths. Potential relationships to the factors listed in section 2.7.4.2.1.1 should also be considered. Although cause-specific mortality can be difficult to determine, some deaths are relatively easy to interpret. Thus, deaths due to causes expected in the patient population (heart attacks and sudden death in an angina population) are individually not considered to be informative, but even one death due to a QT interval prolongation-associated arrhythmia, aplastic anaemia, or liver injury may be informative. Special caution is appropriate before an unusual death is attributed to concomitant illness.

2.7.4.2.1.3 Other Serious Adverse Events
Summaries of all serious adverse events (other than death but including the serious adverse events temporally associated with or preceding the deaths) should be displayed. Serious adverse events that occurred after the drug use was discontinued should be included in this section. The display should include major laboratory abnormalities, abnormal vital signs, and abnormal physical observations that are considered serious adverse events using the ICH E2A definitions. Results of analyses or assessments of serious adverse events across studies should be presented. Serious events should be examined for frequency over time, particularly for drugs that may be used chronically. Potential relationships to the factors listed in section 2.7.4.2.1.1 should also be considered.

2.7.4.2.1.4 Other Significant Adverse Events
Marked hamatologic and other laboratory abnormalities (other than those meeting the definition of serious) and any events that led to a substantial intervention (premature discontinuation of study drug, dose reduction, or substantial additional concomitant therapy), other than those reported as serious adverse events, should be displayed.

Events that led to premature discontinuation of study drug represent an important safety concern and deserve particular attention in the analysis of drug safety for two reasons. First, even for expected events (based on pharmacological activity), the need to discontinue (or otherwise alter) treatment reflects the severity and perceived importance of the event to patient and physician. Second, discontinuation may represent a drug-related event not yet recognised as drug related. Adverse events leading to treatment discontinuation should be considered possibly drug-related even if this was not recognised initially and even if the event was thought to represent intercurrent illness. Reasons for premature treatment discontinuations should be discussed and rates of discontinuations should be compared across studies and compared with those for placebo and/or active control treatment. In addition, the study data should be examined for any potential relationships to the factors listed in section 2.7.4.2.1.1.

2.7.4.2.1.5 Analysis of Adverse Events by Organ System or Syndrome
Assessment of the causality of, and risk factors for, deaths, other serious events, and other significant events is often complicated by the fact that they are uncommon. As a result, consideration of related events as a group, including less important events of potentially related pathophysiology, may be of critical value in understanding the safety profile. For example, the relationship to treatment of an isolated sudden death may become much clearer when considered in the context of cases of syncope, palpitations, and asymptomatic arrhythmias.

It is thus generally useful to summarize adverse events by organ system so that they may be considered in the context of potentially related events including laboratory abnormalities. Such presentations of adverse events by organ system should be placed in subsections of section 2.7.4.2.1.5, labelled as 2.7.4.2.1.5.1, 2.7.4.2.1.5.2, etc., and titled by the organ system under consideration. The list of organ systems to be addressed and the approach to grouping certain events should be selected as appropriate to best present the adverse event data for the medicinal product. If some adverse events tend to occur in syndromes (e.g., influenza-like syndrome, cytokine release syndrome), the sponsor may choose to create some subsections of 2.7.4.2.1.5 for syndromes rather than organ systems.

The same data and summarizations should generally not be repeated in more than one subsection of section 2.7.4.2.1. Instead, a summary presentation may be placed in one subsection and cross-referenced as needed in the other.

2.7.4.2.2 Narratives
The locations in the application of individual narratives of patient deaths, other serious adverse events, and other significant adverse events deemed to be of special interest because of clinical importance (as described in ICH E3 individual study reports) should be referenced here for the convenience of the reviewer. The narratives themselves should be a part of the individual study reports, if there is such a report. In cases where there is no individual study report (e.g., if many open studies are pooled as part of a safety analysis and are not individually described), narratives can be placed in Module 5, section 5.3.5.3. Narratives should not be included here, unless an abbreviated narrative of particular events is considered critical to the summary assessment of the drug.

2.7.4.3 Clinical Laboratory Evaluations
This section should describe changes in patterns of laboratory tests with drug use. Marked laboratory abnormalities and those that led to a substantial intervention should be reported in section 2.7.4.2.1.3 or 2.7.4.2.1.4. If these data are also presented in this section, this duplicate reporting should be made clear for the reviewer. The appropriate evaluations of laboratory values will in part be determined by the results seen, but, in general, the analyses described below should be provided. For each analysis, comparison of the treatment and control groups should be carried out, as appropriate and as

compatible with study sizes. In addition, normal laboratory ranges should be given for each analysis (ICH E3). Where possible, laboratory values should be provided in standard international units.

A brief overview of the major changes in laboratory values across the clinical studies should be provided. Laboratory data should include hematology, clinical chemistry, urinalysis, and other data as appropriate. Each parameter at each time over the course of the study (e.g., at each visit) should be described at the following three levels:

- the central tendency, that is, the group mean and median values;
- the range of values, and the number of subjects with abnormal values or with abnormal values of a certain size (e.g., twice the upper limit of normal, 5 times the upper limit; choices should be explained). When data are pooled from centers with differences in normal laboratory ranges, the methodology used in pooling should be described. The analysis of individual subject changes by treatment group can be shown with a variety of approaches (e.g., shift tables, see ICH E3 for examples); and
- individual clinically important abnormalities, including those leading to discontinuations. The significance of the laboratory changes and the likely relation to the treatment should be assessed (e.g., by analysis of such features as relationship to dose, relation to drug concentration, disappearance on continued therapy, positive dechallenge, positive rechallenge, and the nature of concomitant therapy). Potential relationships to other factors listed in section 2.7.4.2.1.1 should also be considered.

2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety

The manner of presenting cross-study observations and comparisons of vital signs (e.g., heart rate, blood pressure, temperature, respiratory rate), weight, and other data (e.g., electrocardiograms, x-rays) related to safety should be similar to that for laboratory variables. If there is evidence of a drug effect, any dose–response or drug concentration–response relationship or relationship to individual variables (e.g., disease, demographics, concomitant therapy) should be identified and the clinical relevance of the observation described. Particular attention should be given to changes not evaluated as efficacy variables and to those considered to be adverse events. Particular attention should be given to studies that were designed to evaluate specific safety issues, for example, studies of QT interval prolongation.

2.7.4.5 Safety in Special Groups and Situations

2.7.4.5.1 Intrinsic Factors

This section should summarize safety data pertinent to individualizing therapy or patient management on the basis of demographic and other factors defined as "intrinsic ethnic factors" in ICH E5. These factors include age, sex, height, weight, lean body mass, genetic polymorphism, body composition, other illness, and organ dysfunction. Safety in the paediatric population should be routinely analyzed in applications for a proposed indication that occurs in children. Analysis of the impact of such factors on safety outcomes should have been presented in other sections but should be summarized here, together with pertinent PK or other information, for example, in patients with renal or hepatic disease. If a sufficiently large number of subjects with a given comorbid condition such as hypertension, heart disease, or diabetes, was enrolled, analyses should be carried out to assess whether the comorbid condition affected the safety of the drug under study. Cross-reference should be made to the tables or description of adverse events when analyses of such subgroups has been carried out.

2.7.4.5.2 Extrinsic Factors

This section should summarize safety data pertinent to individualizing therapy or patient management on the basis of factors defined as "extrinsic ethnic factors" in ICH E5. These are factors associated with the patient environment. Examples are the medical environment, use of other drugs (see 2.7.4.5.3, Drug Interactions), use of tobacco, use of alcohol, and food habits.

For example, if a potential interaction with alcohol is suggested by the metabolic profile, by the results of studies, by postmarketing experience, or by information on similar drugs, information should be provided here.

2.7.4.5.3 Drug Interactions

Studies on potential drug–drug or drug–food interactions should be summarized in the Summary of Clinical Pharmacology Studies section of the CTD (section 2.7.2). The potential impact on safety of such interactions should be summarized here, based on PK, PD, or clinical observations. Any observed changes in the adverse event profile, changes in blood levels thought to be associated with risk, or changes in drug effects associated with other therapy should be presented here.

2.7.4.5.4 Use in Pregnancy and Lactation

Any information on safety of use during pregnancy or breastfeeding that becomes available during clinical development or from other sources should be summarized here.

2.7.4.5.5 Overdose

All available clinical information relevant to overdose, including signs/symptoms, laboratory findings, and therapeutic measures/treatments and antidotes (if available) should be summarized and discussed. Information on the efficacy of specific antidotes and dialysis should be provided if available.

2.7.4.5.6 Drug Abuse

Any relevant studies/information regarding the investigation of the dependence potential of a new therapeutic agent in animals and in humans should be summarized and cross-referenced to the nonclinical summary. Particularly susceptible patient populations should be identified.

2.7.4.5.7 Withdrawal and Rebound

Any information or study results pertinent to rebound effects should be summarized. Events that occur, or increase in severity, after discontinuation of double-blind or active study medication should be examined to see if they are the result of withdrawal of the study medication. Particular emphasis should be given to studies designed to evaluate withdrawal and/or rebound.

Data concerning tolerance should be summarized under section 2.7.3.5 in the Summary of Clinical Efficacy.

2.7.4.5.8 Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Safety data related to any impairment in the senses, coordination, or other factor that would result in diminished ability to drive a vehicle or operate machinery or that would impair mental ability should be summarized. This includes relevant adverse effects reported in safety monitoring

(e.g., drowsiness) and specific studies concerning effects on ability to drive or operate machinery or impairment of mental ability.

2.7.4.6 Postmarketing Data
If the drug has already been marketed, all relevant postmarketing data available to the applicant (published and unpublished, including periodic safety update reports if available) should be summarized. The periodic safety update reports can be included in Module 5. Details of the number of subjects estimated to have been exposed should be provided and categorized, as appropriate, by indication, dosage, route, treatment duration, and geographic location. The methodology used to estimate the number of subjects exposed should be described. If estimates of the demographic details are available from any source, these should be provided.

A tabulation of serious events reported after the drug is marketed should be provided, including any potentially serious drug interactions.

Any postmarketing findings in subgroups should be described.

2.7.4.7 Appendix
Tabular presentations should be provided that summarize the important results from all studies pertinent to the evaluation of safety and particularly to support product labeling.

Tables and figures should be embedded in the text of the appropriate sections when that enhances the readability of the document. Lengthy tables can be provided in the appendix at the end of the section.

A few illustrative tables are provided, but a clinical summary will routinely need tables and figures that have been developed for the particular drug, drug class, and clinical indication(s).

See sections 2.7.4.2.1, 2.7.4.2.2.3, and 2.7.4.3 of this guidance for additional discussion regarding the content of section 2.7.4 tables.

Table 2.7.4.1	Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure
Table 2.7.4.2	Demographic Profile of Patients in Controlled Trials
Table 2.7.4.3	Incidence of Adverse Events in Pooled Placebo- and Active Controlled Trials
Table 2.7.4.4	Incidence of Adverse Events in the Largest Trials
Table 2.7.4.5	Patient Withdrawals by Study: Controlled Trials
Table 2.7.4.6	Listing of Deaths

2.7.5 Literature References
A list of references cited in the Clinical Summary should be provided. Copies of all important references should be provided in Module 5, section 5.4. The reference list should indicate which references are available in Module 5, section 5.4. All references that have not been provided should be available upon request.

2.7.6 Synopses of Individual Studies
The ICH E3 guideline (Structure and Content of Clinical Study Reports) suggests inclusion of a study synopsis with each clinical study report, and provides one example of a format for such synopses.

This section should include the table entitled Listing of Clinical Studies, described in guidance for Module 5, followed by all individual study synopses organized in the same sequence as the study reports in Module 5.

It is expected that one synopsis will be prepared per study for use in all regions, and that the same synopsis will be included in this section and as part of the clinical study report in Module 5. The length of a synopsis will usually be up to three pages, but a synopsis for a more complex and important study may be longer, for example, 10 pages. Within the individual synopsis, tables and figures should be used as appropriate to aid clarity.

Table 2.7.1.1

Summary of Bioavailability Studies
Table 2.7.1.2

Summary of In vitro Dissolution Studies
Table 2.7.2.1

Summary of Drug–Drug Interaction PK Studies

MODULE 5: CLINICAL STUDY REPORTS

Preamble
Through the ICH process, a guideline has been published on the structure and content of clinical study reports (E3). This document provides guidance on the organization of these study reports, other clinical data, and references within a CTD for registration of a pharmaceutical product for human use. These elements should facilitate the preparation and review of a marketing application.

This guideline is not intended to indicate what studies are required for successful registration. It indicates an appropriate organization for the clinical study reports that are in the application.

Detailed Organization of Clinical Study Reports and Related Information in Module 5.
This guideline recommends a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation such as "not applicable" or "no study conducted" should be provided when no report or information is available for a section or subsection.

5.1 Table of Contents of Module 5

A Table of Contents for study reports should be provided.
5.1 ..... Table of Contents of Module 5
5.2 ..... Tabular Listing of All Clinical Studies
5.3 ..... Clinical Study Reports
5.3.1..... Reports of Biopharmaceutical Studies
5.3.1.1 .... Bioavailability (BA) Study Reports
5.3.1.2 .... Comparative BA and BE Study Reports
5.3.1.3 .... In vitro–In vivo Correlation Study Reports
5.3.1.4 .... Reports of Bioanalytical and Analytical Methods for Human Studies

5.2 Tabular Listing of All Clinical Studies

A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 5.1 of this guideline. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in section 5.3 below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

5.3 Clinical Study Reports

5.3.1 Reports of Biopharmaceutical Studies

BA studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or in vitro dissolution end points, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in section 5.3.1, and referenced in sections 5.3.1.1 and/or 5.3.1.2.

5.3.1.1 Bioavailability (BA) Study Reports

BA studies in this section should include

- studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously or as an oral liquid dosage form;
- dosage form proportionality studies; and
- food-effect studies.

5.3.1.2 Comparative BA and BE Study Reports

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between

- the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product,
- the drug product used in clinical studies supporting effectiveness and the drug product used in stability batches, and
- similar drug products from different manufacturers.

5.3.1.3 In Vitro –In Vivo Correlation Study Reports

In vitro dissolution studies that provide BA information, including studies used in seeking to correlate in vitro data with in vivo correlations, should be placed in section 5.3.1.3. Reports of in vitro dissolution tests used for batch quality control and/or batch release should be placed in the Quality section of the CTD.

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Bioanalytical and/or analytical methods for biopharmaceutical studies or in vitro dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and its validation should be included once in section 5.3.1.4 and referenced in the appropriate individual study reports.

5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Human biomaterials is a term used to refer to proteins, cells, tissues, and related materials derived from human sources that are used in vitro or ex vivo to assess PK properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes and transport processes, and human albumin that is used to assess plasma protein binding. Of particular importance is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways and to assess drug–drug interactions with these pathways. Studies using biomaterials to address other properties (e.g., sterility or pharmacodynamics) should not be placed in the Clinical Study Reports Section, but in the Nonclinical Study Section (Module 4).

5.3.2.1 Plasma Protein Binding Study Reports

Ex vivo protein binding study reports should be provided here. Protein-binding data from PK blood and/or plasma studies should be provided in Section 5.3.3.

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

Reports of hepatic metabolism and metabolic drug interaction studies with hepatic tissue should be placed here.

5.3.2.3 Reports of Studies Using Other Human Biomaterials

Reports of studies with other biomaterials should be placed in this section.

5.3.3 Reports of Human PK Studies

Assessment of the PK of a drug in healthy subjects and/or patients is considered critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant

drug use, and to interpreting observed PD differences. These assessments should provide a description of the body's handling of a drug over time, focusing on maximum plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and accumulation of the parent drug and its metabolite(s), in particular those that have pharmacological activity.

The PK studies whose reports should be included in sections 5.3.3.1 and 5.3.3.2 are generally designed to (1) measure plasma drug and metabolite concentrations over time, (2) measure drug and metabolite concentrations in urine or faces when useful or necessary, and/or (3) measure drug and metabolite binding to protein or red blood cells.

On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in section 5.3.3.1 to 5.3.3.2, as appropriate. These studies should characterize the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or formation of antibodies) are of particular interest and should be included in sections 5.3.3.1 and/or 5.3.3.2. Apart from describing mean PK in normal and patient volunteers, PK studies should also describe the range of individual variability. In the ICH E5 guideline on Ethnic Factors in the Acceptance of Foreign Data, factors that may result in different responses to a drug in different populations are categorized as intrinsic ethnic factors or extrinsic ethnic factors. In this document, these categories are referred to as intrinsic factors and extrinsic factors, respectively. Additional studies can also assess differences in systemic exposure as a result of changes in PK due to intrinsic (e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) and extrinsic (e.g., drug–drug interactions, diet, smoking, and alcohol use) factors. Reports of PK studies examining the influence of intrinsic and extrinsic factors on exposure should be organized in sections 5.3.3.3 and 5.3.3.4, respectively.

In addition to standard multiple-sample PK studies, population PK analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose-PK-response relationship. Because the methods used in population PK studies are substantially different from those used in standard PK studies, these studies should be placed in section 5.3.3.5.

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in healthy subjects should be placed in this section.

5.3.3.2 Patient PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in patients should be placed in this section.

5.3.3.3 Intrinsic Factor PK Study Reports

Reports of PK studies to assess effects of intrinsic factors should be placed in this section.

5.3.3.4 Extrinsic Factor PK Study Reports

Reports of PK studies to assess effects of extrinsic factors should be placed in this section.

5.3.3.5 Population PK Study Reports

Reports of population PK studies based on sparse samples obtained in clinical trials including efficacy and safety trials should be placed in this section.

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

Reports of studies with a primary objective of determining the PD effects of a drug product in humans should be placed in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, should be placed in section 5.3.5.

This section should include reports of (1) studies of pharmacological properties known or thought to be related to the desired clinical effects (biomarkers), (2) short-term studies of the main clinical effect, and (3) PD studies of other properties not related to the desired clinical effect. Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and metabolite concentrations is usually of interest, PD information is frequently collected in dose–response studies or together with drug concentration information in PK studies (concentration-response or PK/PD studies). Relationships between PK and PD effects that are not obtained in well-controlled studies are often evaluated using an appropriate model and used as a basis for designing further dose–response studies or, in some cases, for interpreting effects of concentration differences in population subsets.

Dose-finding, PD, and/or PK–PD studies can be conducted in healthy subjects and/or patients, and can also be incorporated into the studies that evaluate safety and efficacy in a clinical indication. Reports of dose-finding, PD, and/or PK/PD studies conducted in healthy subjects should be placed in section 5.3.4.1, and the reports for those studies conducted in patients should be placed in section 5.3.4.2.

In some cases, the short-term PD, dose-finding, and/or PK–PD information found in PD studies conducted in patients will provide data that contribute to assessment of efficacy, either because they show an effect on an acceptable surrogate marker (e.g., blood pressure) or on a clinical benefit end point (e.g., pain relief). Similarly, a PD study may contain important clinical safety information. When these studies are part of the efficacy or safety demonstration, they are considered clinical efficacy and safety studies that should be included in section 5.3.5, not in section 5.3.4.

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

PD and/or PK/PD studies having nontherapeutic objectives in healthy subjects should be placed in this section.

5.3.4.2 Patient PD and PK/PD Study Reports

PD and/or PK/PD studies in patients should be submitted in this section.

5.3.5 Reports of Efficacy and Safety Studies

This section should include reports of all clinical studies of efficacy and/or safety carried out with the drug, conducted by the sponsor, or otherwise available, including all completed and all ongoing studies of the drug in proposed and nonproposed indications. The study reports should provide the level of detail appropriate to the study and its role in the application. ICH E3 describes the contents of a full report for a study contributing evidence pertinent to both safety and efficacy. Abbreviated reports can be provided for some studies (see ICH E3 and individual guidance by region).

Within section 5.3.5, studies should be organized by design (controlled, uncontrolled) and, within controlled studies, by type of control. Within each section, studies should be

categorized further, ordered by whether the study report is complete or abbreviated (ICH E3), with completely reported studies presented first. Published reports with limited or no further data available to the sponsor should be placed last in this section.

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate section 5.3.5 for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it should be included in the appropriate section 5.3.5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate section 5.3.5 and referenced as necessary in other sections 5.3.5, for example, section 5.3.5A, section 5.3.5B.

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication
The controlled clinical study reports should be sequenced by type of control:

- Placebo control (could include other control groups, such as an active comparator or other doses)
- No-treatment control
- Dose response (without placebo)
- Active control (without placebo)
- External (historical) control, regardless of the control treatment

Within each control type, where relevant to assessment of drug effect, studies should be organized by treatment duration. Studies of indications other than the one proposed in the application, but that provide support for efficacy in the proposed use, should be included in section 5.3.5.1.

Where a PD study contributes to evidence of efficacy, it should be included in section 5.3.5.1. The sequence in which studies were conducted is not considered pertinent to their presentation. Thus, placebo-controlled trials, whether early or late, should be placed in section 5.3.5.1. Controlled safety studies, including studies in conditions that are not the subject of the application, should also be reported in section 5.3.5.1.

5.3.5.2 Study Reports of Uncontrolled Clinical Studies
Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included in section 5.3.5.2. This includes studies in conditions that are not the subject of the marketing application.

5.3.5.3 Reports of Analyses of Data from More than One Study
Many clinical issues in an application can be addressed by an analysis considering data from more than one study. The results of such an analysis should generally be summarized in the clinical summary documents, but a detailed description and presentation of the results of such analyses are considered critical to their interpretation. Where the details of the analysis are too extensive to be reported in a summary document, they should be presented in a separate report. Such reports should be placed in section 5.3.5.3. Examples of reports that would be found in this section include: a report of a formal meta-analysis or extensive exploratory analysis of efficacy to determine an overall estimate of effect size in all patients and/or in specific subpopulations, and a report of an integrated analysis of safety that assesses such factors as the adequacy of the safety database, estimates of event rates, and safety with respect to variables such as dose, demographics, and concomitant medications. A report of a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information (e.g., PK and PD information), should be placed in this section if the analysis is too lengthy for inclusion in the Clinical Summary.

5.3.5.4 Other Study Reports
This section can include

- Reports of interim analyses of studies pertinent to the claimed indications
- Reports of controlled safety studies not reported elsewhere
- Reports of controlled or uncontrolled studies not related to the claimed indication
- Published reports of clinical experiences with the medicinal product that are not included in section 5.3.5.1. However, when literature is important to the demonstration or substantiation of efficacy, it should be included in section 5.3.5.1
- Reports of ongoing studies

5.3.6 Reports of PostMarketing Experience
For products that are currently marketed, reports that summarize marketing experience (including all significant safety observations) should be included in section 5.3.6.

5.3.7 Case Report Forms and Individual Patient Listings
Case report forms and individual patient data listings that are described as Appendices 16.3 and 16.4 in the ICH clinical study report guideline, should be placed in this section when submitted, in the same order as the clinical study reports and indexed by study.

5.4 Literature References
Copies of referenced documents, including important published articles, official meeting minutes, or other regulatory guidance or advice should be provided here. This includes copies of all references cited in the Clinical Overview, and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5, section 5.3. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available on request.

1. General Questions

Format or Content?
Will a dossier using the CTD format (Modules 2–5) be identical for all regions? Not necessarily. The CTD provides a common format for the submission of information to regulatory authorities in the three ICH regions. However, the CTD does not address the content of submissions. There are many regional requirements, as well as applicants' preferences, that could affect the contents of dossiers submitted in each region.

Expert Reports: Are expert reports still required for submissions under the CTD format? No. Expert reports are replaced by Module 2. (N.B. For specific European requirements regarding experts' signatures, please refer to the European Commission Web site.)

Tables of Contents and Pagination: For a paper CTD submission, the guideline states that, for the comprehensive Table of Contents in Module 1, no page numbers should be used. Does this apply only to the TOC in Module 1, or for all TOCs in every module? Also, besides the volume numbers and tab identifiers, should the module numbers also be

included? For Modules 3, 4, and 5, should the volume number be part of the Table of Contents? There are no specific guidelines for the page numbers of the TOC. Module numbers, volume numbers, and tab dividers should be part of all TOCs.

How to Paginate Literature References: When provided, how should Literature References be paginated in a paper CTD? Should each reference start with page 1, or should the page number from the source (journal, abstract, etc.) be the only page number included? Literature References should be paginated according to the page numbering of the source (journal, abstract, etc).

Subheading Numbering, or Numbering Within Sections: How should subnumbering within a document be organized? Some documents can be up to 50 pages in length with no defined CTD guideline heading, and potentially therefore no TOC entries or bookmarks (in the electronic version). Some guidance would be welcome to avoid regional interpretations on what is considered acceptable. Within the document, the applicant can use section numbers at a lower level than those specified in the CTD guideline. However, there should be no other headings appearing in the overall TOC going below the numbering given in the CTD guideline. *For example, for section 3.2.P.3.3 it would be possible to use subsequent numbers (3.2.P.3.3.1, 3.2.P.3.3.2, etc.) to provide further navigation within the document. These should not appear in the overall TOC but can be included as bookmarks within the PDF files.*

Titles of Documents Within Sections (e.g., reports etc.): In the header or footer of each document in a dossier, the appropriate TOC title entry should be included. In case of, for example, a clinical report, the TOC entry is the title of the report and this can be really long. Would the use of the report number (alone) be considered sufficient? In other words, can the layout of the pages throughout the dossier be different: One page layout for reports and another one for Quality sections? It is recommended that a distinct identifier be put in headers/footers on every page. However, it does not need to be the full title. An abbreviation would suffice.

Cross-References/Cross-Strings (in Paper Submissions): It is stated in the CTD that the section should be indicated in cross-strings. What is meant here: The section number, or the section number and section name? (The section name is in many cases too long to indicate in a cross-string.) Providing the section header in addition to the section number improves the clarity of the reference, particularly for the uninitiated reader. To reduce the length of the cross-string while maintaining the ease of use, it is recommended to include only the section number in the cross-string and write the text so the reader will also know the section content. For example, "...as seen in the population PK study 101 (5.3.3.5)" helps the reader to find the referenced study report under the Population PK Study Reports section. The text "...no safety problems were noted in the uncontrolled pneumonia study 101A (5.3.5.2)" helps the reader find the referenced study report under the section Study Reports of Uncontrolled Clinical Studies for the Pneumonia indication.

General Glossary of Terms: Will there be a general glossary of recommended terminology for use in the CTD?

No glossary of terms is planned at this time.

Location of the Information on Biological Comparability: A combined comparability section might be beneficial to the review process. Is it possible to consider a modification to the CTD to provide for such a section for Biological products? N.B. *Currently, comparability data should be included under 2.3.S.2/3; preclinically as proposed; and clinically under 2.5.2 and 2.5.6. Each part should summarize briefly the conclusions from the other sections (in the clinical summary, antigenicity should go under either 2.7.4.3 or 2.7.4.4 and in the clinical summary, "AEs of special interest" and "Mortality and Hospital Readmission" should go under 2.7.4.2.1.4 (Other significant AEs).* No, for the moment, the CTD does not foresee any separate section combining all the comparability data.

Information for Generic Drug Applications: Should the preclinical and clinical summary sections of the CTD be included in applications for generic drug approvals? More specifically, are Module 4 and 5 of the CTD applicable to Abbreviated New Drug Applications (ANDA) in the US and Abridged Marketing Authorization applications in the EU? Both categories of applications apply to generic drug applications, which ordinarily provide preclinical and clinical data based on available literature. The CTD provides a format for the submission of information to regulatory authorities. It does not define content. Please refer to region-specific requirements to determine content requirements for the specific submission type.

Font Style: On the basis of corporate identity, we use the font style "Arial" for all of our documents. Can we use the font style "Arial" for CTDs, or do we have to use "Times New Roman" style to match the recommendation for narrative texts according to the Guidance for Industry "Organization of the CTD"? "Times New Roman 12 point" is recommended for use in the CTD. This corresponds to MS Mincho, 10.5 point for the text written in Japanese.

Language: Can the CTD be in any language (e.g., Japanese, German, French, English)? Is it limited to a single language? The CTD does not address this issue. Please refer to regional guidance.

Changes of Numbering and Section Headers: With regard to the changes regarding numbering and section headers (September 11–12, 2002), are the details in brackets (e.g., name, manufacturer or name, dosage form) only for use in eCTD format or for paper files also? Headers and page numbering: What is your guidance for externally produced documents, for example chromatograms, CTD format DMF, regarding page numbering and appropriate headers? Are there allowances regarding these documents with regard to pagination and headers, that is, are we allowed to submit them in the relevant document without a header or page number? Tab: Do Tabs have to be printed? Do we have to use the full title with the number string on the tab? This is very difficult if the title is long. These changes in recommendation apply to all CTD/eCTD submissions. Please refer to the CTD General Q & As No. 5 on the ICH Web site. Tabs should be printed for a paper submission. Tab abbreviations are acceptable.

Is there a difference in the level of analysis in the nonclinical overview and the clinical overview in Module 2? Is there a difference between "critical analysis" (nonclinical overview) and "critical assessment" (clinical overview). Please refer to the general guidance for both the nonclinical and clinical overviews. The level of analysis does not differ between these two overviews. The guidance describes the information that should be included in the "critical and integral" assessment/analysis in both overviews.

Is the term "section," defined in the CTD? Is there a different use of the term in Module 2 and 3? Do the ICH regions define sections differently? Each section in the CTD is identified by a number and a heading. Please refer to the Granularity Document Annex for a description documents to be provided in each section. The annex delineates when multiple documents per heading may be provided. Also, refer to regional guidance as to when one or multiple documents should be provided per heading.

Does the deadline for mandatory submission of the CTD in Japan, the EU, and the US (highly recommended in the US) also refer to eCTD? Has ICH considered planning a seminar to help with CTD and eCTD submissions? The deadline does not refer to the eCTD although the regulatory authorities are accepting eCTD submissions. Please refer to regional guidance for specific guidance on eCTD submissions. Currently the ICH is not planning to conduct a CTD seminar. However, the ICH6 Conference, November 2003 in Osaka Japan, will focus on the CTD and eCTD.

Has the DTD reached its final stage of approval in the ICH process? The eCTD DTD has reached step 5 in the ICH process, which is the implementation step.

Is there a definition of which attachments should be included in the CTD? It is not suggested that additional attachments be included in the CTD.

CTD training

Does ICH recommend any particular comprehensive training course on the implementation of the CTD? No, there are no general ICH recommendations for training on CTD implementation.

Applicant's Logo: is it allowed to add the applicant's logo either on top of the CTD, or in the titles of CTD sections. The applicant is free to put his logo on top of the CTD. However, logos are not acceptable in CTD sections' titles. (The latter have been harmonized internationally; therefore, applicants are not allowed to modify them.)

Herbal CTD: Will a Herbal Products version of the CTD be published and how much will it vary from the pharmaceutical CTD. ICH does not plan to issue any specific version of the CTD for Herbal Products.

Granularity: Section headings and numbers, documents location/hierarchy, documents pagination: The CTD specifies many section headings and numbers. Could guidance be provided for all modules on headings in relation to document location and the section headings within those documents? Could guidance also be provided on where in the CTD and eCTD multiple documents can be located in the hierarchy? As a consequence of this definition, could guidance be given on how documents should be paginated and on what the module Table of Contents should therefore include? Please refer to the Annex of the Organization of the Common Technical Document: "Granularity Document".

Amendments and Variations in CTD Format: Is there a separate format for amendments/variations submitted in CTD format or should applicants use the CTD format as it is now? If used as it is now, is it enough to simply indicate whatever modules are not used? The CTD structure is suitable for amendments and variations (refer to regional guidance for applicabilities). The applicant should not submit the modules that are not used, that is, it is unnecessary to include "not applicable" pages against unused CTD headings.

2. Questions Regarding Location Issues

Introduction: This document is intended to provide additional guidance for the preparation of an application file in the CTD-Q format (see section 2: General Issues). It should be read in conjunction with the CTD-Q guideline (Modules 2 and 3). The document also addresses the relationship between linked CTD-Q sections for certain parameters, such as polymorphism, impurities, or particle size (see section 3: Associated Information Located in Different Sections). This document also clarifies location issues; that is, it indicates in which CTD-Q section(s), requested information should be placed (see section 4: Location Issues in Drug Substance, section 5: Location Issues in Drug Product, and section 6: Location Issues in Appendices). This document does not address the content of an application file. For content questions, refer to regional guidance.

General Issues

Separate or Repeated Sections. There can be a number of instances where repeated sections can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to by creating a distinguishing title in parentheses following the CTD-Q heading, for example, 2.3.S Drug Substance (Name, Manufacturer A).

Drug Substance. When more than one drug substance is used in a drug product, information should be presented separately as one complete Drug Substance section followed by other complete Drug Substance sections. In some cases, for a single drug substance, it could be considered appropriate and logical to have information presented in multiple Drug Substance sections. For example, separate sections can be warranted when a single drug substance is made at two different manufacturing sites with differences in the manufacturing processes. However, despite these differences, it is likely that these different processes will be described within the same relevant subsection of 3.2.S. If, on the other hand, the differences result in, for example, different specifications, then adding an additional Drug Substance section is recommended (see also Regional Guidance).

Drug Product. Depending upon regional requirements, different drug product presentations (e.g., strengths, container closure types and configurations, formulations) and/or manufacturing schemes (e.g., aseptic and terminal sterilization) can be submitted in the same dossier. In general, when a single dossier can be submitted, information for each of the product presentations and manufacturing schemes should be combined and presented together in one Drug Product section, with information for each of the product presentations and manufacturing schemes provided in the Appendices and Regional Information sections, as warranted. For example, if 100-mg tablets will be marketed in a bottle and a unit-dose blister package, the information should be presented in one Drug Product section. Where most of the quality information would be identical for the two drug products, the data common to both presentations should appear only once. The information that differs between the two should be presented as separate documents under the appropriate subsections (e.g., 3.2.P.7 Container Closure System, 3.2.P.8 Stability). In some cases, however, for product presentations or manufacturing schemes that can be included in a single dossier, it is considered more appropriate and logical to have information presented separately. Information presented separately means one complete Drug Product section followed by other complete Drug Product sections. One such example is that information on a drug product supplied with a reconstitution diluent should be presented in separate Drug Product sections for the drug product and the reconstitution diluent. These could be titled 3.2.P (Drug Product) and 3.2.P (Diluent).

Excipients. If appropriate, where a novel or noncompendial nonnovel excipient is proposed and a significant amount of data is provided for the excipient, this information should be provided in 3.2.A.3 Excipients, which follows the same format and level of subsections as the Drug Substance section. There should be a complete section of 3.2.A.3 Excipients for each novel excipient, or noncompendial nonnovel excipient.

Appendices. There can be occasions where it is appropriate to repeat an Appendix. For example, where a sponsor registers more than one manufacturing facility for the manufacture of a "Biotech" drug, the Appendix 3.2.A.1 should then be repeated.

Regional Information. The content of the Regional Information section (3.2.R) is not harmonized. In this section the documents, their titling and their order should be consistent with the requirements of the relevant region.

Multiple Containers. When there are two containers (e.g., PVC blister and PE bottle) for one drug product, the documents for the drug product part in Module 3 should generally be common. In this case, one set of documentation, 3.2.P.1 through 3.2.P.8, should be provided. The information for the blister and the bottle should be presented in the corresponding sections of the single drug product part in Module 3 (e.g., 3.2.P.7, 3.2.P.8), divided by subsections for each type of container and identified by the type of container.

Bioanalytical Methods. In the CTD, under what section should bioanalytical methods and their associated validation reports be included? In this context, bioanalytical methods are understood to mean analytical procedures used in clinical studies (human clinical pharmacology/bioavailability/bioequivalence) and/or nonclinical studies (nonhuman pharm/tox. studies). The description of analytical procedures and associated validation reports should be submitted in those modules where the corresponding studies are described (i.e., in Module 4, section 4.2.2.1 for analytical procedures and associated validation reports for nonclinical studies and in Module 5, section 5.3.1.4 for analytical procedures and associated validation reports used in clinical studies).

Drug Master Files (DMFs). Can the Drug Master File use the CTD format? Since the DMF systems differ in the three regions, ICH does not address this issue. Consequently, the applicant should check with the relevant competent authority in the region(s).

Drug Substance Containing Additives. If a drug substance is used in the form of a preparation (e.g., a [commercially available] vitamin trituration) in which module/section should the excipient(s) included in the preparation be described? Should the relevant information be given for example in section 3.2.S Drug Substance or in section 3.2.P.4 Drug Product—Control of Excipients? If the drug substance is defined as two or more materials, the manufacturing information would be described in 3.2.S.2.2 and the control of the additional material(s) [e.g., excipient(s)] would be described in 3.2.S.2.3.

3. Associated Information Located in Different Sections

Below, examples of multiple references in CTD-Q are proposed for polymorphism, particle size, and impurities. They indicate for some parameters that the information should not necessarily be located in one section, but should be split into different sections.

3.1 Polymorphism

3.2.S.1.3	If called for, list the polymorphic form(s) present in the proposed active as a characteristic of the drug substance.
3.2.S.2.2	Description of manufacturing process and process controls should indicate which polymorphic form is synthesized.
3.2.S.3.1	Studies performed to identify the potential polymorphic forms of the drug substance, including study results. Total number of polymorphs should be listed here and those intended to form the active should be summarized in 3.2.S.1.3.
3.2.S.4.1	Specification. If a polymorph is to be defined or limited, it should be discussed here.
3.2.S.4.2	Analytical procedures.
3.2.S.4.3	Validation of analytical procedures.
3.2.S.4.4	Results of batch analyses.
3.2.S.4.5	Justification of specification (if appropriate). Reasons as to why a particular limit on form is appropriate (should also probably refer to 3.2.P.2).
3.2.P.2. 1.1 and 3.2.P.2.2.3	Identifies the influence of polymorphism on the drug substance and dosage form.
3.2.P.5.1	Specification. If polymorphs are to be controlled in the drug product, they should appear here.
3.2.P.5.6	Justification of specification (if called for).

3.2 Particle Size

3.2.S.2.2	Description of manufacturing process and process controls.
3.2.S.3.1	Studies performed to identify the particle size distribution of the drug substance.
3.2.S.4.1	Specification.
3.2.S.4.2	Analytical procedures.
3.2.S.4.3	Validation of analytical procedures.
3.2.S.4.4	Results of batch analyses.
3.2.S.4.5	Justification of specification.
3.2.P.2.1.1 and 3.2.P.2.2.1	Identification of the influence of particle size on, for instance, dissolution performance (consult the ICH Q6A Decision Tree).

3.3 Impurities

3.2.S.3.2	Here, the discussion on impurities and information on their qualification should take place (reference to preclinical and clinical studies): For example, absolute amount at which the impurities can be considered as qualified.
3.2.S.4.1	Specification.
3.2.S.4.2	Analytical procedures.
3.2.S.4.3	Validation of analytical procedures.
3.2.S.4.4	Results of batch analyses (all batches including development, clinical, stability).
3.2.S.4.5	Justification of specification.
3.2.P.5.1	Specification.
3.2.P.5.2	Analytical procedures.
3.2.P.5.3	Validation of analytical procedures.
3.2.P.5.4	Results of batch analyses (all batches including development, clinical, stability).

3.2.P.5.5 Characterization of impurities (for those impurities not already discussed under section 3.2.S).

3.2.P.5.6 Justification of specification.

3.4 New Location of Quality Information for Investigational Formulations

How does the CTD link information on drug substance batch numbers, drug product batch numbers, nonclinical and clinical study numbers, the levels of impurities, history of formulation development, and any other relevant information? Please clarify the assignment of this information to the nonclinical and clinical sections. The history of development for the drug substance should be included in 3.2.S.2.6.A description of batches and the result of batch analyses should be included in 3.2.S.4.4. The history of formulation development should be included in 3.2.P.2.2.1.A description (including a summary table) of batches and the results of batch analyses for the drug product should be included in 3.2.P.5.4. This information on the history of development and description of batches can also be linked to the impurity levels of batches described in 3.2.S.3.2 and 3.2.P.5.5. Appropriate references to Modules 4 and 5 for the nonclinical and clinical studies can also be made.

3.5 Where Would the Information Related to Nonviral Adventitious Agents be Placed Within Module 3.2?

The following guidance supersedes the first sentence under 3.2.A.2 for nonviral adventitious agents: The detailed information regarding the routine manufacturing control of adventitious agents, such as bacteria, mycoplasma, and fungi, typically using well-established (e.g., pharmacopoeial) analytical procedures, should be provided in the appropriate sections within Module 3.2.S and 3.2.P. If well-established (e.g., pharmacopoeial) analytical procedures are not used, more detailed information regarding the analytical procedure(s) used should also be included in 3.2.S and 3.2.P. With respect to other nonviral adventitious agents, such as transmissible spongiform encephalopathy agents and prions, the detailed information, should be placed in 3.2.A.2.

3. Location Issues Questions in Drug Substance: 3.2.S

CTD-Q Section 3.2.	Issues/Questions	Answers
S.1 General Information		
S.1.1 Nomenclature		
S 1.2 Structure	Should drawings to show secondary and tertiary structures and, if applicable, quaternary structures of proteins be provided in 3.2.S.1.2?	Drawings to show secondary and tertiary structures and, if applicable, quaternary structures should be provided in 3.2.S.3.1.
S.1.3 General Properties	How much detailed information on the general properties of the drug substance should be included in 3.2.S.1.3?	As stated in CTD-Q, a list of physicochemical and other relevant properties of the drug substance, including biological activity, should be included in 3.2.S.1.3. The information on general properties should be provided only for the form of the drug substance used in the drug product, not possible alternative forms (e.g., polymorphs). More detailed information on the properties of the drug substance, including possible alternative forms, should be included in 3.2.S.3.1.
S.2 Manufacture		
S.2.1 Manufacturers		
S.2.2 Description of the Manufacturing Process and Process Controls	Should information on process controls be provided in section 3.2.S.2.2 or 3.2.S.2.4?	All process controls should be identified in 3.2.S.2.2. For critical controls, additional information should be provided in 3.2.S.2.4.
S.2.3 Control of Materials	Should the discussion and justification of starting materials be included in 3.2.S.2.3?	The discussion and justification of starting materials should be included in 3.2.S.2.3.
	Where should analytical procedures for materials described in 3.2.S.2.3 be included?	The analytical procedures for the control of materials (e.g., starting materials, reagents, raw materials, solvents) should be presented in section 3.2.S.2.3. For materials of biological origin, analytical procedures related to adventitious agent safety evaluation, if applicable, should be presented in 3.2.A.2.
	Since the addition of new headings is not an option, where in the CTD should one locate (Quality Section) information regarding a reagent used in the production of the drug substance when the reagent is manufactured via recombinant DNA technology?	The information should be located in 3.2.S.2.3: "Control of Materials."
S.2.4 Control of Critical Steps and Intermediates	Should batch data for intermediates or critical steps be included in 3.2.S.2.4?	Batch data, together with analytical procedures and acceptance criteria for intermediates or critical steps, would be presented in 3.2.S.2.4.
	If release tests are performed on intermediates and at critical steps instead of on drug substance, where would the information on the analytical procedures and acceptance criteria be presented in 3.2.S.4?	Acceptance criteria should be referred to in 3.2.S.4.1 and analytical procedures should be referred to in 3.2.S.4.2.

CTD-Q Section 3.2.	Issues/Questions	Answers
S.2.5 Process Validation and/or Evaluation	Where should justification for reprocessing be included?	If justification for reprocessing is warranted by a regional authority, the information would be included as part of the description of the manufacturing process in 3.2.S.2.2. If there are critical controls associated with the reprocessing operation, the critical controls should be included in 3.2.S.2.4. If validation information is warranted, the validation information should be included in 3.2.S.2.5.
S.2.6 Manufacturing Process Development	Should bioavailability/bioequivalence study results that demonstrate product comparability following process changes be described in 3.2.S.2.6?	Reports of Bioavailability/Bioequivalence studies that demonstrate comparability/equivalence after formulation or process changes should be presented in Module 5. Cross-references to these reports should be placed in section 3.2.S.2.6 (for drug substance process changes), 3.2.P.2.2.1 (for drug product formulation changes), or 3.2.P.2.3 (for drug product process changes).A brief summary of the reports can be placed in these sections when considered appropriate.
S.3 Characterization		
S.3.1 Elucidation of Structure and Other Characteristics	Where should studies conducted to determine the physicochemical characteristics of the drug substance be included?	Information on the studies conducted to determine the physicochemical characteristics of the drug substance should be included in 3.2.S.3.1. Only a list of the general properties of the drug substance should be included in 3.2.S.1.3.
S.3.2 Impurities	Should structural characterization data and a summary of the method of preparation of impurities be included in 3.2.S.3.2?	This information should be included in 3.2.S.3.2. Characterization of impurity reference standards should be provided in 3.2.S.5. See also Q&A under 3.3.
	Where should chromatograms be provided for impurities?	ICH Q3A identifies the chromatograms as part of the analytical validation studies. Therefore, relevant chromatograms should be included in 3.2.S.4.3.
	Where should nonclinical and clinical data supporting impurity levels be summarized?	The qualified level of each impurity with cross-reference to the supporting nonclinical/clinical studies should be included in 3.2.S.3.2.
	Should data on impurities reported in batch analyses be included in 3.2.S.3.2 or 3.2.S.4.4?	Data on observed impurities for relevant batches (e.g., clinical, nonclinical, stability) should be provided in 3.2.S.3.2. The data should be provided whether or not the impurity is included in the specification. This information can be cross-referenced to support other sections of the dossier as appropriate.
S.4 Control of Drug Substance		
S.4.1 Specification	If there are different specifications for a drug substance manufacturer and/ or applicant, should they all be provided in 3.2.S.4.1?	When appropriate, more than one specification should be included in 3.2.S.4.1.
	If alternative analytical procedures are used to control the drug substance, should they also be listed in the specification (3.2.S.4.1)?	Any analytical procedure used to control the drug substance, and the associated acceptance criteria, should be listed in the specification.
S.4.2 Analytical Procedures	Often an analytical procedure changes during the development of the drug substance. If this analytical procedure is submitted to support the dossier, in which section should these analytical procedures be placed?	Information on historical analytical procedures used to generate data included in the batch analyses should be included in 3.2.S.4.4.
	Should an analytical procedure that is only used for stability studies be included in 3.2.S.4.2?	Information on analytical procedures that are used only for stability studies should be included in 3.2.S.7.3.
	If the analytical methods for a drug substance and drug product are identical, can these methods and corresponding validation, if applicable, be described in either 3.2.S or 3.2.P, with a corresponding reference (e.g., a reference from 3.2.S to 3.2.P)?	The analytical methods should be placed in both the relevant sections of 3.2.S and 3.2.P, because the sample preparation, at least, will differ.
S.4.3 Validation of Analytical Procedures	Where should chromatograms be included?	Relevant chromatograms should be included in 3.2.S.4.3.
S.4.4 Batch Analyses	Where should results from all relevant batches be provided?	Results from all relevant batches (e.g., clinical, nonclinical, stability), including those batches used to justify acceptance criteria should be provided in 3.2.S.4.4.
	If there are results from tests that are not listed in the specifications, where should they be provided?	If results are submitted from tests that are not listed in the specification, they should be provided in 3.2.S.4.
	Where should collated data for a test from multiple batch analyses be presented?	If collated data from batch analyses is warranted, the data should be presented in 3.2.S.4.4.

CTD-Q Section 3.2.	Issues/Questions	Answers
S.4.5 Justification of Specification	Should justification for skip testing be included in 3.2.S.4.5? Rather than repeating information, can a summary of data from other sections with a cross-reference to the detailed information be provided to support the justification of specification section of the dossier?	If skip testing is considered appropriate, the justification should be included in 3.2.S.4.5. A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.
S.5 Reference Standards or Materials	Reference standards might be available for the active moiety and impurities. Should information on all reference standards be included in 3.2.S.5? Where should characterization data for a reference standard be placed in the CTD-Q?	If information is warranted for a reference standard, the information should be included in 3.2.S.5. Characterization data for the reference standard should be included in 3.2.S.5. Cross-reference to information in other sections (e.g., 3.2.S.3.2) can be included as considered appropriate.
S.6 Container Closure System		
S.7 Stability		
S.7.1 Stability Summary and Conclusions		
S.7.2 Postapproval Stability Protocol and Stability Commitment		
S.7.3 Stability Data	Should stress studies be located in 3.2.S.7.3? Should information on any changes in analytical procedures over the course of generating stability data be included in 3.2.S.7.3? Can data from supporting studies be included in 3.2.S.7.3? Should information on analytical procedures unique to the stability program be presented in 3.2.S.7.3?	Stress studies should be located in 3.2.S.7.3. These data can be referenced for validation of analytical procedures as considered appropriate. Information on historical analytical procedures used to generate the stability data should be included in 3.2.S.7.3. Data from supporting studies can be included in 3.2.S.7.3, if considered appropriate. Information on analytical procedures unique to the stability program should be included in 3.2.S.7.3.

4. Location Issues in Drug Product: 3.2.P

CTD-Q Section 3.2.	Issues/Questions	Answers
P.1 Description and Composition of the Drug Product	Where should information related to the composition of inks used on the drug product be placed? Where should information on reconstitution diluents be included? Should an overfill be indicated in 3.2.P.1? Can information on the composition of a drug product, other than what is listed in the CTD-Q guideline, be included in 3.2.P.1?	1. *All drug product components should be listed in 3.2.P.1. The composition (e.g., components of the capsule shell, components of inks) should also be included in 3.2.P1. In some regions, the qualitative composition of proprietary components can be replaced with reference to appropriate DMFs.* 2. *If the diluent is copackaged with the drug product, the information on the diluent should be placed in a separate Drug Product section. The compatibility of the drug product with reconstitution diluents should be discussed in 3.2.P.2.6.* 3. *The use of an overfill should be indicated in 3.2.P.1. The rationale for an overfill should be included in 3.2.P.2.2.1.* 4. When called for, additional information can be included to adequately describe the composition of the drug product, for example, (1) total weight, volume, etc., of unit, (2) tracers or markers, (3) composition statement for (purchased) mixtures, and (4) capsule shells.

CTD-Q Section 3.2.	Issues/Questions	Answers
P.2 Pharmaceutical Development		
P.2.1 Components of the Drug Product	Where should information on the development of copackaged diluents be placed?	There should be a separate Drug Product (Diluent) section for copackaged diluents. Choice and development of copackaged diluents should be included in 3.2.P.2.2.1 and 3.2.P.2.6.
P.2.1.1 Drug Substance	Where should a discussion of the drug substance stability or key physicochemical characteristics that might influence the manufacturing process of the drug product be provided? Where should a discussion of the effect of modification of active moiety (e.g., salt) on key drug substance physicochemical characteristics be provided? Where should data from studies on drug product to evaluate the potential effect of key drug substance physicochemical characteristics be provided?	Drug substance stability data should be included in 3.2.S.7 and cross-referenced as needed in 3.2.P.2 as appropriate. Discussion of key drug substance physicochemical characteristics that can influence manufacturability of the drug product should be included in 3.2.P.2.1.1. Discussion of effect of modification of active moiety (e.g., salt) on key drug substance physicochemical characteristics should be included in 3.2.P.2.1.1. Data from studies on drug product to evaluate the potential effect of key drug substance physicochemical characteristics should be provided in 3.2.P.2.1.1 [see ICH Q6A Decision Trees 3 and 4 (Part 2)].
P.2.1.2 Excipients	Should justification for using an excipient if there is evidence of incompatibility be included in 3.2.P.2.1.1 or 3.2.P.2.1.2? Where should a discussion of an excipient's influence on the manufacturability of the drug product be included? Where should a discussion of the ability of a functional excipient to perform through shelf-life be included?	Justification for using an excipient, if there is evidence of incompatibility should be included in 3.2.P.2.1.1 Discussion of excipients that can influence the manufacturability of the drug product should be included in 3.2.P.2.1.2. Discussion of the ability of functional excipients (e.g., antioxidants, penetration enhancers) to perform through shelf life should be included in 3.2.P.2.1.2. The effectiveness of antimicrobial preservatives should be discussed in 3.2.P.2.5.
P.2.2 Drug Product	Where should tables that describe the composition of formulations used in development studies be included?	Tables describing different development formulations should be included in 3.2.P.2.2.1.
P.2.2.1 Formulation Development	Where should information on IV–IV correlation be included in CTD-Q? Can cross-reference be made to bioequivalence information in other modules? Where should information to justify a scoring of tablets be included? Should the release mechanism of the dosage form for controlled release drug products be described in 3.2.P.2.2.1?	Summarized information on the in vivo–in vitro (IV–IV) correlation should be included in 3.2.P.2.2.1 with a cross-reference to the studies in Module 5. Cross-referencing to both Modules 2 and 5 can be included to facilitate the review process. The rationale/justification for scoring of tablets should be provided in 3.2.P.2.2.1. Description of the release mechanism in the dosage form for controlled release drug products should be included in 3.2.P.2.2.1.
P.2.2.2 Overages	Where should overages be justified?	Justification for overages should be included in 3.2.P.2.2.2.
P.2.2.3 Physicochemical and Biological Properties	Where should any discussion on dissolution development be included? Where should a discussion of the key drug product physicochemical or biological characteristics that might influence the manufacturing process of the drug product be provided? Where should data from studies on the potential effects of key drug substance physiochemical characteristics on the performance of the drug product be provided?	1. A summary of dissolution development should be included in 3.2.P.2.2.3, with cross-reference to studies in Module 5, as considered appropriate. The justification for the dissolution test should be included in 3.2.P.5.6. 2. A discussion of key drug product physicochemical or biological characteristics that can influence manufacturability of the drug product should be included in 3.2.P.2.2.3. 3. Data from studies on drug product to evaluate the appropriateness of the drug product acceptance criteria for physicochemical/ biological properties should be included in 3.2.P.2.2.3 [see ICH Q6A Decision Trees 4 (Part 3) and 7 (Part 1)].
P.2.3 Manufacturing Process Development	Where should justification of sterilization be provided? What information on clinical trial formulations should be included in 3.2.P.2.3?	1. When called for, justification of sterilization should be included in 3.2.P.2.3. 2. Information on clinical trial formulations should be included in 3.2.P.2.2.1. Information on the differences in the manufacturing process among supporting batches (e.g., clinical, stability) and the proposed production process should be included in 3.2.P.2.3.

CTD-Q Section 3.2.	Issues/Questions	Answers
P.2.4 Container Closure System	1. Should information on container closure system leachables and extractables be included in 3.2.P.2.4? 2. Where should performance characteristics of a container closure be provided? 3. Where should information on studies relating to cleaning of metered dose inhalers be included? 4. Where should information on the light protection characteristics of the container closure be provided?	1. Information on both should be included in 3.2.P.2.4. When warranted, information on leachables should also be included in 3.2.P.5.1 and 3.2.P.5.5. Also, if leachables are confirmed through shelf life as part of the formal stability studies, the results would be reported in 3.2.P.8.3. 2. Information on performance of the container closure system should be included in 3.2.P.2.4 (e.g., priming and repriming studies for metered dose inhalers). 3. Information on cleaning of metered dose inhalers should be included in 3.2.P.2.4. 4. Suitability of the container closure system to protect from light (e.g., light transmission data) should be discussed in 3.2.P.2.4. Photostability data should be provided in 3.2.P.8.3 (defined as a stress study in Q1A/ Q1B).
P.2.5 Microbiological Attributes	Should discussion of Decision Tree 6 from ICH Q6A be included in 3.2.P.2.5?	Discussions relating to ICH Q6A Decision Tree #6 (nonsterile drug substance and excipients) and Decision Tree #8 (nonsterile solid) should be provided in 3.2.P.2.5.
P.2.6 Compatibility	1. Where should data from constitution or dilution studies performed as part of the formal stability studies to confirm product quality through shelf life be provided? 2. Should compatibility of coadministered drugs be provided in 3.2.P.2.6? 3. Should information on incompatible diluents be provided in 3.2.P.2.6?	1. Information on the compatibility of reconstitution diluents to support claims on the label should be included in 3.2.P.2.6. Data from constitution or dilution studies that are performed as part of the formal stability studies to confirm product quality through shelf life should be reported in 3.2.P.8.3. 2. Compatibility with coadministered drugs should be included in 3.2.P.2.6. 3. Information on incompatible diluents should be provided in 3.2.P.2.6.
P.3 Manufacture		
P.3.1 Manufacturer(s)		
P.3.2 Batch Formula	Should overages be included in 3.2.P.3.2?	Overages should be included in the batch fomula in 3.2.P.3.2.
P.3.3 Description of Manufacturing Process and Process Controls	1. Where should reprocessing be described? 2. Should critical steps and intermediates be identified in P.3.3? 3. Should an overfill be identified in 3.2.P.3.3? 4. Should a statement regarding manipulation of ruminant-derived materials in the drug product manufacturing facility be included in 3.2.P.3.3?	1. Reprocessing should be included as part of the description of the manufacturing process in 3.2.P.3.3. If there are critical controls associated with the reprocessing operation, the critical controls should be included in 3.2.P.3.4. If validation information is warranted, the validation information should be included in 3.2.P.3.5. 2. All process controls should be identified in 3.2.P.3.3. For critical controls, additional information should be provided in 3.2.P.3.4. 3. An overfill should be identified in 3.2.P.3.3. 4. A statement regarding manipulation of ruminant-derived materials in the drug product manufacturing facility should be included here (3.2.P.3.3). If a potential for cross-contamination with adventitious agents exists, additional information should be provided in 3.2.A.1 and 3.2.A.2.
P.3.4 Controls of Critical Steps and Intermediates	Should the detailed information on critical steps and intermediates that have been identified in 3.2.P.3.3 be included in 3.2.P.3.4? Should critical process control values from relevant batches be included in 3.2.P.3.4 to support numeric ranges, limits, etc., for the critical process controls? Where should information on the analytical procedures for an in-process material test performed in lieu of a finished product test be included? If a process test were to replace an end-product test, where would it be mentioned in the specification?	Detailed information should be provided in 3.2.P.3.4 for critical steps and all intermediates that are controlled. Critical process control values from relevant batches to support numeric ranges, limits, etc., for critical process controls should be included in 3.2.P.3.4. In 3.2.P.3.4, the same information should be provided for an in-process material test performed in lieu of a finished product test as that submitted for a finished product test (analytical procedure, methods validation information). If a process test takes the place of an end-product test, it should be listed in the specification (3.2.P.5.1) and specified as a process test (see ICH Q6A).

CTD-Q Section 3.2.	Issues/Questions	Answers
P.3.5 Process Validation and/or Evaluation		
P.4 Control of Excipients	If a significant amount of data for an excipient (e.g., a novel excipient or a noncompendial nonnovel excipient) needs to be provided, where would it be placed?	This information should be included in 3.2.A.3 excipients, if required. If only a minimal amount of information was necessary for these excipients (e.g., pharmacopoeial), this information should be provided in 3.2.P.4.1 and/or 3.2.P.2.1.2.
P.4.1 Specifications		
P.4.2 Analytical Procedures		
P.4.3 Validation of Analytical Procedures		
P.4.4 Justification of Specifications	Where should certificates of analysis or batch data for excipients be included? Can a summary of data from other sections with a cross-reference to the detailed information be provided, rather than repeating this information to support the Justification of Specifications section of the dossier?	Certificates of analysis or batch data for excipients should be included in 3.2.P.4.4. A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.
P.4.5 Excipients of Human or Animal Origin	Where should information on excipients of human or animal origin be located?	Information on excipients of human or animal origin should be included in 3.2.P.4.5. Information on adventitious agent safety evaluation should be included in 3.2.A.2. For the location of certifications relating to TSE/BSE, see region specific guidance.
P.4.6 Novel Excipients		
P.5 Control of Drug Product		
P.5.1 Specification(s)	Where should release and shelf life specifications be located? If alternative analytical procedures are used to control the drug product, should they be listed in the specification (3.2.P.5.1) also?	Both specifications should be included in 3.2.P.5.1 (See also question for 3.2.P.8.1). Any analytical procedure used to control the drug product, and the associated acceptance criteria, should be listed in the specification.
P.5.2 Analytical Procedures	Often an analytical procedure changes during the development of the drug product. If this analytical procedure is submitted to support the dossier, in which section should it be placed? Should an analytical procedure that is only used for stability studies be included in 3.2.P.5.2? If the analytical methods for a drug substance and drug product are identical, can these methods and corresponding validation, if applicable, be described in either 3.2.S or 3.2.P, with a corresponding reference (e.g., a reference from 3.2.S to 3.2.P)?	Information on historical analytical procedures used to generate data included in the Batch Analyses section should be included in 3.2.P.5.4. Information on analytical procedures that are used only for stability studies should be included in 3.2.P.8.3. The analytical methods should be placed in both the relevant sections of 3.2.S and 3.2.P because the sample preparation, at least, will usually differ.
P.5.3 Validation of Analytical Procedures		
P.5.4 Batch Analyses	Should results from all batches be provided in 3.2.P.5.4? Should the description of the batches (e.g., batch number, manufacturing site, use) be included in 3.2.P.5.4? If there are results from tests that are not listed in the specifications, where should they be provided? Where should collated data for a test from multiple batch analyses be presented?	Results from all relevant batches (e.g., clinical, nonclinical, stability), including those batches used to justify acceptance criteria, should be provided in 3.2.P.5.4. Information describing the batches should also be included in 3.2.P.5.4. If results are submitted from tests that are not listed in the specification, they should be provided in 3.2.P.5.4. If collated data from batch analyses is warranted, the data should be presented in 3.2.P.5.4.
P.5.5 Characterization of Impurities	Should all observed impurities be listed in 3.2.P.5.5 even if they are not included in the drug product specification?	All observed impurities should be listed. Justification for not including an observed impurity in the specification should be included in 3.2.P.5.6.

CTD-Q Section 3.2.	Issues/Questions	Answers
P.5.6 Justification of Specification(s)	Should justification for skip testing be included in 3.2.P.5.6? Can a summary of data from other sections with a cross-reference to the detailed information be provided to support the justification of the specification rather than repeating information?	If skip testing is considered appropriate, the justification should be included in 3.2.P.5.6. A summary of data from other sections with a cross-reference to the detailed information can be provided to support the justification of specification.
P.6 Reference Standards or Materials	Reference standards might be available for the active moiety and impurities. Should information on all reference standards be included in 3.2.P.6?	Where considered appropriate, a reference standard cited in 3.2.S.5 can be cross-referenced in 3.2.P.6. Information on all other reference standards should be included in 3.2.P.6.
P.7 Container Closure System		
P.8 Stability		
P.8.1 Stability Summary and Conclusion	Should the shelf life specification be repeated under this section? Where should the design and justification for a reduced stability design (e.g., bracketing or matrixing) be discussed?	The shelf life specification should be indicated in 3.2.P.8.1. The design and justification for a reduced stability design should be included in 3.2.P.8.3.
P.8.2 Postapproval Stability Protocol and Stability Commitment		
P.8.3 Stability Data	Should stress studies be located in 3.2.P.8.3? Should information on any changes in analytical procedures over the course of generating stability data be included in 3.2.P.8.3? Can data from supporting studies be included in 3.2.P.8.3? Should information on analytical procedures unique to the stability program be presented in 3.2.P.8.3? Where should the statistical analysis of the stability data be included?	Stress studies should be located in 3.2.P.8.3. These data can be referenced for validation of analytical procedures as considered appropriate. Information on historical analytical procedures used to generate the stability data should also be included in 3.2.P.8.3. Data from supporting studies can be included in 3.2.P.8.3, if considered appropriate. Information on analytical procedures unique to the stability program should be included in 3.2.P.8.3. The detailed statistical analysis report, if included, should go in 3.2.P.8.3, and a summary or conclusions of the statistical analysis should go in 3.2.P.8.1.

5. **Location Issues in Appendices: 3.2.A**

CTD-Q Section 3.2.	Issues/ Questions	Answers
A Appendices	If information for both the drug substance and the drug product should be included in an appendix (e.g., 3.2.A.1), how should it be presented? Should 3.2.A.3 be retitled from Novel Excipients to Excipients to include noncompendial nonnovel excipients?	If drug substance and drug product information is included in the appendices, then the preferred presentation is drug substance first and then drug product within each section, for example, 3.2.A.1 (Drug Substance, then Drug Product), then 3.2.A.2 (Drug Substance, then Drug Product), then 3.2.A.3 (Drug Substance, if applicable, then Drug Product). At ICH, the title of 3.2.A.3 was changed to Excipients (see 3.2.P.4) to include noncompendial nonnovel excipients.

6. Safety

Kinetics in Pregnant Animals and Neonates: Kinetics in pregnant animals and neonates are included in the PK section. Is it expected that these data will come from PK studies, or can they be from kinetics in the Segment 2 studies? The CTD-S guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

Conduct/Nonconduct of Specific Studies: **If a particular category of toxicology studies (e.g., carcinogenicity) is not conducted for a drug because of the nature of the drug (e.g., oncology agent), should the section heading be maintained in the CTD document with an explanation provided as to why these studies were not conducted, or should the heading section be deleted and subsequent sections renumbered?** Section headings should be maintained in the CTD document and a brief explanation provided as to why these studies were not conducted.

Pivotal Studies: Would a 3-month toxicity study that was needed to support clinical studies of 3-month duration, that was later replaced with a 9-month toxicity study, be considered "pivotal" and tabulated as in Table 2.6.7.7? Yes. There should be one table for each of the repeat-dose toxicity studies specified by ICH Guideline M3, as well as any other repeat-dose toxicity studies that could be considered pivotal.

Tabulated Summary: Are only toxicologically significant changes, as considered by applicants, to be tabulated in CTD? Only noteworthy findings should be tabulated in CTD. These might include statistically significant differences from controls, as well as noteworthy findings that are not statistically significant.

Impurity Data Table in CTD-Safety—(1) Generally speaking, it is unlikely to have the finalized specification for related substances and their analytical method throughout drug development. Therefore, direct comparison of related-substance data between different stages of development would be very difficult, because of analytical method changes. One purpose of the "Drug Substance" table is to facilitate a review of the qualification of the specified impurities. If the analytical methods have changed, information on early batches may not be applicable for qualification of impurities. In this case, it is recommended to use footnotes in the "Drug Substance" table to identify the batches that are relevant to qualification of impurities.

Impurity Data Table in CTD Safety—(2) Should impurity-specification test results of test articles used in early stage toxicology studies be included in CTD tables? Do test articles of non-GLP studies in the CTD need to have specification test data? There is no requirement to analyze the drug substance used in non-GLP studies. However, if such analyses have been conducted, the results should be included in the "Drug Substance" table.

List of References: A section for list of references of the nonclinical summary (2.6.8 or 2.6.2.8 plus 2.6.4.11 plus 2.6.6.11) is not covered in the guidance, unlike for the clinical summary and both nonclinical and clinical overview. Could you please provide clarity where in these summaries lists of references should be included? Applicants can place the list of references in the most appropriate location and create new subsection numbers as far as it facilitates the best possible understanding by the regulatory reviewers.

Nonclinical PKs: A number of studies in nonclinical PKs could appear more than one place in this section. Should we add nonclinical PK studies to all PKs sections? In such a case, the sponsor could either put that study report in the first place in the CTD module (i.e., Absorption section) and then cross reference to this study report in the remaining sections, or place the full study report in each adequate section. If submitting an eCTD, a sponsor needs not submit multiple files are not required. References to the one file should be provided.

Microbiology data: The microbiology data will include both in vitro **and** in vivo **studies. Where should the microbiology summary, overview, and study reports be included?** The Microbiology data from both in vitro and in vivo studies should be included with the Efficacy information. The summary information should be provided in the appropriate section 2.7 Clinical Summary and the reports should be filed in section 5.3.5.4 Other Study Reports. In addition, the microbiology information can be described in the Nonclinical sections as appropriate.

The template for local tolerances (2.6.7.16) in M4S does not provide an example of a tabulated summary of a local tolerance. Is there one available? The template for 2.6.7.16 is the same as the template for 2.6.7.17. Therefore for an example of 2.6.7.16, please refer to the example of 2.6.7.17.

In the development of human monoclonal antibodies, part of the nonclinical development is to perform two cross-reactivity studies (1) animal species cross reactivity study and (2) human tissue cross reactivity study. The animal species cross reactivity test is not really a toxicity study, and the human tissue cross reactivity study is not a study generally performed. We are in doubt where to place these in Module 4. Where should these studies be placed in Module 4? Under 4.2.3.7 Other toxicity studies? Applicants can place such studies in the most appropriate location in Module 4 in order to facilitate the best possible understanding by the regulatory reviewers. *(This can be the similar answer to the Question 8.)*

7. Efficacy

Clinical study reports contained in Module 5 are cited in the Clinical Overview and/or the Clinical Summary in Module 2. Each clinical study report may be given a unique short name when cited. Does the method of citing and naming have to be uniform throughout all modules? We recommend that each study have a unique short identifier that is used consistently throughout the application. The applicant can select the identifier. The full title of the study is provided in the Tabular Listing of All Clinical Studies (section 5.2).

Definitions/Terminology: What is the definition of "Common Adverse Events" as used in the CTD? Guidance is provided by ICH E3 Guideline.

Section Numbering/Title (in Module 5): In the module 5 of the CTD, is it necessary to have a section number for each clinical study report in a certain section, or is it enough just to mention the title:

How many pages should a Clinical Summary be for an application that contains multiple indications? (section 2.7): The estimated size of this document is 50 to 400 pages, assuming one indication. Applications that include multiple indications will be larger, reflecting the submission of multiple efficacy sections.

Section "2.7.3.3" Comparisons and Analyses of Results across Studies: The Guideline provides "This section should also cross-reference important evidence from section 2, such as data that supports the dosage and administration section of the labeling." However, this

Guideline also provides "section 2.7.3.4. Analysis of Clinical Information Relevant to Recommended Dose." Please specify how to differentiate the two sections "2.7.3.3" and "2.7.3.4." Section 2.7.3.3 summarizes the data across all studies that characterize efficacy of the drug; section 2.7.3.4 provides an integrated summary of the dose–response or blood concentration–response relationships of effectiveness. In both cases, supportive data from section 2.7.2 can also be incorporated.

Overall Extent of Exposure (section 2.7): In the Guideline, a table is required to be generated to present the overall extent of drug exposure in all phases of the clinical development. Should the table include "patients alone" or "patients and healthy subjects"? The table should refer to all subjects exposed to at least one dose of the drug product. Appropriate subsets of subjects relevant to the proposed indications should also be identified and considered.

Summary of Clinical Safety (section 2.7): Where should information be described concerning the validity of extrapolation of foreign clinical safety data to a new region? Summaries of any bridging studies using clinical end points [i.e., certain studies intended to evaluate the ability to extrapolate certain types of foreign clinical data to the new region (see ICH E5)] should be included in section 2.7.3.2. Where appropriate, such information should also be described in the summarization of safety data as related to intrinsic and extrinsic ethnic factors (ICH E5), in sections 2.7.4.5.1 and 2.7.4.5.2. Finally, some applications might include in section 5.3.5.3a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information. Such information should be included in that detailed analysis of bridging.

Bioavailability/Bioequivalence Study Data (Module 5): Where should the information on bioequivalence studies for a generic application be included? Bioavailability study reports should be included in Module 5 (Clinical documentation), under section 5.3.1 "Reports of Biopharmaceutical Studies." More specifically, reports of comparative Bioavailability/Bioequivalence studies should go under section 5.3.1.2.

Tabular Listing of Clinical Studies in Paper CTD: In module 5, 5.2 is denoted as the "Tabular Listing of all Clinical Studies." Is this section for a summary listing of all clinical studies in the submission, or it is for the listings of the individual study reports? In other words, should the listings from the appendices of the individual study reports be included here, rather than as an appendix to the CSR, or are these only listings that summarize all studies?

The tabular listing described in section 5.2 is a listing of all clinical studies in the submission.

ISS/ISE

Does the CTD section on safety in Module 2 replace the section under 21 CFR 314.50(d)(5)(v, vi) calling for integrated summary of safety and effectiveness (ISS/ISE)? The ISS/ISE are critical components of the safety and effectiveness submission and are expected to be submitted in the application in accordance with the regulation. FDAs Guideline for the Format and Content of Clinical and Statistical Sections of Application gives advice on how to construct these summaries. Note that, despite the name, these are integrated analyzes of all relevant data, not summaries. The Clinical Safety sections of the CTD follow approximately the outline of the sections of the ISS/ISE, although they are somewhat modified by experience with ICH E-3 (Structure and Content of Clinical Study Reports). The CTD Clinical Overview and Summary in Module 2 will not usually contain the level of detail expected for an ISS. It may contain the level of detail needed for an ISE, but this would need to be determined on a case-by-case basis. If, the requirements of 21 CFR 314.50 can be met for a particular application by what is in the CTD Module 2 summary, then the CTD Module 2 section would fulfill the need for an ISS/ISE. In some cases it will be convenient to write much of what is needed in the CTD Module 2 with appropriate appendices in Module 5. In other cases, the ISS/ISE would be summarized in Module 2, with detailed reports in Module 5. Any questions about these matters can be raised with the reviewing division.

Microbiology Data: The microbiology data will include both in vitro and in vivo studies. Where should the microbiology summary, overview and study reports be included? The Microbiology data from both in vitro and in vivo studies should be included with the Efficacy information. The summary information should be provided in the appropriate section 2.7 Clinical Summary and the reports should be filed in section 5.3.5.4 Other Study Reports. In addition, the microbiology information can be described in the nonclinical sections as appropriate.

Clinical Variation: For a clinical variation application, is it mandatory to submit a clinical overview and a clinical summary, or is it acceptable to submit either only an overview or only a summary? What are the parameters/conditions to be taken into account for choosing one or the other approach? Since variation is a term from the EU regulations, the answer should be provided by the EMEA.

Integrated analysis of efficacy (ISE) – Section 2.7 Clinical Summary—Statistical Listings: What approach should applicants take for the formatting and presentation of their integrated analyzes when they have large amounts of statistical output to present (several thousands of pages)?

As stated in section Reports of Analyzes From More Than One Study 5.3.5.3, where the details of the analysis are too extensive to be reported in a summary document, for example, section Clinical Summary 2.7, they should be presented in a separate report. Such report should be placed in section 5.3.5.3.

Cross references/Cross-strings (in Paper Submissions): It is stated in the CTD that the section should be indicated in cross-strings. What is meant here: The section number, or the section number and section name? (The section name is in many cases too long to indicate in a cross-string.) Providing the section header in addition to the section number improves the clarity of the reference, particularly for the uninitiated reader. To reduce the length of the cross-string while maintaining the ease of use, it is recommended to include only the section number in the cross-string and write the text so the reader will also know the section content. For example, ". . .as seen in the population PK study 101 (5.3.3.5)" helps the reader to find the referenced study report under the Population PK Study Reports section. The text ". . .no safety problems were noted in the uncontrolled pneumonia study 101A (5.3.5.2)" helps the reader find the referenced study report under the section Study Reports of Uncontrolled Clinical Studies for the Pneumonia indication.

Limitations of the Safety Database and Potential Implications: Section 2.5 Clinical Overview and section 2.5.5 Overview of Safety both refer to an assessment of the limitations of the safety database but give few details on

how to describe them. How should these limitations be described? In addition, there is no specific reference to any postmarketing steps the applicant can take to remedy those limitations. Where should a discussion of any postmarketing pharmacovigilance and other postmarketing study plans go? A fuller discussion of how to describe in the CTD the limitations of the safety database and the potential implications for the safety of the drug when marketed is as follows:

- Nonclinical toxicology and safety pharmacology concerns, such as those arising from reproductive/developmental toxicity, carcinogenicity, hepatic injury, central nervous system injury, or effects on cardiac repolarization that are not fully resolved by available human data, or that arise from incomplete testing.
- Limitations of human safety database, such as:
  - Patient selection criteria that excluded people who are likely to be candidates for treatment in medical practice.
  - Evaluations that were deficient for certain purposes (e.g., many drugs with sedative properties are not evaluated for effects on cognitive function in the elderly).
  - Limited exposure of demographic or other subgroups, such as children, women, the elderly, or patients with abnormal hepatic or renal function.
- Identified adverse events and potential adverse events that require further characterization or evaluation with respect to frequency and/or seriousness in the general population or in specific subgroups.
- Important potential risks (e.g., known risks of pharmacologically related drugs) that require further evaluation.
- Drug–drug interactions that have not been assessed adequately.

Such information should be described and discussed in section 2.5.5 Overview of Safety, with appropriate cross references to section 2.7.4 Summary of Clinical Safety and any other relevant sections.

A discussion of any planned postmarketing activity or study to address the limitations of the premarketing safety database, should also be included in section 2.5.5 Overview of Safety, with any protocols for specific studies provided in section 5.3.5.4 Other Clinical Study Reports or other sections as appropriate (e.g., module 4 if the study is a nonclinical study).

An ICH guideline (E2E Pharmacovigilance Planning) is being developed to further address the question of how to describe the safety data and its limitations and how to describe planned postmarketing activities and studies.

Multiple Indications: When submitting one dossier for multiple indications, how should the applicant present them in the clinical part of the registration dossier, for example sections 2.5 Clinical Overview, 2.7.3 Summary of Clinical Efficacy and 5.3.5 Reports of Efficacy and Safety Studies? One section 2.5 Clinical Overview is recommended for multiple indications to be registered along with development rationale and cross-referencing to the corresponding 2.7.3 and 5.3.5 sections; the "benefit/risk" conclusions should support corresponding claimed indications. For section 2.7.3 Summary of Clinical Efficacy, in the case of more than one indication, the following organization is recommended as applicable. The current CTD numbering should be retained with identification of the indication, for example:

2.7.3.UTI	Summary of Clinical Efficacy
2.7.3.1.	UTI Background
2.7.3.2.	UTI Summary of Results of Individual Studies
2.7.3.3.	UTI Comparison and Analysis
2.7.3.3.1	UTI Study Population
2.7.3.3.2.	UTI Comparison of Efficacy Results
2.7.3.	Pneumonia Summary of Clinical Efficacy
2.7.3.1.	Pneumonia Background

Other sections follow the same organization where applicable.

For section 5.3.5 Reports of Efficacy and Safety Studies, in case of more than one indication, the following organization is recommended as applicable. The current CTD numbering should be retained with identification of the indications, for example:

5.3.5.	UTI
5.3.5.1.	UTI Controlled Studies
5.3.5.2.	UTI Uncontrolled Studies
5.3.5.	Pneumonia
5.3.5.1.	Pneumonia Controlled Studies
5.3.5.2.	Pneumonia Uncontrolled Studies

Other sections follow the same organization, where applicable.

Narrative descriptions: The CTD guidance for Section Overall Safety Evaluation Plan and Narratives of Safety Studies 2.7.4.1.1 states that narrative descriptions for studies that contributed both efficacy and safety should be included in Section Summary of Results of Individual Studies 2.7.3.2 and only referenced in the safety section. Please clarify whether the narrative to be included in 2.7.3.2 should include the safety results as well as "enough detail to allow the reviewer to understand the exposure. . . and how safety data were collected" or whether the results should be included in section 2.7.4.1.1. In general, safety results should be described in section 2.7.4.1.1, because section Summary of Clinical Efficacy 2.7.3 is devoted to efficacy. To avoid the need to describe the same study twice, section 2.7.3.2 asks for a reasonably complete description of studies pertinent to both safety and efficacy, including, in study narratives, information about the extent of exposure of study subjects to the test drug and how safety data were collected. This approach is confirmed in section 2.7.4.1.1, which notes that narratives for studies contributing both safety and efficacy data should be included in section 2.7.3.2. As noted in section Background and Overview of Clinical Efficacy 2.7.3.1, however, any results of these studies that are pertinent to evaluation of safety should be discussed in section Summary of Clinical Safety 2.7.4.

According to ICH E3 Structure and Content of Clinical Study Reports, the case report forms should be located in Appendix 16.3, the individual patient data listings in Appendix 16.4 and the publications and literature references in Appendices 16.1.11 and 16.1.12 respectively. The CTD organization provides locations for case report forms and individual patient data listings in Module 5.3.7 and for literature references in Module 5.4. Can clarity be provided as

to where these items should actually be placed in CTD and the eCTD submissions? For paper submissions, case report forms and individual patient data listings should be located in Module 5.3.7, identified by study. For eCTD, PDF files for case report forms and individual patient data listings should be organized by study in the folder for Module 5.3.7. However, in the *index.xml* file the leaf elements for the case report forms and individual patient data listings should be included under the same heading as other study report files with additional information included with any accompanying study tagging file. In addition, a repeat of the leaf element can be placed under the heading 5.3.7 Case Report Forms and Individual Patient Data Listings. Datasets, if required by the region, should be organized according to regional guidance. For paper submissions publications and literature references should be located in Module 5.4. For eCTD, the files for publications and literature references should be located in the folder for Module 5.4. However, in the *index.xml* file the leaf elements for the publications and literature references should be included under the same heading as other study report files with additional information included with any accompanying study tagging file. In addition, a repeat of the leaf element should be placed under the heading for 5.4 Literature References.

4

Process Validation: General Principles and Practices

I. INTRODUCTION

This guidance outlines the general principles and approaches that FDA considers to be appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients (API or drug substance), collectively referred to in this guidance as drugs or products. This guidance incorporates principles and approaches that manufacturers can use in validating a manufacturing process based on guidance principles listed in the references at the end of this chapter.

This guidance aligns process validation activities with the product lifecycle concept and with existing FDA guidance. The lifecycle concept links product and process development, qualification of the commercial manufacturing process, and maintenance of the process in a state of control during routine commercial production. This guidance promotes modern manufacturing principles, process improvement, innovation, and sound science and applies to all drugs, human, veterinary, biological, finished products, pharmaceutical and biological API but is not relevant for dietary supplements, medical devices, type A medicated articles and human transplant tissues.

This guidance also does not specifically discuss the validation of automated process control systems (i.e., computer hardware and software interfaces), which are commonly integrated into modern drug manufacturing equipment. This aspect is discussed elsewhere in another chapter. This guidance is relevant, however, to the validation of processes that include automated equipment in processing.

II. BACKGROUND

In the Federal Register of May 11, 1987 (52 FR 17638), FDA issued a notice announcing the availability of a guidance entitled "Guideline on General Principles of Process Validation" (the 1987 guidance). This guidance includes many changes to the original concepts of validation and includes FDA's current thinking on process validation in concordance with the goals of FDA's initiative entitled "Pharmaceutical CGMPs for the 21st Century—A Risk-Based Approach," particularly with regard to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality system tools and concepts.

FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The current good manufacturing practice (CGMP) regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess [21 CFR 211.100(a) and 211.110(a)]. Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use; this principle incorporates the understanding that the following conditions exist:

- Quality, safety, and efficacy are designed or built into the product.
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.
- Each step of a manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes including specifications.

For purposes of this chapter, process validation is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products. Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes the process validation activities in three stages.

- Stage 1—Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2—Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.
- Stage 3—Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

This chapter describes activities typical in each stage, but in practice, some activities in different stages might overlap.

Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained a high degree of assurance in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity, and potency. The assurance should be obtained from objective information and data from laboratory-, pilot-, and/or commercial-scale studies. Information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions, including those conditions that pose a high risk of process failure.

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control that is appropriate for the manufacturing process. Manufacturers should

- understand the sources of variation,
- detect the presence and degree of variation,
- understand the impact of variation on the process and ultimately on product attributes, and
- control the variation in a manner commensurate with the risk it represents to the process and product.

Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the product. Focusing on qualification efforts without understanding the manufacturing process may not lead to adequate assurance of quality. After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change.

III. STATUTORY AND REGULATORY REQUIREMENTS FOR PROCESS VALIDATION

Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement under section 501(a)(2)(B) of the Act, which states the following:

> A drug . . . shall be deemed to be adulterated . . . if . . . the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

FDA regulations describing CGMP are provided in 21 CFR parts 210 and 211.

Process validation is required, in both general and specific terms, by the CGMP regulations in parts 210 and 211. The foundation for process validation is provided in § 211.100(a), which states that "[t]here shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess" (emphasis added). This regulation requires that manufacturers design a process including operations and controls that will result in a product meeting these attributes. Product quality in the context of process validation means that product performance is consistent from batch-to-batch and unit-to-unit. Many products are single-source or involve complicated processes to manufacture. Validation also offers assurance that a process is reasonably safeguarded from sources of variability affecting production output, the loss of which can cause supply problems, thereby negatively affecting public health.

Other CGMP regulations define the various aspects of validation. Section 211.110(a), Sampling and testing of in-process materials and drug products, requires that control procedures ". . . be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product" (emphasis added). This regulation establishes the requirement that even well-designed processes must include in-process control procedures to assure final product quality.

CGMP regulations require that batch samples represent the batch under analysis [see, e.g., § 211.160(b)(3)] and that the sampling plan result in statistical confidence [§ 211.165(c) and (d)] that the batch meets its predetermined specifications [§ 211.165(a)]. Section 211.110(b) provides two principles to follow when establishing in-process specifications. The first principle is that ". . . in-process specifications for such characteristics (of in-process material and the drug product) shall be consistent with drug product final specifications . . . ." Accordingly, in-process material should be controlled to assure that the final drug product will meet its quality requirements. The second principle in this regulation further requires that in-process specifications ". . . shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate." This requirement, in part, establishes the need for manufacturers to analyze process performance and control batch-to-batch variability.

The CGMP regulations also describe and define activities connected with process design, development, and maintenance. Section 211.180(e) requires that information and data about product performance and manufacturing experience be periodically reviewed to determine whether any changes to the established process are warranted. Ongoing feedback about product performance is an essential feature of process maintenance.

In addition, the CGMP regulations require that facilities in which drugs are manufactured be of suitable size, construction, and location to facilitate proper operations (21 CFR 211.42). Equipment must be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use (21 CFR 211.63). Automated, mechanical, and electronic equipment must be calibrated, inspected, or checked according to a written program designed to assure proper performance (21 CFR 211.68).

In summary, the CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably.

IV. RECOMMENDATIONS

A. General Considerations for Process Validation

In all stages of the product lifecycle, good project management and good archiving that capture scientific knowledge will make the process validation program more effective and efficient. These practices should ensure uniform collection and assessment of information about the process, reduce the chance for redundant information gathering and analysis, and enhance the accessibility of such information later in the product lifecycle.

An integrated team approach is recommended to process validation that includes expertise from a variety of disciplines, including process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance. Project plans, along with the full support of senior management, are essential elements for success.

Throughout the product lifecycle, various studies can be initiated to discover, observe, correlate, or confirm information about the product and process. All studies should be planned and conducted according to sound scientific principles, appropriately documented, and should be approved in accordance with the established procedure appropriate for the stage of the lifecycle.

B. Specific Stages and Activities of Process Validation in the Product Lifecycle

The following subsections describe the recommended stages and specific activities.

1. Stage 1—Process Design

a. Building and Capturing Process Knowledge and Understanding

Process design is the activity of defining the commercial manufacturing process that will be reflected in the master production and control records. The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its critical quality attributes.

Generally, early process design experiments do not need to be performed under CGMP conditions. They should, however, be conducted in accordance with sound scientific methods and principles, including good documentation practices. This recommendation is consistent with ICH guidance for industry, Q10 Pharmaceutical Quality System. Decisions and justification of the controls should be sufficiently documented and internally reviewed to verify and preserve their value for use later in the lifecycle of the process and product.

There are exceptions, however. For example, viral and impurity clearance studies have a direct impact on drug safety and should be performed under CGMP conditions, even when performed at small scale. The quality unit should be involved with these studies as is typical during commercial production.

Product-development activities provide key inputs to the design stage, such as the intended dosage form, the quality attributes, and a general manufacturing pathway. Process information available from the product-development stage can be leveraged in the process-design stage. However, the full spectrum of input variability typical of commercial production is not generally known at this stage. The functionality and limitations of commercial manufacturing equipment should be considered, as well as the contributions of variability by different component lots, production operators, environmental conditions, and measurement systems in the production setting. Laboratory or pilot-scale models designed to be representative of the commercial process can be used to estimate variability. However, it is not a regulatory expectation that the process be developed and tested until it fails, but rather that a process be controlled within commercial manufacturing conditions, including those combinations of conditions posing a high risk of process failure.

Designing an efficient process with an effective process control approach is dependent on the process knowledge and understanding obtained. Design of Experiment (DOE) studies can help develop process knowledge by revealing relationships, including multifactorial interactions, between the variable inputs (e.g., component characteristics or processing parameters) and the resulting outputs (e.g., in-process material, intermediates, or the final product). Risk analysis tools can be used to screen potential variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained. The results of DOE studies can provide justification for establishing ranges of incoming component quality, equipment parameters, and in-process material quality attributes.

Other activities, such as experiments or demonstrations at laboratory or pilot scale, allow evaluation of certain conditions and prediction of performance of the commercial process. These activities also provide information that can be used to model or simulate the commercial process. Computer-based or virtual simulations of certain unit operations or dynamics can provide process understanding and avoid problems at commercial scale. It is important to understand the degree to which models represent the commercial process, including any differences that might exist, as this may have an impact on the relevance of information derived from the studies.

It is essential that activities and studies resulting in product understanding be documented. Documentation should reflect the basis for decisions made about the process. For example, manufacturers should document the variables studied for a unit operation and the rationale for those variables identified as significant. This information is useful during the process qualification and continued process verification stages, including when the design is revised or the strategy for control is refined or changed.

b. Establishing a Strategy for Process Control

Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall. Strategies for process control can be designed to reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output), or combine both approaches.

Process controls address variability to assure quality of the product. Controls can consist of material analysis and equipment monitoring at significant processing points designed to assure that the operation remains on target and in control with respect to output quality. Special attention to control of the process through operational limits and in-process monitoring is essential (1) where the product attribute is not readily measurable due to limitations of sampling or detectability (e.g., viral clearance or microbial contamination), or (2) when intermediates and products cannot be highly characterized and well-defined quality attributes cannot be identified. These controls are included in the master production and control records [see 21 CFR 211.186(a) and (b)(9)].

More advanced strategies, such as process analytical technology (PAT), use timely analysis and control loops to adjust the processing conditions so that the output remains constant. Manufacturing systems of this type can provide a higher degree of process control. In the case of PAT strategy, the approach to process qualification will be different from that for other process designs. Further information on PAT processes can be found in FDA's guidance for industry on PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (available on the Internet at http://www.fda.gov/cder/guidance/index.htm).

The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next stage for confirmation.

2. Stage 2—Process Qualification

During the process qualification stage of process validation, the process design is confirmed as being capable of reproducible commercial manufacture. This stage has two elements: (1) design of the facility and qualification of the equipment and utilities, and (2) performance qualification (PQ). During this stage, CGMP-compliant procedures must be followed and successful completion of this stage is necessary before commercial distribution. Products manufactured during this stage, if acceptable, can be released.

a. Design of a Facility and Qualification of Utilities and Equipment

Proper design of a manufacturing facility is required under 21 CFR part 211, subpart C, of the CGMP regulations on Buildings and Facilities. It is essential that activities performed to

assure proper facility design and commissioning precede PQ. Activities undertaken to demonstrate that utilities and pieces of equipment are suitable for their intended use and perform properly is referred to in this guidance as qualification. These activities necessarily precede manufacturing products at the commercial scale.

Qualification of utilities and equipment generally includes the following activities:

- Selecting utilities and equipment construction materials, operating principles, and performance characteristics based on whether they are appropriate for their specific use.
- Verifying that utility systems and equipment are built and installed in compliance with the design specifications (e.g., built as designed with proper materials, capacity, and functions, and properly connected and calibrated).
- Verifying that the utility system and equipment operate in accordance with the process requirements in all anticipated operating ranges. This should include challenging the equipment or system functions while under load comparable to that expected during routine production. It should also include the performance of interventions, stoppage, and start-up as is expected during routine production. Operating ranges should be shown capable of being held as long as would be necessary during routine production.

Qualification of utilities and equipment can be covered under individual plans or as part of an overall project plan. The plan should consider the requirements of use and can incorporate risk management to prioritize certain activities and to identify a level of effort in both the performance and documentation of qualification activities. The plan should identify (1) the studies or tests to use, (2) the criteria appropriate to assess outcomes, (3) the timing of qualification activities, (4) responsibilities, and (5) the procedures for documenting and approving the qualification. It should also include the firm's requirements for the evaluation of changes. Qualification activities should be documented and summarized in a report with conclusions that address criteria in the plan. The quality control unit must review and approve the qualification plan and report (21 CFR 211.22).

b. Performance Qualification Approach

The PQ is the second element of stage 2, process qualification. The PQ combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected.

Success at this stage signals an important milestone in the product lifecycle and needs to be completed before a manufacturer commences commercial distribution of the drug product. The decision to begin commercial distribution should be supported by data from commercial batches. Data from laboratory and pilot studies can provide additional assurance.

The approach to PQ should be based on sound science and the manufacturer's overall level of product and process understanding. The cumulative data from all relevant studies (e.g., designed experiments; laboratory, pilot, and commercial batches) should be used to establish the manufacturing conditions in the PQ. For example, to have sufficient understanding of the commercial process, the manufacturer will need to consider the effects of scale; however, it is not typically necessary to explore the entire operating range at commercial scale if assurance can be provided by other data. Previous credible experience with sufficiently similar products and processes can also be considered. In addition, it is strongly recommended that firms employ objective measures (e.g., statistical metrics), wherever feasible and meaningful to achieve adequate assurance.

In most cases, PQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance. The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch during processing. This greater scrutiny accompanied by a higher level of sampling should continue through the process verification stage, as appropriate.

The extent to which some materials, such as column resins or molecular filtration media, can be reused without adversely affecting product quality can be assessed in relevant laboratory studies, and their usable lifetime should be confirmed by an ongoing PQ protocol during commercial manufacture.

A manufacturing process that uses PAT may warrant a different PQ approach. Such a process is one that is designed to measure in real time the attributes of an in-process material and then adjust the process in a timely control loop so the process maintains the desired quality of the output material. The process design stage and the process qualification stage should have as a focus the measurement system and control loop. Regardless, the goal remains the same: establishing scientific evidence that the process is reproducible and will consistently deliver quality products.

c. Performance Qualification Protocol

A written protocol that specifies the manufacturing conditions, controls, testing, and expected outcomes is essential for this stage of process validation. It is recommended that the protocol discuss

- The manufacturing conditions including operating parameters, processing limits, and component (raw material) inputs.
- The data to be collected and when and how it will be evaluated.
- Tests to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step.
- The sampling plan including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination. Sampling during this stage should be more extensive than is typical during routine production.
- Criteria that provide for a rational conclusion of whether the process consistently produces quality products. The criteria should include the following:
- A description of the statistical methods to be used in analyzing all collected data (e.g., statistical metrics defining both intra-batch and inter-batch variability).
- Provision for addressing deviations from expected conditions and handling of nonconforming data. Data should not be excluded from further consideration in terms of PQ without a documented, science-based justification.
- Design of facilities and the qualification of utilities and equipment, personnel training and qualification, and

verification of material sources (components and container/closures), if not previously accomplished.
- Status of the validation of analytical methods used in measuring the process, in-process materials, and the product.
- Review and approval by appropriate departments and the quality unit.

d. Protocol Execution and Report

Protocol execution should not begin until the protocol has been reviewed and approved by all appropriate departments, including the quality unit. Departure from the established protocol must be made according to established procedure or provisions in the protocol. Such departures must be justified and approved by all appropriate departments and the quality unit before implementation (§ 211.100).

The commercial manufacturing process and routine procedures must be followed [§§ 211.100(b) and 211.110(a)]. The PQ lots should be manufactured under normal conditions by personnel expected to routinely perform each step of each unit operation in the process. Normal operating conditions should cover the utility systems (e.g., air handling and water purification), material, personnel, environment, and manufacturing procedures.

A report documenting and assessing adherence to the written protocol should be prepared in a timely manner after the completion of the protocol. This report should

- Discuss and cross-reference all aspects of the protocol.
- Summarize data collected and analyze the data, as specified by the protocol.
- Evaluate any unexpected observations and additional data not specified in the protocol.
- Summarize and discuss all manufacturing nonconformances such as deviations, aberrant test results, or other information that has bearing on the validity of process.
- Describe in sufficient detail any corrective actions or changes that should be made to existing procedures and controls.
- State a clear conclusion as to whether the data indicates the process met the conditions established in the protocol and whether the process is considered to be in a sufficient state of control. If not, the report should state what should be accomplished before such a conclusion can be reached. This conclusion should be based on a documented justification for the approval of the process, and release of lots produced by it to the market in consideration of the entire compilation of knowledge and information gained from the design stage through the process qualification stage.
- Include all appropriate department and quality unit review and approvals.

3. Stage 3—Continued Process Verification

The goal of the third validation stage is to continually assure that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal. Adherence to the CGMP requirements, specifically including the collection and evaluation of information and data about the performance of the process (see below), will allow detection of process drift. The evaluation should determine whether action must be taken to prevent the process from drifting out of control [§ 211.180(e)].

An ongoing program to collect and analyze product and process data that relate to product quality must be established [§ 211.180(e)]. The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the critical quality attributes are being controlled throughout the process.

It is recommended that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability. Procedures should describe how trending and calculations are to be performed. Procedures should guard against overreaction to individual events as well as against failure to detect process drift. Production data should be collected to evaluate process stability and capability. The quality unit should review this information. If done properly, these efforts can identify variability in the process and/or product; this information can be used to alert the manufacturer that the process should be improved.

Good process design and development should anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits. However, a process is likely to encounter sources of variation that were not previously detected or to which the process was not previously exposed. Many tools and techniques, some statistical and others more qualitative, can be used to detect variation, characterize it, and determine the root cause. It is recommended that the manufacturer use quantitative, statistical methods whenever feasible. It is also recommended that it scrutinize intra-batch as well as inter-batch variation as part of a comprehensive continued process verification program.

It is recommended continued monitoring and/or sampling at the level established during the process qualification stage until sufficient data is available to generate significant variability estimates. Once the variability is known, sampling and/or monitoring should be adjusted to a statistically appropriate and representative level. Process variability should be periodically assessed and sampling and/or monitoring adjusted accordingly.

Variation can also be detected by the timely assessment of defect complaints, out-of-specification findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports. Production line operators and quality unit staff should be encouraged to provide feedback on process performance. Operator errors should also be tracked to measure the quality of the training program; to identify operator performance issues; and to look for potential batch record, procedural, and/or process improvements that could help to reduce operator error. It is recommended that the quality unit meet periodically with production staff to evaluate data, discuss possible trends or drifts in the process, and coordinate any correction or follow-up actions by production.

Data gathered during this stage might suggest ways to improve and/or optimize the process by altering some aspect of the process or product such as the operating conditions (ranges and set-points), process controls, component, or in-process material characteristics. A description of the planned change, a well-justified rationale for the change, an implementation plan, and quality unit approval before implementation must be documented (21 CFR 211.100). Depending on the significance to product quality, modifications may warrant performing additional process design and process qualification activities.

Maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in control. Once established, qualification status must be maintained through routine monitoring, maintenance, and calibration procedures and schedules (21 CFR part 211, subparts C and D). The data should be assessed periodically to determine whether requalification should be performed and the extent of that requalification. Maintenance and calibration frequency should be adjusted based on feedback from these activities.

V. CONCURRENT RELEASE OF PERFORMANCE QUALIFICATION BATCHES

In most cases, the PQ protocol needs to be completed before the commercial distribution of a product. In special situations, the PQ protocol can be designed to release a PQ batch for distribution before completion of the protocol. The conclusions about the manufacturing process should be made when the protocol is completed and the data is fully evaluated.

FDA expects that concurrent release will be used rarely. Concurrent release might be appropriate for processes used infrequently because of limited demand for the product (e.g., orphan drugs), processes with necessarily low production volume per batch (e.g., radiopharmaceuticals, including positron emission tomography drugs), and processes manufacturing medically necessary drugs to alleviate a short supply, which should be coordinated with the Agency (FDA).

When warranted and used, concurrent release should be accompanied by a system for careful oversight of the distributed batch to facilitate rapid customer feedback. For example, customer complaints and defect reports should be rapidly assessed to determine root cause and whether the process should be improved or changed. It is recommended that each batch in a concurrent release program also undergo stability testing and that this test data be promptly evaluated to ensure rapid detection and correction of any problems.

VI. DOCUMENTATION

Documentation at each stage of the process validation lifecycle is essential for effective communication in complex, lengthy, and multidisciplinary projects. Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each stage of the lifecycle. In addition to being a fundamental tenet of following the scientific method, information transparency and accessibility are essential so that organizational units responsible and accountable for the process can make informed, science-based decisions that ultimately support the release of a product to commerce.

The degree and type of documentation required by CGMP is greatest during stage 2, process qualification, and stage 3, continued process verification. Studies during these stages must conform to CGMPs and must be approved by the quality unit in accordance with the regulations (see 21 CFR 211.22 and 211.100). Viral and impurity clearance studies, even when performed at small scale, also require full quality unit oversight as is necessary during routine commercial production.

CGMP documents for commercial manufacturing [i.e., the initial commercial master batch production and control record (21 CFR 211.186) and supporting procedures] are key outputs of stage 1, process design. It is recommended that firms diagram the process flow for the full-scale process. Process flow diagrams should describe each unit operation, its placement in the overall process, monitoring and control points, and the component, as well as other processing material inputs (e.g., processing aids) and expected outputs (i.e., in-process materials and finished product). It is also useful to generate and preserve process flow diagrams of the various scales as the process design progresses to facilitate comparison and decision-making about their comparability.

VII. ANALYTICAL METHODOLOGY

Process knowledge is dependent on accurate and precise measuring techniques that are used to test and examine the quality of drug components, in-process materials, and finished products. For data to have value in predicting process outcomes, it is essential that the analytical tests be scientifically sound (as required under 21 CFR 211.160). While validated analytical methods are not required during product- and process-development activities, methods should be scientifically sound (e.g., specific, sensitive, and accurate), suitable, and reliable for the specified purpose. There should be assurance of proper equipment function for laboratory experiments. Procedures for analytical method and equipment maintenance, documentation practices, and calibration practices supporting process-development efforts should be documented or described. Analytical methods supporting clinical supply production, particularly stage 2 and 3 studies, must follow appropriate CGMPs in parts 210 and 211.

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5

Bioequivalence Regulatory Compliance

I. BACKGROUND

Bioequivalence (BE) is defined in 21 CFR 320.1 as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." FDA usually considers that the plasma concentration of a drug is a surrogate for the concentration at the site of action for a systemically acting drug. 21 CFR 320.24 outlines options for BE testing. Proving equivalence therefore requires integration of several studies such as pharmacokinetic (PK), pharmacodynamic (PD), controlled-clinical, in vitro studies, and any other specific model or study that may prove useful in proving equivalence.

The concept of BE and the required proof by the regulatory agencies has evolved over the past several decades.

- In the United States, the 1902 federal law for biologics, particularly vaccines, required evaluation for "safety, purity and potency."
- The 1906 Food and Drugs Act added drugs other than biologics.
- The 1938 FDC act created FDA and evaluation of new drugs based on data in a filed NDA.
- The 1962 law added effectiveness requirement for the approval of NDA.
- 1960s, FDA permits marketing of "similars" while corresponding pioneer products undergo DESI reviews. "Similars" came into market between 1938 and 1962.
- The 1970 FDA terminates marketing of "similars" unless
  - DESI pioneer showed safety and efficacy, and
  - "Similar" manufacturer submits aNDA with formulation and manufacture information (The Supreme Court in the United States v. Generix Drug Corporation supported FDA requirement for aNDA.).
  - The 1984 generic law in the United States (Waxman-Hatch) created a generic approval system for all new drugs, including those approved after 1962. FDA finalized the bioequivalence (BA/BE) regulations (21 CFR 320) wherein the pioneer shows BA in NDA; "similars" to DESI-effective pioneers show BE leading to first U.S. first generics. Several revisions to 21 CFR 320 were made including the most recent one in April 2006. The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub.L. No. 98–417) (the Hatch-Waxman Amendments) created section 505(j) of the act, which established the current aNDA approval process. The showing that must be made for an aNDA to be approved is quite different from what is required in an NDA. An NDA applicant must prove that the drug product is safe and effective. An aNDA does not have to prove the safety and effectiveness of the drug product because an aNDA relies on the finding FDA has made that the reference-listed drug (RLD) is safe and effective. Instead, an aNDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD [21 USC 355(j)(2)(A)(iv)]. The scientific premise underlying the Hatch-Waxman amendments is that in most circumstances bioequivalent drug products may be substituted for each other. The Generic Animal Drug and Patent Term Restoration Act (GADPTRA) signed into law on November 16, 1988, permits sponsors to submit an abbreviated New Animal Drug Application (aNADA) for a generic version of any off-patent–approved animal drug (with certain exceptions noted in the law) regardless of whether the drug was approved prior to 1962 and subject to the National Academy of Sciences/National Research Council/Drug Effectiveness Study Implementation (NAS/NRC/DESI) review.

A generic drug is bioequivalent to the listed drug if "the rate and extent of the absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses" [21 USC 355(j)(8)(B)(i)].

In vivo and/or in vitro BE testing is required for most generic drug products submitted for marketing approval. A proposed generic drug product must be compared in vivo and/or in vitro to the officially designated reference drug product. Harmonized BE criteria for the interchangeability of pharmaceutical products address the issue of waivers for in vivo trials, which are expensive and, as recently concluded, not always discriminating enough to form the sole basis of approval of interchangeability. As discussed later, the worldwide requirements to demonstrate BE vary widely, mostly as a result of the ability of the regulatory authorities to enforce such requirements, both from an economic as well as ethical perspective.

Drug regulatory authorities must ensure that all pharmaceutical products, including generic drug products, conform to the same standards of quality, efficacy, and safety required of innovator drug products. Therefore, regulatory frameworks must be able to respond to varied and emerging drugs and dosage forms where BE demonstration is required; issues such as BE of topical products, products acting locally, endogenous therapeutic proteins, and more recently, botanical products now need regulatory pathways, besides streamlining and reducing cost of evaluation of more traditional dosage forms where cost considerations, especially in the Third World, and often a lack of good correlation between in vivo studies and clinical response are observed. This chapter addresses these issues and provides a pathway for the prospective filers of marketing approval applications worldwide.

Table 1 Data Requirement for Drug Approval in the United States

	FD&C505(b)(1)	FD&C505(b)(2)	FD&C505(j)	PHS
Application	NDA	NDA	aNDA	BLA
Preclinical	Yes	Yes/No	No	Yes
Clinical	Yes	Yes/No	No	Yes
CMC	Yes	Yes	Yes (PE)	Yes
PK & bioequivalence	Yes	Yes		Yes
Labeling	Yes	Yes	Yes	Yes

Abbreviations: aNDA, abbreviated New Drug Application; CMC, chemistry, manufacturing, and control; FD&C, Food, Drug, and Cosmetic Act; NDA, New Drug Application PHS, Public Health Service; BLA, Biologic License Application.

II. REGULATORY ASPECTS

The regulation of drug quality involves three arrangements in this country. First, the U.S. Congress gave the *U.S. Pharmacopoeia* and the National Formulary revision committees the authority to set standards of strength, quality, and purity of drugs and their finished preparations. The FDA, also authorized by the U.S. Congress, establishes regulations for the development and manufacture of safe and effective drugs. Finally, in-house GMPs of the manufacturer, mostly dictated by the FDA regulations, ensure quality of drug products. The FDA has also decreed on the bioavailability (BA) and BE of drug products. All NDAs and amended NDAs must demonstrate in vivo BA of the drug product that is followed by an in vitro test, usually a dissolution test, of individual batches to ensure the quality. Table 1 shows a comparison of regulatory filing requirements under various applications.

Applicants submitting an NDA or New Animal Drug Application (NADA) under the provisions of section 505(b) in the Federal Food, Drug, & Cosmetic Act (the Act) are required to document BA [21 CFR 320.21(a)]. If approved, an NDA drug product may subsequently become an RLD. Under section 505(j) of the act, a sponsor of an aNDA or aNADA must document first pharmaceutical equivalence and then BE to be deemed therapeutically equivalent to an RLD. Defined as relative BA, BE is documented by comparing the performance of the generic (test) and listed (reference) products. (Pharmaceutical equivalents are drugs that have the same active ingredient; in the same strength; the same dosage form and route of administration; and have comparable labeling and meet compendia or other standards of identity, strength, quality, purity and potency.)

In addition to the standard CMC tests, the active bulk drug substance for an NDA should be studied and controlled via appropriate specifications for polymorphic form, particle size distribution, and other attributes important to the quality of the resulting drug product. To the extent possible and using compendial monographs where appropriate, sponsors of aNDAs should attempt to duplicate the specifications considered important for the RLD. Where the necessary information is not available, applicants may wish to rely on in vitro release to ensure batch-to-batch consistency. CMC guidances available from FDA are generally applicable to ensure the identity, strength, quality, purity, and potency of the drug substance and drug product for a topical dermatological drug product.

As stated in 21 CFR 320.24, approaches to document BE in order of preference are (1) PK measurements based on measurement of an active drug and/or metabolite in blood, plasma, and/or urine; (2) PD measurements; (3) comparative clinical trials; and (4) in vitro studies.

The science of BE is still undergoing major changes and final rules are established after years of debate and validation of protocols. The U.S. FDA has finalized or drafted several guidelines (Table 2).

III. EQUIVALENCE DOCUMENTATION FOR MARKETING AUTHORIZATION

Pharmaceutically equivalent multisource pharmaceutical products must be verified to be therapeutically equivalent

Table 2 Final and Draft-Stage Biopharmaceutics Guidelines of the U.S. FDA

Guideline	Date Finalized/Draft Issued
Bioanalytical method validation—final	23 May 2001
Bioavailability and bioequivalence studies for orally administered drug products—general considerations (revised)—final	19 March 2003
Cholestyramine powder in vitro bioequivalence—final	15 July 1993
Clozapine tablets: in vivo bioequivalence and in vitro dissolution testing—final	20 June 2005
Corticosteroids, dermatological (topical) in vivo—final	2 June 1999
Dissolution testing of immediate-release solid oral dosage forms—final	25 August 1997
Extended-release oral dosage forms: development, evaluation, and application of in vitro/in vivo correlations—final	26 September 1997
Metaproterenol sulfate and albuterol metered dose inhalers—final	27 June 1989
Statistical approach to establishing bioequivalence—final	2 February 2001
Waiver of in vivo bioavailability and bioequivalence studies for immediate-release solid oral dosage forms on a biopharmaceutical classification system—final	31 August 2000
Potassium chloride (slow-release tablets and capsules) in vivo bioequivalence and in vitro dissolution testing	6 June 1994
Food-effect bioavailability and fed bioequivalence studies	December 2002
Antifungal (topical)—draft	24 February 1990
Antifungal (vaginal)—draft	24 February 1990
Bioavailability and bioequivalence studies for nasal aerosols and nasal sprays for local action—draft	3 April 2003

to one another to be considered interchangeable. Several test methods are available to assess equivalence, including:

- Comparative BA (BE) studies, in which the active drug substance or one or more metabolites is measured in an accessible biologic fluid such as plasma, blood or urine.
- Comparative PD studies in humans.
- Comparative clinical trials.
- In vitro dissolution tests in combination with the Biopharmaceutics Classification System (BCS, see below)

Acceptance of any test procedure in the equivalence documentation between two pharmaceutical products by a drug regulatory authority depends on many factors, including characteristics of the active drug substance and the drug product and the availability of resources to carry out a specific type of study. Wherever a drug produces meaningful concentrations in an accessible biological fluid, such as plasma, BE studies are preferred. Wherever a drug does not produce measurable concentrations in an accessible biological fluid, comparative clinical trials or PD studies may be necessary to document equivalence. In vitro testing, preferably based on a documented in vitro/in vivo correlation or on consideration based on the BCS, may sometimes provide an indication of equivalence between two pharmaceutical products

Oral drugs/drug products for which in vivo equivalence documentation is important: Regulatory authorities require equivalence documentation for multisource pharmaceutical products in which the product is compared to the reference pharmaceutical product. Studies must be carried out using the formulation proposed for marketing. For certain drugs and dosage forms, in vivo equivalence documentation, through either a BE study, a comparative clinical PD study, or a comparative clinical trial, is considered especially important. The following are the factors for oral drug products that should be considered when requiring in vivo equivalence documentation.

Immediate-release oral pharmaceutical products with systemic action when one or more of the following criteria apply.

1. Indicated for serious conditions requiring definite therapeutic response
2. Narrow therapeutic window/safety margin, steep dose-response curve
3. PKs complicated by variable or incomplete absorption or absorption window, nonlinear PKs, pre-systemic elimination/high first-pass metabolism >70%
4. Unfavorable physicochemical properties, e.g., low solubility, instability, metastable modifications, poor permeability
5. Documented evidence of BA problems related to the drug or drugs of similar chemical structure or formulations
6. Where there is a high ratio of excipients to active ingredients

Nonoral and nonparenteral pharmaceutical products designed to act through systemic absorption (such as transdermal patches, suppositories): Plasma concentration measurements over time (BE) are normally sufficient proof for efficacy and safety.

Sustained or otherwise modified-release pharmaceutical products designed to act through systemic absorption: Plasma concentration measurements over time (BE) are normally sufficient proof for efficacy and safety.

Fixed combination products (see WHO Technical Report Series No. 825, 1992) with systemic action: Plasma concentration measurements over time (BE) are normally sufficient proof for efficacy and safety.

Nonsolution pharmaceutical products for nonsystemic use (oral, nasal, ocular, dermal, rectal, vaginal application) and intended to act without systemic absorption: In these cases, the BE concept is not suitable and comparative clinical or PD studies are required to prove equivalence. This does not, however, exclude the potential need for drug concentration measurements to assess unintended partial absorption.

IV. THERAPEUTIC CLASSIFICATION

FDA has also provided a therapeutic classification of drugs and dosage forms for the purpose of BE testing (Table 3).

V. TOPICS RELATED TO REGULATORY COMPLIANCE

A. Is a BE Study Required?

The submission of an NDA, aNDA, or supplemental application requires that it contains in vivo BA and BE data either by direct measurement of in vivo BA of the drug product that is the subject of the application or information to permit FDA to waive the submission of evidence measuring in vivo BA. The supplemental application involves a change in the manufacturing site or a change in the manufacturing process, including a change in product formulation or dosage strength, beyond the variations provided for in the approved application, or a change in the labeling to provide for a new indication for use of the drug product, for which a new clinical trial may be required.

FDA may approve a full NDA, or a supplemental application proposing any of the changes set forth earlier that does not contain evidence of in vivo BA or information to permit waiver of the requirement for in vivo BA data.

- For certain drug products, the in vivo BA or BE of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the BA or demonstrating the BE of these drug products. A drug product's in vivo BA or BE may be considered self-evident based on other data in the application.
- If the drug product is a parenteral solution intended solely for administration by injection, or an ophthalmic or otic solution, and contains the same active and inactive ingredients in the same concentration as a drug product that is the subject of an approved full NDA or aNDA; or
- if the drug product is administered by inhalation as a gas, for example, a medicinal or an inhalation anesthetic, and contains an active ingredient in the same dosage form as a drug product that is the subject of an approved full NDA or aNDA; or
- if the drug product is a solution for application to the skin, an oral solution, elixir, syrup, tincture, a solution for aerosolization or nebulization, a nasal solution, or similar other solubilized form and contains an active drug ingredient in the same concentration and dosage form as a drug product that is the subject of an approved full NDA or aNDA and contains no inactive ingredient or other change in formulation from the drug product that is the subject of the approved full NDA or aNDA that may significantly affect absorption of the active drug ingredient or active moiety for products that are systemically absorbed, or that may significantly affect systemic or local availability for products intended to act locally.

Table 3 Therapeutic Equivalence Code Classifications of the U.S. FDA

Name	Definition	FDA code
Products in conventional dosage forms not presenting bioequivalence problems	Products coded as AA contain active ingredients and dosage forms that are not regarded as presenting either actual or potential bioequivalence problems or drug quality or standards issues. However, all oral dosage forms must, nonetheless, meet an appropriate in vitro test(s) for approval.	AA
Products meeting necessary bioequivalence requirements	Products generally will be coded AB if a study is submitted demonstrating bioequivalence. Even though drug products of distributors and/or repackagers are not included in the list, they are considered therapeutically equivalent to the application holder's drug product if the application holder's drug product is rated AB or is single source in the List. The only instance in which a multisource product will be rated AB on the basis of bioavailability rather than bioequivalence is where the innovator product is the only one listed under that drug ingredient heading and has completed an acceptable bioavailability study. However, it does not signify that this product is therapeutically equivalent to the other drugs under the same heading. Drugs coded AB under an ingredient heading are considered therapeutically equivalent only to other drugs coded AB under that heading.	AB
Solutions and powders for aerosolization	Uncertainty regarding the therapeutic equivalence of aerosolized products arises primarily because of differences in the drug delivery system. Solutions and powders intended for aerosolization that are marketed for use in any of several delivery systems are considered to be pharmaceutically and therapeutically equivalent and are coded AN. Those products that are compatible only with a specific delivery system or those products that are packaged in and with a specific delivery system are coded BN, unless they have met an appropriate bioequivalence standard because drug products in their respective delivery systems are not necessarily pharmaceutically equivalent to each other and, therefore, are not therapeutically equivalent.	AN
Injectable oil solutions	The absorption of drugs in injectable (parenteral) oil solutions may vary substantially with the type of oil employed as a vehicle and the concentration of the active ingredient. Injectable oil solutions are therefore considered to be pharmaceutically and therapeutically equivalent only when the active ingredient, its concentration, and the type of oil used as a vehicle are all identical.	AO
Injectable aqueous solutions	It should be noted that even though injectable (parenteral) products under a specific listing may be evaluated as therapeutically equivalent, there may be important differences among the products in the general category, Injectable; Injection. For example, some injectable products that are rated therapeutically equivalent are labeled for different routes of administration. In addition, some products evaluated as therapeutically equivalent may have different preservatives or no preservatives at all. Injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection are all considered to be pharmaceutically and therapeutically equivalent provided they are designed to produce the same concentration prior to injection and are similarly labeled. Consistent with accepted professional practice, it is the responsibility of the prescriber, dispenser, or individual administering the product to be familiar with a product's labeling to ensure that it is given only by the route(s) of administration stated in the labeling. Certain commonly used large volume intravenous products in glass containers are not included on the list (e.g., dextrose injection 5%, dextrose injection 10%, sodium chloride injection 0.9%) since these products are on the market without FDA approval and the FDA has not published conditions for marketing such parenteral products under approved NDAs. When packaged in plastic containers, however, FDA regulations require approved applications prior to marketing. Approval then depends on, among other things, the extent of the available safety data involving the specific plastic component of the product. All large volume parenteral products are manufactured under similar standards, regardless of whether they are packaged in glass or plastic. Thus, FDA has no reason to believe that the packaging container of large volume parenteral drug products that are pharmaceutically equivalent would have any effect on their therapeutic equivalence.	AP
Topical products	There are a variety of topical dosage forms available for dermatologic, ophthalmic, otic, rectal, and vaginal administration, including solutions, creams, ointments, gels, lotions, pastes, sprays, and suppositories. Even though different topical dosage forms may contain the same active ingredient and potency, these dosage forms are not considered pharmaceutically equivalent. Therefore, they are not considered therapeutically equivalent. All solutions and DESI drug products containing the same active ingredient in the same topical dosage form for which a waiver of in vivo bioequivalence has been granted and for which chemistry and manufacturing processes are adequate, are considered therapeutically equivalent, and coded AT. Pharmaceutically equivalent topical products that raise questions of bioequivalence including all post 1962 topical drug products are coded AB when supported by adequate bioequivalence data, and BT in the absence of such data.	AT
Extended-release dosage forms (capsules, injectables, and tablets)	An extended-release dosage form is defined by the official compendia as one that allows at least a twofold reduction in dosing frequency as compared to that drug presented as a conventional dosage form (e.g., as a solution or a prompt drug-releasing, conventional solid dosage form). Although bioavailability studies have been conducted on these dosage forms, they are subject to bioavailability differences, primarily because firms developing extended-release products for the same active ingredient rarely employ the same formulation approach. FDA, therefore, does not consider different extended-release dosage forms containing the same active ingredient in equal strength to be therapeutically equivalent unless equivalence between individual products in both rate and extent has been specifically demonstrated through appropriate bioequivalence studies. Extended-release products for which such bioequivalence data have not been submitted are coded BC, while those for which such data are available have been coded AB.	BC

(Continued)

Table 3 (Continued)

Name	Definition	FDA code
Active ingredients and dosage forms with documented bioequivalence problems	The BD code denotes products containing active ingredients with known bioequivalence problems and for which adequate studies have not been submitted to FDA demonstrating bioequivalence. Where studies showing bioequivalence have been submitted, the product has been coded AB.	BD
Delayed-release oral dosage forms	A delayed-release dosage form is defined by the official compendia as one that releases a drug (or drugs) at a time other than promptly after administration. Enteric-coated articles are delayed-release dosage forms. Drug products in delayed-release dosage forms containing the same active ingredients are subject to significant differences in absorption. Unless otherwise specifically noted, the agency considers different delayed-release products containing the same active ingredients as presenting a potential bioequivalence problem and codes these products BE in the absence of in vivo studies showing bioequivalence. If adequate in vivo studies have demonstrated the bioequivalence of specific delayed-release products, such products are coded AB.	BE
Products in aerosol nebulizer drug delivery systems	This code applies to drug solutions or powders that are marketed only as a component of, or as compatible with, a specific drug delivery system. There may, for example, be significant differences in the dose of drug and particle size delivered by different products of this type. Therefore, the agency does not consider different metered aerosol dosage forms containing the same active ingredient(s) in equal strengths to be therapeutically equivalent unless the drug products meet an appropriate bioequivalence standard.	BN
Active ingredients and dosage forms with potential bioequivalence problems	FDA's bioequivalence regulations (21 CFR 320.33) contain criteria and procedures for determining whether a specific active ingredient in a specific dosage form has a potential for causing a bioequivalence problem. It is FDA's policy to consider an ingredient meeting these criteria as having a potential bioequivalence problem even in the absence of positive data demonstrating inequivalence. Pharmaceutically equivalent products containing these ingredients in oral dosage forms are coded BP until adequate in vivo bioequivalence data are submitted. Injectable suspensions containing an active ingredient suspended in an aqueous or oleaginous vehicle have also been coded BP. Injectable suspensions are subject to bioequivalence problems because differences in particle size, polymorphic structure of the suspended active ingredient, or the suspension formulation can significantly affect the rate of release and absorption. FDA does not consider pharmaceutical equivalents of these products bioequivalent without adequate evidence of bioequivalence.	BP
Suppositories or enemas that deliver drugs for systemic absorption	The absorption of active ingredients from suppositories or enemas that are intended to have a systemic effect (as distinct from suppositories administered for local effect) can vary significantly from product to product. Therefore, FDA considers pharmaceutically equivalent systemic suppositories or enemas bioequivalent only if in vivo evidence of bioequivalence is available. In those cases where in vivo evidence is available, the product is coded AB. If such evidence is not available, the products are coded BR.	BR
Products having drug standard deficiencies	If the drug standards for an active ingredient in a particular dosage form are found by FDA to be deficient so as to prevent an FDA evaluation of either pharmaceutical or therapeutic equivalence, all drug products containing that active ingredient in that dosage form are coded BS. For example, if the standards permit a wide variation in pharmacologically active components of the active ingredient such that pharmaceutical equivalence is in question, all products containing that active ingredient in that dosage form are coded BS.	BS
Topical products with bioequivalence issues	This code applies mainly to post 1962 dermatologic, ophthalmic, otic, rectal, and vaginal products for topical administration, including creams, ointments, gels, lotions, pastes, and sprays, as well as suppositories not intended for systemic drug absorption. Topical products evaluated as having acceptable clinical performance, but that are not bioequivalent to other pharmaceutically equivalent products or that lack sufficient evidence of bioequivalence will be coded BT.	BT
Drug products for which the data are insufficient to determine therapeutic equivalence	The code BX is assigned to specific drug products for which the data that have been reviewed by the agency are insufficient to determine therapeutic equivalence under the policies stated in this document. In these situations, the drug products are presumed to be therapeutically inequivalent until the agency has determined that there is adequate information to make a full evaluation of therapeutic equivalence.	BX

Abbreviation: DESI, Drug Effectiveness Study Implementation.

FDA also waives the requirement for the submission of evidence measuring the in vivo BA or demonstrating the in vivo BE of a solid oral dosage form (other than a delayed-release or extended-release dosage form) of a drug product determined to be effective for at least one indication in a Drug Efficacy Study Implementation (DESI) notice or which is identical, related, or similar (IRS) to such a drug product unless FDA has evaluated the drug product, included the drug product in the Approved Drug Products with Therapeutic Equivalence Evaluations List, and rated the drug product as having a known or potential BE problem. A drug product so rated reflects a determination by FDA that an in vivo BE study is required. [A DESI drug is any drug that lacks substantial evidence of effectiveness (less than effective [LTE]) and is subject by FDA to a Notice of Opportunity for Hearing (NOOH). This includes drugs, which are IRS to DESI drugs. Valid values: 2 = safe and effective or non-DESI drug; 3 = drug under review (no NOOH issued); 4 = LTE/IRS drug for *some* indications; 5 = LTE/IRS drug for *all* indications; 6 = LTE/IRS drug withdrawn from market.]

For certain drug products, BA may be measured or BE may be demonstrated by evidence obtained in vitro in lieu of in vivo data. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the BA or

demonstrating the BE of the drug product if the drug product meets one of the following criteria:

- The drug product is in the same dosage form, but in a different strength, and is proportionally similar in its active and inactive ingredients to another drug product for which the same manufacturer has obtained approval and the following conditions are met that the BA of this other drug product has been measured and both drug products meet an appropriate in vitro test approved by FDA and the applicant submits evidence showing that both drug products are proportionally similar in their active and inactive ingredients. (except for the delayed-release or extended-release products).
- The drug product is, on the basis of scientific evidence submitted in the application, shown to meet an in vitro test that has been correlated with in vivo data.
- The drug product is a reformulated product that is identical, except for a different color, flavor, or preservative that could not affect the BA of the reformulated product, to another drug product for which the same manufacturer has obtained approval and the following conditions are met. The BA of the other product has been measured, and both drug products meet an appropriate in vitro test approved by FDA.

FDA, for good cause, may waive a requirement for the submission of evidence of in vivo BA or BE if waiver is compatible with the protection of the public health. For full NDAs, FDA may defer a requirement for the submission of evidence of in vivo BA if deferral is compatible with the protection of the public health.

FDA, for good cause, may require evidence of in vivo BA or BE for any drug product if the agency determines that any difference between the drug product and a listed drug may affect the BA or BE of the drug product.

B. Prior Review

The Commissioner of Food and Drugs strongly recommends that, to avoid the conduct of an improper study and unnecessary human research, any person planning to conduct a BA or BE study submit the proposed protocol for the study to FDA for review prior to the initiation of the study. FDA may review a proposed protocol for a BE study and will offer advice with respect to whether the conditions an appropriate design, the choice of reference product, and the proposed chemical and statistical analysis methods are met.

The Commissioner of Food and Drugs shall consider the following factors, when supported by well-documented evidence, to identify specific pharmaceutical equivalents and pharmaceutical alternatives that are not or may not be bioequivalent drug products.

- Evidence from well-controlled clinical trials or controlled observations in patients that such drug products do not give comparable therapeutic effects.
- Evidence from well-controlled BE studies that such products are not bioequivalent drug products.
- Evidence that the drug products exhibit a narrow therapeutic ratio, for example, there is less than a twofold difference in median lethal dose (LD50) and median effective dose (ED50) values, or have less than a twofold difference in the minimum toxic concentrations and minimum effective concentrations in the blood, and safe and effective use of the drug products requires careful dosage titration and patient monitoring.
- Competent medical determination that a lack of BE would have a serious adverse effect in the treatment or prevention of a serious disease or condition.
- The physicochemical evidence that the active drug ingredient has a low solubility in water, for example, less than 5 mg/mL, or, if dissolution in the stomach is critical to absorption, the volume of gastric fluids required to dissolve the recommended dose far exceeds the volume of fluids present in the stomach (taken to be 100 mL for adults and prorated for infants and children); or, the dissolution rate of one or more such products is slow, for example, less than 50% in 30 minutes when tested using either a general method specified in an official compendium or a paddle method at 50 revolutions/min in 900 mL of distilled or deionized water at 37°C, or differs significantly from that of an appropriate reference material such as an identical drug product that is the subject of an approved full NDA; or, the particle size and/or surface area of the active drug ingredient is critical in determining its BA; or, certain physical structural characteristics of the active drug ingredient, for example, polymorphic forms, conforms, solvates, complexes, and crystal modifications, dissolve poorly and this poor dissolution may affect absorption; or, such drug products have a high ratio of excipients to active ingredients, for example, greater than 5:1; or, specific inactive ingredients, for example, hydrophilic or hydrophobic excipients and lubricants, either may be required for absorption of the active drug ingredient or therapeutic moiety or, alternatively, if present, may interfere with such absorption.
- The PK evidence that the active drug ingredient, therapeutic moiety, or its precursor is absorbed in large part in a particular segment of the GI tract or is absorbed from a localized site, or, the degree of absorption of the active drug ingredient, therapeutic moiety, or its precursor is poor, for example, less than 50%, ordinarily in comparison to an intravenous dose, even when it is administered in pure form, for example, in solution; or, there is rapid metabolism of the therapeutic moiety in the intestinal wall or liver during the process of absorption (first-class metabolism) so the therapeutic effect and/or toxicity of such drug product is determined by the rate as well as the degree of absorption; or, the therapeutic moiety is rapidly metabolized or excreted so that rapid dissolution and absorption are required for effectiveness; or, the active drug ingredient or therapeutic moiety is unstable in specific portions of the GI tract and requires special coatings or formulations, for example, buffers, enteric coatings, and film coatings, to ensure adequate absorption; or, the drug product is subject to dose-dependent kinetics in or near the therapeutic range, and the rate and extent of absorption are important to BE.

VI. RECORD MAINTENANCE

All records of in vivo or in vitro tests conducted on any marketed batch of a drug product to ensure that the product meets a BE requirement shall be maintained by the manufacturer for at least 2 years after the approval of the application submitted and would available to the FDA on request.

- If the formulation of the test article is the same as the formulation(s) used in the clinical studies demonstrating substantial evidence of safety and effectiveness for the test article's claimed indications, a reserve sample of the test article used to conduct an in vivo BA study comparing

the test article to a reference oral solution, suspension, or injection
- If the formulation of the test article differs from the formulation(s) used in the clinical studies demonstrating substantial evidence of safety and effectiveness for the test article's claimed indications, a reserve sample of the test article and of the reference standard used to conduct an in vivo BE study comparing the test article to the formulation(s) (reference standard) used in the clinical studies
- For a new formulation, new dosage form, or a new salt or ester of an active drug ingredient or therapeutic moiety that has been approved for marketing, a reserve sample of the test article and of the reference standard used to conduct an in vivo BE study comparing the test article to a marketed product (reference standard) that contains the same active drug ingredient or therapeutic moiety

Each reserve sample shall consist of a sufficient quantity to permit FDA to perform 5 times all of the release tests required in the application or supplemental application. Each reserve sample shall be adequately identified so that the reserve sample can be positively identified as having come from the same sample as used in the specific BA study. Each reserve sample shall be stored under conditions consistent with product labeling and in an area segregated from the area where testing is conducted and with access limited to authorized personnel. Each reserve sample shall be retained for a period of at least 5 years following the date on which the application or supplemental application is approved, or, if such application or supplemental application is not approved, at least 5 years following the date of completion of the BA study in which the sample from which the reserve sample was obtained was used.

Authorized FDA personnel will ordinarily collect reserve samples directly from the applicant or contract research organization at the storage site during a PAI. If authorized FDA personnel are unable to collect samples, FDA may require the applicant or contract research organization to submit the reserve samples to the place identified in the agency's request. If FDA has not collected or requested delivery of a reserve sample, or if FDA has not collected or requested delivery of any portion of a reserve sample, the applicant or contract research organization shall retain the sample or remaining sample for the 5-year period.

Upon release of the reserve samples to FDA, the applicant or contract research organization shall provide a written assurance that, to the best knowledge and belief of the individual executing the assurance, the reserve samples came from the same samples as used in the specific BA or BE study identified by the agency. The assurance shall be executed by an individual authorized to act for the applicant or contract research organization in releasing the reserve samples to FDA.

A contract research organization may contract with an appropriate independent third party to provide storage of reserve samples provided that the sponsor of the study has been notified in writing of the name and address of the facility at which the reserve samples will be stored. If a contract research organization conducting a BA or BE study that requires reserve sample retention goes out of business, it shall transfer its reserve samples to an appropriate independent third party, and shall notify in writing the sponsor of the study of the transfer and provide the study sponsor with the name and address of the facility to which the reserve samples have been transferred.

The applicant of an abbreviated application or a supplemental application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act, or, if BE, testing was performed under contract, the contract research organization shall retain reserve samples of any test article, and reference standard used in conducting an in vivo or in vitro BE study required for approval of the abbreviated application or supplemental application and beyond as required.

VII. CLARIFICATION ON REQUIREMENTS

After the revision of the note for guidance (NfG) on the Investigation on BA and Bioequivalence in 2002, (http://www.emea.europa.eu/pdfs/human/qwp/140198enfin.pdf), it appears that some harmonization in the interpretation of critical parts of the guideline is needed.

A. In Which Cases Is It Allowed to Use a Wider Acceptance Range for the Ratio of Cmax?

NfG states under 3.6.2 "With respect to the ratio of Cmax the 90% CI for this measure of relative bioavailability should lie within an acceptance range of 0.80 – 1.25. In specific cases, such as a narrow therapeutic range, the acceptance interval may need to be tightened."

NfG also states "In certain cases a wider interval may be acceptable. The interval must be prospectively defined, e.g. 0.75 – 1.33, and justified addressing in particular any safety or efficacy concerns for patients switched between formulations."

The possibility offered here by the guideline to widen the acceptance range of 0.80 to 1.25 for the ratio of Cmax (not for AUC) should be considered exceptional and limited to a small widening (0.75–1.33). Furthermore, this possibility is restricted to those products for which at least one of the following criteria applies:

1. Data regarding PK/PD relationships for safety and efficacy are adequate to demonstrate that the proposed wider acceptance range for Cmax does not affect PD s in a clinically significant way.
2. If PK/PD data are either inconclusive or not available, clinical safety and efficacy data may still be used for the same purpose, but these data should be specific for the compound to be studied and persuasive.
3. The reference product has a highly variable within-subject BA. Please refer to the question on highly variable drug or drug products for guidance on how to address this issue at the planning stage of the BE trial.

A post hoc justification of an acceptance range wider than defined in the protocol cannot be accepted. Information that would be required to justify results lying outside the conventional acceptance range at the post hoc stage should be utilized at the planning stage, either for a scientific justification of a wider acceptance range for Cmax, or for selecting an experimental approach that allows the assessment of different sources of variability.

B. When Can Subjects Classified as Outliers Be Excluded from the Analysis in BE Studies?

Under 3.6.3 the NfG states "Post-hoc exclusion of outliers is generally not accepted" but at the same time acknowledges "the protocol should also specify methods for identifying biologically implausible outliers."

Unbiased assessment of results from randomized studies requires that all subjects are observed and treated according to the same rules that should be independent from treatment or outcome. In consequence, PK data can only be excluded based on nonstatistical reasons that have been either defined previously in the protocol or, at the very least, established before reviewing the data. Acceptable explanations to exclude PK data or to exclude a subject would be protocol violations like vomiting, diarrhea, analytical failure. The search for such explanations must apply to all subjects in all groups independently of the size of the observed PK parameters or its outlying position. Exclusion of data can never be accepted on the basis of statistical analysis or for PK reasons alone, because it is impossible to distinguish between formulation effects and PK effects.

Exceptional reasons may justify post hoc data exclusion but this should be considered with utmost care. In such a case, the applicant must demonstrate that the condition stated to cause the deviation is present in the outlier(s) only and absence of this condition has been investigated using the same criteria for all other subjects.

Results of statistical analyses with and without the group of excluded subjects should be provided.

C. If One Side of the 90% CI of a PK Variable for Testing BE Lies on 0.80 or 1.25, Can We Conclude that the Products Are Bioequivalent?

For establishing BE, the 90% CI should lie *within* the acceptance interval (in most cases, 0.80–1.25), the borders being included. The conclusion that products are bioequivalent is based on the overall scientific assessment of the PK studies, not only on meeting the acceptance range.

D. In Which Cases May a Nonparametric Statistical Model Be Used?

NfG states under 3.6.1, statistical analysis, "AUC and Cmax should be analysed using ANOVA after log transformation."

The reasons for this request are the following:

a. The AUC and Cmax values as biological parameters are usually not normally distributed.
b. A multiplicative model may be plausible.
c. After log transformation, the distribution may allow a parametric analysis.

However, the true distribution in a PK data set usually cannot be characterized due to the small sample size, so it is *not* recommended to have the analysis strategy depend on a pretest for normality. Parametric testing using analysis of variance (ANOVA) on log-transformed data should be the rule. Results from nonparametric statistical methods or other statistical approaches are nevertheless welcome as sensitivity analyses. Such analyses can provide reassurance that conclusions from the experiment are robust against violations of the assumptions underlying the analysis strategy.

For Tmax, the use of nonparametric methods on the original data set is recommended.

E. When Should Metabolite Data Be Used to Establish BE?

According to the guideline, the only situations where metabolite data *can be used* to establish BE are

- "*If the concentration of the active substance is too low to be accurately measured in the biological matrix, thus giving rise to significant variability.*" Comments. Metabolite data can only be used if the applicant presents convincing, state-of-the-art arguments that measurements of the parent compound are unreliable. Even so, it is important to point out that Cmax of the metabolite is less sensitive to differences in the rate of absorption than Cmax of the parent drug. Therefore, when the rate of absorption is considered of clinical importance, BE should, if possible, be determined for Cmax of the parent compound, if necessary at a higher dose. Furthermore, when using metabolite data as a substitute for parent drug concentrations, the applicant should present data supporting the view that the parent drug exposure will be reflected by metabolite exposure.
- "*If metabolites significantly contribute to the net activity of an active substance and the pharmacokinetic system is nonlinear.*" Comments. To evaluate the significance of the contribution of metabolites, relative AUCs and nonclinical or clinical PD activities should be compared with those of the parent drug. PK/PD modeling may be useful. If criteria for significant contribution to activity and PK nonlinearity are met, then "it is necessary to measure both parent drug and active metabolite plasma concentrations and evaluate them separately." Any discrepancy between the results obtained with the parent compound and the metabolites should be discussed based on relative activities and AUCs. If the discrepancy lies in Cmax, the results of the parent compound should usually prevail. Pooling of the plasma concentrations or PK parameters of the parent drug and its metabolite for calculation of BE is not acceptable.

F. When Using Metabolite Data to Establish BE, May One Use the Same Justification for Widening the Cmax Acceptance Criteria as in the Case of the Parent Compound?

In principle, the same criteria apply as for the parent drug (see question on widening the acceptance range for Cmax). However, as stated earlier (see question regarding when metabolite data can be used), Cmax of the metabolite is less sensitive to differences in the rate of absorption than Cmax of the parent drug. Therefore, widening the Cmax acceptance range when using metabolites instead of the parent compound is generally not accepted. When the metabolite has a major contribution to, or is completely responsible for, the therapeutic effect, and if it can be demonstrated that a widened acceptance range would not lead to any safety or efficacy concerns, which will usually prove more difficult than for the parent compound (see question on widening the acceptance range for Cmax), then a widened acceptance range for Cmax of metabolite may be accepted.

G. What is a "Highly Variable Drug or Drug Product"?

The standard approach to the analysis of a two-treatment, two-sequence, two-period crossover trial is an ANOVA for the log-transformed PK parameters, where the factors formulation, period, sequence, and subject nested within sequence are used to explain overall variability in the observations. The residual coefficient of variation (CV) is a measure of the variability that is unexplained by the aforementioned factors. Amongst others, within-subject variability, formulation variability, analytical errors, and subject by formulation interaction can contribute to this residual variance.

A drug product is called highly variable if its intra-individual (i.e., within-subject) variability is greater than 30%. A high CV as estimated from the ANOVA model is thus an indicator for high within-subject variability. However, a replicate design is needed to assess within-subject variability.

When testing for BE of a product with a nonlinear PK, how should one select the strengths with the largest sensitivity to detect differences in the two products?

Section 5.4 of the guideline states "If a new application concerns several strengths of the active substance a bioequivalence study investigating only one strength may be acceptable" provided five conditions are fulfilled, among which, when PKs is not linear over the therapeutic dose range "the strengths where the sensitivity is largest to identify differences in the two products should be used". Nonlinear PK, in this case, should reflect a nonlinear drug input rate as stated in the guideline.

Generally, it is the studied dose and not the studied formulation strength that is of importance when considering BE for drugs with nonlinear PK characteristics. An exception is when BA is governed by the solubility of the active ingredient. Then BE studies should include the highest formulation strength.

When studies are warranted at the high dose range, they should be performed at the highest commonly recommended dose. If this dose cannot be administered to volunteers, the study may need to be performed in patients. If the study is conducted at the highest acceptable dose in volunteers, the applicant should justify this and discuss how BE determined at this dose can be extrapolated to the highest commonly recommended dose.

When proof of linear absorption or elimination kinetics is lacking, or if evidence of nonlinearity is available, BE between test and reference formulations should be established with both the lowest and the highest doses unless adequately justified by the applicant. This approach is the most sensitive for detecting differences in rate and extent of absorption for substances with dose-dependent PKs. On the other hand, if only one dose is chosen in the BE studies, which dose to choose depends on the cause of nonlinearity. For instance, single-strength studies may be conducted

- On the highest dose for drugs with a demonstrated greater than proportional increase in AUC or Cmax with increasing dose during single or multiple dose studies. In this case an additional steady-state study may be needed if the drug accumulates (steady-state concentrations are higher than those reached after single dose administration).
- On the lowest dose (or a dose in the linear range) for drugs with a demonstrated less than proportional increase in AUC or Cmax with increasing dose, for example, if this phenomenon is due to saturable absorption.

When BA of a substance with nonlinear PK is governed by the solubility of the active substance, resulting in a less than proportional increase in AUC with increasing dose, BE should be established with both the lowest and the highest dose (which may exceed the recommended initial dose) and should include the highest formulation strength.

It is worth mentioning that in case of linear kinetics but low or critical solubility, there is a similar need to test the highest strength and dose.

H. What Are the Conditions for Using Urinary PK Data for BE Assessment?

Section 3.3 of the guideline states "The use of urinary excretion data may be advantageous in determining the extent of drug input in case of products predominantly excreted renally, but has to be justified when used to estimate the rate of absorption."

The extent of drug input may be determined by the use of urinary excretion data provided elimination is dose-linear and is predominantly renal as intact drug. However, the use of urinary data has to be carefully justified when used to estimate the rate of absorption. If reliable plasma Cmax can be determined, this should be combined with urinary data on the extent of absorption for assessing BE.

I. Standardization of BE Studies with Regard to Food Intake. How Strictly Should the Guideline Be Interpreted?

Section 3.2.2 of the guideline states "If the Summary of Product Characteristics (SPC) of the reference product contains specific recommendations in relation to food intake related to food interaction the study should be designed accordingly."

The recommendations concerning food intake in the SPC are not sufficient for regulatory decisions on the adequacy of BE studies. Preferably, the following conditions should be considered separately when the SPC recommends administration of the substance together with food intake.

- If the recommendation of food intake in the SPC is based on PK properties such as higher BA, then a BE study under fed conditions is generally required.
- If the recommendation of food intake is intended to decrease adverse events or improve tolerability, a BE study under fasting conditions is considered acceptable although it would be advisable to perform the study under fed conditions.
- If the SPC leaves a choice between fasting and fed conditions, then BE should preferably be tested under fasting conditions as this situation will be more sensitive to differences in PKs.

The composition of the meal should be described and taken into account, since a light meal might sometimes be preferable to mimic clinical conditions, especially when the fed state is expected to be less sensitive to differences in PKs. However, for modified-release products, a high fat meal is required.

For products with release characteristics differing from conventional immediate release (e.g., improved release, dissolution, or absorption), even if they cannot be classified as modified-release products with prolonged or delayed release, BE studies may be necessary in both the fasted and fed states.

J. Worldwide Considerations

Whereas there is a general consensus among the West European, North American, and Japanese regulatory authorities on the BE requirements for marketing authorization of generic products, such is not the case in the rest of the world. For example, the varied nature of the requirement in South America perhaps typifies the heterogeneity in other continents. For example, an examination of the regulatory systems of the ten South American agencies showed that out of the 96 active ingredients, only 4 active ingredients commonly require BE studies in all 10 countries: valproic acid, carbamazepine, cyclosporine, and phenytoin. All of them are considered high health risks. The countries with least number of active ingredients with BE study requirements are Colombia (only 5) followed by Costa Rica (only 7) and the countries with the highest number of requirements remain the United States and Canada. Chile is in the process of establishing the requirement for all active ingredients that require BE studies. Whereas the WHO has established certain guidelines, these are not widely followed in much of the Third World countries

and BE studies remain haphazardly managed. Following are some of the common occurrences in the marketing approvals of generic products in the Third World countries:

- Nonvalidated test methods
- Statistically incorrect experimental designs
- Lack of authenticity of study
- Lack of assurance that the study is conducted on the manufactured batches; the MNCs routinely submitting studies from their filings in the West in support of products to be manufactured locally

VIII. POSTAPPROVAL CHANGES

Information on the types of in vitro dissolution and in vivo BE studies that should be conducted for immediate-release and modified-release drug products approved as NDAs or aNDAs in the presence of specified postapproval changes is provided in the FDA guidance for industry titled *SUPAC-IR: Immediate Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (November 1995) and *SUPAC-MR: Modified Release Solid Oral Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* (September 1997). In the presence of certain major changes in components, composition, or methods of manufacture after approval, in vivo BE should be redemonstrated. For approved NDAs, the drug product after the change should be compared with the drug product before the change. For approved aNDAs, the drug product after the change should be compared with the RLD. Under section 506A(c)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 USC 356a(c)(2)(B)], postapproval changes requiring completion of studies in accordance with Part 320 must be submitted in a supplement and approved by FDA before distributing a drug product made with the change.

A. NDAs: BA and BE Studies

An NDA can be submitted for a previously unapproved new molecular entity or for a new salt, new ester, prodrug, or other noncovalent derivative of a previously approved new molecular entity, formulated as a modified-release drug product. The first modified-release drug product for a previously approved immediate-release drug product should be submitted as an NDA. Subsequent modified-release products that are pharmaceutically equivalent and bioequivalent to the listed drug product should be submitted as aNDAs. BA requirements for the NDA of an extended-release product are listed in 21 CFR 320.25(f). The purpose of an in vivo BA study for which a controlled-release claim is made is to determine if all the following conditions are met:

- The drug product meets the controlled-release claims made for it.
- The BA profile established for the drug product rules out the occurrence of any dose dumping.
- The drug product's steady-state performance is equivalent to a currently marketed noncontrolled-release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and is subject to an approved full NDA.
- The drug product's formulation provides consistent PK performance between individual dosage units.

As noted in 21 CFR 320.25(f)(2), "the reference material(s) for such a bioavailability study shall be chosen to permit an appropriate scientific evaluation of the controlled-release claims made for the drug product," such as the following:

- Solution or suspension of the active drug ingredient or therapeutic moiety
- Currently marketed noncontrolled-release drug product containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling
- Currently marketed controlled-release drug product subject to an approved full NDA containing the same active drug ingredient or therapeutic moiety and administered according to the dosage recommendations in the labeling

This guidance recommends that the following BA studies be conducted for an extended-release drug product submitted as an NDA.

- Single-dose fasting study on all strengths of tablets and capsules and highest strength of beaded capsules
- Single-dose food-effect study on the highest strength
- Steady-state study on the highest strength

BE studies are recommended when substantial changes in the components or composition or method of manufacture for an extended-release drug product occur between the to-be-marketed NDA dosage form and the clinical trial material.

B. Waivers of In Vivo BE Studies (Biowaivers): NDAs and aNDAs

1. Beaded Capsules—Lower Strength

For modified-release beaded capsules, where the strength differs only in the number of beads containing the active moiety, a single-dose fasting BE study should be carried out only on the highest strength, with waiver of in vivo studies for lower strengths based on dissolution profiles. A dissolution profile should be generated for each strength using the recommended dissolution method. The f_2 test should be used to compare profiles from the different strengths of the product. An f_2 value of 50 can be used to confirm that further in vivo studies are not needed.

2. Tablets—Lower Strength

For modified-release tablets, when the drug product is in the same dosage form but in a different strength, is proportionally similar in its active and inactive ingredients, and has the same drug release mechanism, an in vivo BE determination of one or more lower strengths can be waived based on dissolution profile comparisons, with an in vivo study only on the highest strength. The drug products should exhibit similar dissolution profiles between the highest strength and the lower strengths, based on the f_2 test in at least three dissolution media (e.g., pH 1.2, 4.5, and 6.8). The dissolution profile should be generated on the test and reference products of all strengths.

C. Risk-Based BE

The guidance defines *narrow therapeutic range* drug products as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or PD monitoring

are narrow therapeutic range drugs, sponsors and applicants should contact the appropriate review division at CDER to determine whether a drug should or should not be considered to have a narrow therapeutic range.

The guidance recommends that sponsors consider additional testing and controls to ensure the quality of drug products containing narrow therapeutic range drugs. The approach is designed to provide increased assurance of interchangeability for drug products containing specified narrow therapeutic range drugs. It is not designed to influence the practice of medicine or pharmacy.

Unless otherwise indicated by a specific guidance, this guidance recommends that the traditional BE limit of 80% to 125% for non-narrow therapeutic range drugs remain unchanged for the BA measures (AUC and Cmax) of narrow therapeutic range drugs.

The selection of active ingredients for which BE studies should be required is a public health decision and as such should take into account the benefit/risk ratio of the same. This situation leads to the health risk concept, that is, which active ingredients require rigorous handling to prevent public health problems. One way of doing this is to take into account which active ingredients, because of their pharmacological characteristics, should be controlled through blood determinations.

As operational definition, the health risk concept should be established in the context of the problems of BE. For this purpose it would be reasonable to establish what are the health consequences when the drug is outside (under or above) the therapeutic window (the margin determined by the nontoxic maximum concentration and the effective minimum concentration). Thus, in relating the therapeutic window (the margin whose limits are the nontoxic maximum and effective minimum concentrations) and adverse effects of the drugs, three risk levels can be established, as described below.

High health risk: This is the probability of the appearance of threatening complications of the disease for the life or the psychophysical integrity of the person and/or serious adverse reactions (death, patient hospitalization, extension of the hospitalization, significant or persistent disability, disability or threat of death), when the blood concentration of the active ingredient is not within the therapeutic window. For purposes of the selection, this risk level was assigned a score of 3 (three).

Intermediate health risk: This is the probability of the appearance of nonthreatening complications of the disease for the life or the psychophysical integrity of the person and/or adverse reactions, not necessarily serious, when the blood concentration of the active ingredient is not found within the therapeutic window. For purposes of the selection, this risk level was assigned a score of 2 (two).

Low health risk: This is the probability of the appearance of a minor complication of the disease and/or mild adverse reactions, when the blood concentration of the active ingredient is not within the therapeutic window. For purposes of the selection, this risk level was assigned a score of 1 (one).

While there are other factors to be considered such as the physicochemical and PK parameters, from the standpoint of public health, the most important element to take into account is the health risk. Table 4 lists the active ingredients classified in accordance with their health risk and the established scores.

Table 4 Classification of Active Ingredients According to Their Health Risk

Active Ingredient	Health Risk
Acetazolamide	1
Allopurinol	1
Calcium folinate	1
Captopril	1
Clomifene	1
Cloxacillin	1
Dexamethasone	1
Diazepam	1
Folic acid + ferrous sulfate	1
Ibuprofen	1
Isosorbide dinitrate	1
Levamisole	1
Mebendazole	1
Mefloquine	1
Nalidixic acid	1
Niclosamide	1
Nifedipine	1
Nystatin	1
Phenoxymethylpenicillin	1
Phytomenadione	1
Pyranatel	1
Praziquantel	1
Pyrazinamide	1
Sulfasalazine	1
Amiloride	2
Amitriptyline	2
Amoxicillin	2
Atenolol	2
Azathioprine	2
Biperiden	2
Chloramphenicol	2
Cimetidine	2
Ciprofloxacin	2
Clofazimine	2
Clomipramine	2
Chlorpromazine	2
Co-trimoxazole	2
Cyclophosphamide	2
Dapsone	2
Diethylcarbamazine	2
Doxycycline	2
Erythromycin	2
Ethinylestradiol	2
Etoposide	2
Flucytosine	2
Fludrocortisone	2
Furosemide	2
Haloperidol	2
Hydrochlorothiazide	2
Indometacin	2
Isoniazid	2
Ketoconazole	2
Levodopa + inhib. DDC	2
Levonorgestrel	2
Levotiroxina	2
6-Mercaptopurine	2
Methotrexate	2
Methyldopa	2
Metoclopramide	2
Metronidazole	2
Nitrofurantoin	2
Norethindrone	2
Oxamniquine	2

Table 4 (Continued)

Active Ingredient	Health Risk
Paracetamol	2
Penicillamine	2
Piperazine	2
Pyridostigmine	2
Procarbazine	2
Promethazine	2
Propranolol	2
Propylthiouracil	2
Pyrimethamine	2
Quinine	2
Rifampicin	2
Salbutamol, sulfate	2
Spironolactone	2
Tamoxifen	2
Tetracycline	2
Carbamazepine	3
Cyclosporine	3
Digoxin	3
Ethambutol	3
Ethosuximide	3
Griseofulvin	3
Lithium carbonate	3
Oxcarbazepine	3
Phenytoin	3
Procainamide	3
Quinidine	3
Theophylline	3
Tolbutamide	3
Valproic acid	3
Verapamil	3
Warfarin	3

D. Typical Examples of Complex BE

1. Digoxin

Digoxin in tablet form is not listed in the Orange Book, since this is a "grandfathered" dosage form of digoxin. Since the tablet formulation of digoxin was established in clinical use before the passage of the Federal Food, Drug, and Cosmetic Act of 1938, generic versions of digoxin tablets may be marketed without an approved aNDA. Data showing BE of generic digoxin tablet products to the innovator product Lanoxin are generally not available or forthcoming, so that comparable rate and extent of absorption between generic products and Lanoxin brand tablets, or between different generic products, is not ensured. Seventeen generic digoxin tablets (0.25 mg) have been listed as currently marketed, though some of these may be marketed by suppliers or distributors of another manufacturer's product. Without PK data to verify the BE of these products to Lanoxin, the clinical responses (both therapeutic and toxic) from these generic products compared with Lanoxin are unpredictable. This inability to guarantee therapeutic equivalence to a reference product opposes the entire premise of generic substitution: the practitioner should expect the same responses (no more, no less) from a therapeutically equivalent generic product. Consequently, generic substitution is not advised. Use of a generic digoxin product as initial therapy may result in lower or higher than expected BA, requiring additional monitoring and dosage adjustment, and ultimately increasing costs of therapy far above the cost savings from a less expensive generic product.

2. Levothyroxine

Levothyroxine sodium tablets are also currently not listed in the Orange Book. In the words of FDA, levothyroxine sodium was first introduced into the market before 1962 without an approved NDA, apparently in the belief that it was not a new drug. The lack of BE data of generic preparations to the two major brand name products Synthroid and Levothroid has been noted, along with the adoption in 1984 of the *U.S. Pharmacopoeia* guidelines for potency of levothyroxine sodium tablets. However, between 1987 and 1994, a total of 58 adverse drug experience reports with levothyroxine sodium tablets were received by FDA, with 47 of the incidences apparently related to subpotency and 9 incidences related to superpotency. These adverse events were caused not only by switching product brands, but also by inconsistencies in BA between different lots from the same source. BE issues regarding levothyroxine sodium tablets were highlighted when the results of a BE study comparing the innovator product Synthroid with several generic brands finally appeared in the literature. The study sponsor (the marketer of Synthroid) attempted to prevent publication of these results, which claimed BE of Synthroid to three other levothyroxine sodium products. After publication of these study results, advertisements appeared in journals and trade magazines advocating the substitution of other brand name levothyroxine sodium products (e.g., Levothroid, Levoxyl) for Synthroid. In addition, statements were made such as "Feel comfortable using Levothroid, Levoxyl, or Synthroid in hypothyroid patients. These three are bioequivalent. . .even though they're not AB-rated."

Several points should be considered before routinely switching marketed brands of levothyroxine sodium tablets (at least 24 products for the 0.1 mg tablet are listed). First, although the conclusions stated in the peer-reviewed BE study cited appear to be generally accepted, the results of this study were not subjected to the scrutiny of the FDA review process. In view of significant stability and potency problems, FDA has issued a Federal Register notice stating that (1) orally administered levothyroxine sodium products are now considered new drugs and (2) manufacturers who intend to continue marketing these products must submit an NDA within 3 years to obtain approval. Recently, FDA extended this deadline for an additional year. Second, the impression that all levothyroxine sodium tablet formulations are likely to be bioequivalent is not currently supported with FDA-substantiated BE data; routine substitution of these products for refills of existing prescriptions is not advisable until FDA review is complete. Third, practitioners must always comply with the substitution laws in their individual states. If a statute mandates substitution of a therapeutically equivalent or bioequivalent product, reliance upon data reported in the scientific literature may not always guarantee these requirements will be satisfied.

3. Warfarin Sodium

Three approved generic versions of warfarin sodium tablets (seven strengths) are currently listed in the Orange Book. Before approval of these generic warfarin sodium products, several states either enacted or were considering legislation to require pharmacists to obtain prescriber and patient approval for generic substitution of drugs with a narrow therapeutic index (NTI). In response, FDA issued a position statement. FDA's position is clear with regard to the issue of tightening CIs and changing study designs for BE determinations of NTI drugs. The present requirements to prove BE, at least in the

United States and Canada, are already so difficult and constrained that there is no possibility, even for NTI drugs, that dosage forms meeting the criteria could lead to therapeutic problems. Drugs approved through the NDA process with NTIs, by definition, must have low intrasubject variability. Otherwise, patients would have cycles of toxicity and lack of efficacy, and therapeutic drug monitoring would be useless. The low intrasubject variability associated with NTI drugs ensures that patient response to a specific drug should be consistent, and the statistical criteria required by FDA for BE appear more than adequate for confidence in generic substitution. This is especially true in light of the notable absence of data that prove otherwise. For the most part, the arguments against generic substitution of NTI drugs appear to be based on economic considerations. Commentaries debating the suitability of generic warfarin products have focused on the results from reports of clinical studies with generic warfarin and the content uniformity requirements for warfarin sodium tablets. As indicated in a letter addressing these issues, no convincing and substantiated scientific data have been published showing bioinequivalence of generic warfarin products or product failure of these products in clinical studies. Recently, an evidence-based medicine approach was used to compare the results reported with Coumadin and a generic warfarin product in clinical studies. No significant differences were found in the international normalized ratio (INR), number of dosage changes to adjust INR in range, or number of hospitalizations or incidences of bleeding between the reference and generic warfarin products. Physicians may sometimes encounter difficulties in maintaining stabilized INR in patients anticoagulated with warfarin, because multiple drug interactions and patient variables affect warfarin levels and create difficulty in achieving consistently therapeutic INR values. However, factors such as diet, concurrent illnesses, interacting drugs, and noncompliance are *intersubject* variables that are unrelated to the BE issue. For crossover studies using log-transformed data, it is largely the within-subject distribution of values (*intrasubject* variability) that determines the validity and efficiency of the standard parametric methods of analysis. For NTI drugs such as warfarin, intrasubject variability, by definition, is low and the available clinical data indicate that lack of BE does not appear to be the explanation for problems experienced during warfarin therapy. Another article introduces the concept of "switchability," that is, the substitution of one approved generic product for another generic product. BE studies submitted to FDA through an aNDA are conducted by comparing data from the proposed generic product and a reference product. The reference product is selected by FDA and is typically the innovator or pioneer product that was originally introduced into the market. Suppose approved generic product A differed from the reference product in at least one parameter (e.g., mean AUC values) by +4%, and that approved generic product B differed from the reference product by –4%. The net difference of generic products A and B would then be 8%; could this magnitude of difference result in bioinequivalence and lack of equivalent therapeutic response for an NTI drug? No data were presented from any clinical studies that could support the contention that switchability for NTI drugs is problematic. Rather, phrases such as "...with NTI drugs, small variations in bioavailability can potentially pose problems" and conceptual arguments are used to suggest the need for special BE criteria to be applied to NTI drugs. Reference is made to the FDA's draft guidance for population and individual BE studies, which propose the use of reference scaling (essentially, modifying the BE criteria to account for the variability of the reference product) for NTI drugs, regardless of the intrasubject variability of the reference product. Since NTI drugs have low intrasubject variability as discussed, this approach would likely result in narrower CI requirements. Finally, a recent report further confirms the BE of generic warfarin to the innovator product. More than 100 subjects anticoagulated with Coumadin were switched to a generic warfarin product for 8 weeks in a nonrandomized comparative clinical observational study. The overall conclusion was that the variability in INR in patients receiving generic warfarin was not statistically significant from that seen in the control group receiving Coumadin. These investigators identified associated factors not related to the product change in subjects whose INR varied by >1.0 from baseline. This further emphasizes the critical role of interpatient factors (physical activity, dietary vitamin K, noncompliance, drug interactions, congestive heart failure, diarrhea, alcohol consumption) affecting the anticoagulant response with warfarin.

4. Albuterol Metered-Dose Inhalers

Four approved generic versions of albuterol metered-dose inhalers are currently listed in the Orange Book as therapeutically equivalent (AB-rated) to the reference product Ventolin. The Proventil product is rated BN, or not therapeutically equivalent to Ventolin or the four generic products. For products administered by metered-dose inhalation and intended for local therapeutic effects, the typical PK methods for evaluating BE cannot be used. Rather, an approach based on acute PD response (forced expiratory volume in 1 second, FEV_1) was proposed, with asthmatic patients as subjects. The statistical criteria and appropriate CIs for BE determination are not as rigidly defined for PD methods as for PK methods. Consequently, variability in patient response may be of slightly greater concern, since albuterol metered-dose inhalers are used as "rescue inhalers" for nocturnal asthma attacks (even though they are not considered NTI drugs). However, FDA is satisfied that these products will produce equivalent therapeutic responses.

E. General PK Study Design and Data Handling

For replicate and nonreplicate in vivo PK BE studies, the following general approaches are recommended, recognizing that the elements may be adjusted for certain drug substances and drug products.

1. Study Conduct

- The test or reference products should be administered with approximately 8 oz (240 mL) of water to an appropriate number of subjects under fasting conditions, unless the study is a food-effect BA and BE study.
- Generally, the highest marketed strength should be administered as a single unit. If warranted for analytical reasons, multiple units of the highest strength can be administered, providing the total single dose remains within the labeled dose range.
- An adequate washout period (e.g., more than five half-lives of the moieties to be measured) should separate each treatment.
- The lot numbers of both test and reference-listed products and the expiration date for the reference product should be stated. The drug content of the test product should not differ from that of the reference-listed product by more than 5%. The sponsor should include a statement of the composition of the test product and, if possible, a side-by-side comparison of the compositions of test and reference-listed products. In accordance with 21 CFR

320.38, samples of the test and reference-listed product must be retained for 5 years.
- Before and during each study phase, subjects should be allowed water, as desired, except for 1 hour before and after drug administration; be provided standard meals no less than 4 hours after drug administration; and abstain from alcohol for 24 hours before each study period and until after the last sample from each period is collected.

2. Sample Collection and Sampling Times
- Under normal circumstances, blood, rather than urine or tissue, should be used. In most cases, drug or metabolites are measured in serum or plasma. However, in certain cases, whole blood may be more appropriate for analysis. Blood samples should be drawn at appropriate times to describe the absorption, distribution, and elimination phases of the drug. For most drugs, 12 to 18 samples, including a predose sample, should be collected per subject per dose. This sampling should continue for at least three or more terminal half-lives of the drug. The exact timing for sample collection depends on the nature of the drug and the input from the administered dosage form. The sample collection should be spaced in such a way that the maximum concentration of the drug in the blood (Cmax) and terminal elimination rate constant (l_z) can be estimated accurately. At least three to four samples should be obtained during the terminal log-linear phase to obtain an accurate estimate of l_z from linear regression. The actual clock time when samples are drawn as well as the elapsed time related to drug administration should be recorded.

3. Subjects with Predose Plasma Concentrations
- If the predose concentration is less than or equal to 5% of the Cmax value in that subject, the subject's data, without any adjustments, can be included in all PK measurements and calculations. If the predose value is greater than 5% of Cmax, the subject should be dropped from all BE study evaluations.

4. Data Deletion due to Vomiting
- Data from subjects who experience emesis during the course of a BE study for immediate-release products should be deleted from statistical analysis if vomiting occurs at or before two times median Tmax. In the case of modified-release products, the data from subjects who experience emesis any time during the labeled dosing interval should be deleted.

5. PK Information Recommended for Submission
- Plasma concentrations and time points
- Subject, period, sequence, treatment
- $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, Cmax, Tmax, k_z, and $t_{1/2}$
- Intersubject, intrasubject, and total variability, if available
- Concentration at the end of a dosing interval (C_{min}), average concentration during a dosing interval (C_{av}), degree of fluctuation [$(C_{max} - C_{min})/C_{av}$], and swing [$(C_{max} - C_{min})/C_{min}$], if steady-state studies are employed
- Partial AUC, if justified.

6. BE Demonstration Measures
- Logarithmic transformation should be provided for measures used for BE demonstration.

7. CI Values
- CI values should not be rounded off; therefore, to pass a CI limit of 80 to 125; the value should be at least 80 and not more than 125.

8. Statistical Information for $AUC_{0\text{-}T}$, $AUC_{0\text{-}\infty}$, and Cmax
- Geometric mean
- Arithmetic mean
- Ratio of means
- CIs

F. Measurement Indices
Whenever comparison of the test product and the reference material is to be based on blood concentration-time curves or cumulative urinary excretion-time curves at steady state, appropriate dosage administration and sampling should be carried out to document attainment of steady state. A more complete characterization of the blood concentration or urinary excretion rate during the absorption and elimination phases of a single dose administered at steady state is encouraged to permit estimation of the total area under concentration-time curves or cumulative urinary excretion-time curves and to obtain PK information, for example, half-life or blood clearance, that is essential in preparing adequate labeling for the drug product.

When comparison of the test product and the reference material is to be based on acute pharmacological effect-time curves, measurements of this effect should be made with sufficient frequency to demonstrate a maximum effect and a lack of significant difference between the test product and the reference material.

G. Dose Selection
Dose selection will depend upon the label claims, consideration of assay sensitivity, and relevance to the practical use conditions of the reference product. A blood level BE study should generally be conducted at the highest dose approved for the pioneer product.

However, FDA will consider a BE study conducted at a higher than approved dose in certain cases. Such a study may be appropriate when a multiple of the highest approved dose achieves measurable blood levels, but the highest approved dose does not. In general, the study would be limited to 2 to 3 times the highest dose approved for the pioneer product. The pioneer product should have an adequate margin of safety at the higher than approved dose level. The generic sponsor should also confirm (e.g., through literature) that the drug follows linear kinetics. A higher than approved dose BE study in food animal species would be accompanied by a tissue residue withdrawal study conducted at the highest approved dose for the pioneer product.

For products labeled for multiple claims involving different pharmacological actions at a broad dose range (e.g., therapeutic and production claims), a single BE study at the highest approved dose will usually be adequate. However, multiple BE studies at different doses may be needed if the drug is known to follow nonlinear kinetics. The sponsor should consult with FDA to discuss the BE study or studies appropriate to a particular drug.

H. Multiple Strengths of Solid Oral Dosage Forms
The generic sponsor should discuss with FDA the appropriate in vivo BE testing and in vitro dissolution testing to obtain approval for multiple strengths (or concentrations) of solid oral dosage forms. FDA will consider the ratio of active to inactive ingredients and the in vitro dissolution profiles of

the different strengths, the water solubility of the drug, and the range of strengths for which approval is sought. One in vivo BE study with highest strength product may suffice if the multiple strength products have the same ratio of active to inactive ingredients and are otherwise identical in formulation. In vitro dissolution testing should be conducted using an FDA approved method, to compare each strength of the generic product to the corresponding strength of the reference product.

I. Manufacturing of Pilot Batch ("Biobatch")

A pilot batch or "biobatch" should be the source of the finished drug product used in the pivotal studies (i.e., BE studies and tissue residue studies), stability studies, and the validation studies for the proposed analytical and stability indicating methods. Batch testing Individual batch testing is necessary to ensure that all batches of the same drug product meet an appropriate in vitro test. The Commissioner will ordinarily terminate a requirement for a manufacturer to submit samples for batch testing on a finding that the manufacturer has produced four consecutive batches that were tested by the FDA and found to meet the BE requirement, unless the public health requires that batch testing be extended to additional batches.

If a BE requirement specifies a currently available in vitro test or an in vitro BE standard comparing the drug product to a reference standard, the manufacturer shall conduct the test on a sample of each batch of the drug product to ensure batch-to-batch uniformity.

J. Dosing by Labeled Concentration

The potency of the pioneer and generic products should be assayed prior to conducting the BE study to ensure that FDA or compendial specifications are met. The center recommends that the potency of the pioneer and generic lots should differ by no more than ±5% for dosage form products.

The animals should be dosed according to the labeled concentration or strength of the product rather than the assayed potency of the individual batch (i.e., the dose should not be corrected for the assayed potency of the product). The BE data or derived parameters should not be normalized to account for any potency differences between the pioneer and generic product lots.

K. Single Dose vs. Multiple Dose Studies

A single dose study at the highest approved dose will generally be adequate for the demonstration of BE. A single dose study at a higher than approved dose may be appropriate for certain drugs.

A multiple dose study may be appropriate when there are concerns regarding poorly predictable drug accumulation, (e.g., a drug with nonlinear kinetics) or a drug with a narrow therapeutic window. A multiple dose study may also be needed when assay sensitivity is inadequate to permit drug quantification out to three terminal elimination half-lives beyond the time when maximum blood concentrations (Cmax) are achieved, or in cases where prolonged or delayed absorption exist. The determination of prolonged or delayed absorption (i.e., flip-flop kinetics) may be made from pilot data, from the literature, or from information contained with FOI summaries pertaining to the particular drug or family of drugs.

L. Guidelines on the Design of a Single-Dose Study

A BE study should be a single-dose comparison of the drug product to be tested and the appropriate reference material conducted in normal adults. The test product and the reference material should be administered to subjects in the fasting state, unless some other approach is more appropriate for valid scientific reasons. A single-dose study should be crossover in design, unless a parallel design or other design is more appropriate for valid scientific reasons, and should provide for a drug elimination period. Unless some other approach is appropriate for valid scientific reasons, the drug elimination period should be either at least 3 times the half-life of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured in the blood or urine or at least 3 times the half-life of decay of the acute pharmacological effect.

When comparison of the test product and the reference material is to be based on blood concentration-time curves, unless some other approach is more appropriate for valid scientific reasons, blood samples should be taken with sufficient frequency to permit an estimate of both the peak concentration in the blood of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured; and the total AUC for a time period at least 3 times the half-life of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured.

In a study comparing oral dosage forms, the sampling times should be identical. In a study comparing an intravenous dosage form and an oral dosage form, the sampling times should be those needed to describe both the distribution and elimination phase of the intravenous dosage form; and the absorption and elimination phase of the oral dosage form.

In a study comparing drug delivery systems other than oral or intravenous dosage forms with an appropriate reference standard, the sampling times should be based on valid scientific reasons.

When comparison of the test product and the reference material is to be based on cumulative urinary excretion-time curves, unless some other approach is more appropriate for valid scientific reasons, samples of the urine should be collected with sufficient frequency to permit an estimate of the rate and extent of urinary excretion of the active drug ingredient or therapeutic moiety, or its metabolite(s), measured.

When comparison of the test product and the reference material is to be based on acute pharmacological effect-time curves, measurements of this effect should be made with sufficient frequency to permit a reasonable estimate of the total AUC for a time period at least 3 times the half-life of decay of the pharmacological effect, unless some other approach is more appropriate for valid scientific reasons.

The use of an acute pharmacological effect to determine BA may further require demonstration of dose-related response. In such a case, BA may be determined by comparison of the dose-response curves as well as the total area under the acute pharmacological effect-time curves for any given dose.

M. Guidelines for Multiple-Dose Study

In selected circumstances it may be necessary for the test product and the reference material to be compared after repeated administration to determine steady-state levels of the active drug ingredient or therapeutic moiety in the body. The test product and the reference material should be administered to subjects in the fasting or nonfasting state, depending upon the conditions reflected in the proposed labeling of the test product.

A multiple-dose study may be required to determine the BA of a drug product in the following circumstances that

there is a difference in the rate of absorption but not in the extent of absorption., there is excessive variability in BA from subject to subject.; the concentration of the active drug ingredient or therapeutic moiety, or its metabolite(s), in the blood resulting from a single dose is too low for accurate determination by the analytical method; the drug product is an extended-release dosage form.

A multiple-dose study should be crossover in design, unless a parallel design or other design is more appropriate for valid scientific reasons, and should provide for a drug elimination period if steady-state conditions are not achieved. A multiple-dose study is not required to be of crossover design if the study is to establish dose proportionality under a multiple-dose regimen or to establish the PK profile of a new drug product, a new drug delivery system, or an extended-release dosage form.

If a drug elimination period is required, unless some other approach is more appropriate for valid scientific reasons, the drug elimination period should be either at least 5 times the half-life of the active drug ingredient or therapeutic moiety, or its active metabolite(s), measured in the blood or urine; or at least 5 times the half-life of decay of the acute pharmacological effect.

Whenever a multiple-dose study is conducted, unless some other approach is more appropriate for valid scientific reasons, sufficient doses of the test product and reference material should be administered in accordance with the labeling to achieve steady-state conditions.

N. Fed vs. Fasted State

Feeding may either enhance or interfere with drug absorption, depending upon the characteristics of the drug and the formulation. Feeding may also increase the inter- and intrasubject variability in the rate and extent of drug absorption. The rationale for conducting each BE study under fasting or fed conditions should be provided in the protocol. Fasting conditions, if used, should be fully described, giving careful consideration to the PKs of the drug and the humane treatment of the test animals. The protocol should describe the diet and feeding regime, which will be used in the study.

If a pioneer product label indicates that the product is limited to administration either in the fed or fasted state, then the BE study should be conducted accordingly. If the BE study parameters pass the agreed upon CIs, then the single study is acceptable as the basis for approval of the generic drug.

However, for certain product classifications or drug entities, such as enteric-coated and oral sustained-release products, demonstration of BE in both the fasted and the fed states may be necessary, if drug BA is highly variable under feeding conditions, as determined from the literature or from pilot data. A BE study conducted under fasted conditions may be necessary to pass the CIs. A second smaller study may be necessary to examine meal effects. FDA will evaluate the smaller study with respect to the means of the pivotal parameters (AUC, Cmax). The sponsors should consult with FDA prior to conducting the studies.

O. Pharmacological End-Point Studies

Where the direct measurement of the rate and extent of absorption of the new animal drug in biological fluids is inappropriate or impractical, the evaluation of a pharmacological end point related to the labeled indications for use will be acceptable.

Typically the design of a pharmacological end-point study should follow the same general considerations as the blood level studies. However specifics such as the number of subjects or sampling times will depend on the pharmacological end point monitored. The parameters to be measured will also depend upon the pharmacological end points and may differ from those used in blood level studies. As with blood level studies, when pharmacological end-point studies are used to demonstrate BE, a tissue residue study will also be required in food-producing animals.

For parameters which can be measured over time, a time versus effect profile is generated, and equivalence is determined with the method of statistical analysis essentially the same as for the blood level BE study.

For pharmacological effects for which effect versus time curves cannot be generated, then alternative procedures for statistical analysis should be discussed with FDA prior to conducting the study.

P. Clinical End-Point Studies

If measurement of the drug or its metabolites in blood, biological fluids, or tissues is inappropriate or impractical, and there are no appropriate pharmacological end points to monitor (e.g., most production drugs and some coccidiostats and anthelmintics), then well-controlled clinical end-point studies are acceptable for the demonstration of BE.

Generally, a parallel group design with three treatment groups should be used. The groups should be a placebo (or negative) control, a positive control (reference/pioneer product), and the test (generic) product. The purpose of the placebo (or negative) control is to confirm the sensitivity or validity of the study. Dosage(s) approved for the pioneer product should be used in the study. Dosage(s) should be selected following consultation with FDA and should reflect consideration for experimental sensitivity and relevance to the common use of the pioneer product.

Studies should generally be conducted using the target animal species, with consideration for the sex, class, body weight, age, health status, and feeding and husbandry conditions, as described on the pioneer product labeling. In general, the length of time that the study is conducted should be consistent with the duration of use on the pioneer product labeling.

In general, the response(s) to be measured in a clinical end-point study should be based upon the labeling claims of the pioneer product and selected in consultation with the Center for Veterinary Medicine (CVM, FDA). It may not be necessary to collect data on some overlapping claims (e.g., for a production drug which is added at the same amount per ton of feed for both growth rate and feed efficiency, data from only one of the two responses need be collected).

When considering sample size, it is important to note that the pen, not the individual animal, is often the experimental unit. As with blood level BE studies, FDA is advocating the use of 90% CIs as the best method for evaluating clinical end-point studies. The bounds for confidence limits [e.g., $\pm 20\%$ of the improvement over placebo (or negative) control] for the particular drug should be agreed upon with FDA prior to initiation of the study.

The analysis should be used to compare the test product and the reference product. In addition, a traditional hypothesis test should be performed comparing both the test and reference products separately to the placebo (or negative) control. The hypothesis test is conducted to ensure that the study has adequate sensitivity to detect differences when they actually occur. If no significant improvement ($\alpha = .05$) is seen in the parameter [i.e., the mean of the test and the mean of the reference products are each not significantly better than

the mean of the placebo (or negative) control], generally, the study will be considered inadequate to evaluate BE.

Assuming that the test and reference products have been shown to be superior to the placebo (or negative) control, the determination of BE is based upon the CI of the difference between the two products.

Some clinical end-point studies may not include a placebo (or negative) control for ethical and/or practical considerations. If the placebo is omitted, then the response(s) to the test and reference products should each provide a statistically significant improvement over baseline.

If the results are ordered categorical data (e.g., excellent, good, fair, or poor), a nonparametric hypothesis test of no difference between test product and placebo (or negative) control and between the reference product and placebo (or negative) control should be performed. As above, if these tests result in significant differences between the test product and control and the reference product and control, then a nonparametric CI on the difference between the test and reference products is calculated.

Another acceptable approach for categorical data is to calculate the CI on the odds ratio between the test and reference products after showing that the test and reference products are significantly better than the control.

Q. Analytical Methods

The analytical method used in an in vivo BA or BE study to measure the concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), in body fluids or excretory products, or the method used to measure an acute pharmacological effect shall be demonstrated to be accurate and of sufficient sensitivity to measure, with appropriate precision, the actual concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), achieved in the body. When the analytical method is not sensitive enough to measure accurately the concentration of the active drug ingredient or therapeutic moiety, or its active metabolite(s), in body fluids or excretory products produced by a single dose of the test product, two or more single doses may be given together to produce higher concentration.

1. Assay Consideration

A properly validated assay method is pivotal to the acceptability of any PK study. Sponsors should discuss any questions or problems concerning the analytical methodology with CVM before undertaking the BE studies. The aNADA submission should contain adequate information necessary for the CVM reviewer to determine the validity of the analytical method used to quantitate the level of drug in the biological matrix (e.g., blood).

The following aspects should be addressed in assessing method performance.

Concentration range and linearity

The quantitative relationship between concentration and response should be adequately characterized over the entire range of expected sample concentrations. For linear relationships, a standard curve should be defined by at least five concentrations. If the concentration response function is nonlinear, additional points would be necessary to define the nonlinear portions of the curve. Extrapolation beyond a standard curve is not acceptable.

Limit of detection

The standard deviation of the background signal and limit of detection (LoD) should be determined. The LoD is estimated as the response value calculated by adding 3 times the standard deviation of the background response to the average background response.

Limit of quantitation

The initial determination of limit of quantitation (LoQ) should involve the addition of 10 times the standard deviation of the background response to the average background response. The second step in determining LoQ is assessing the precision (reproducibility) and accuracy (recovery) of the method at the LoQ. The LoQ will generally be the lowest concentration on the standard curve that can be quantified with acceptable accuracy and precision.

Specificity

The absence of matrix interferences should be demonstrated by the analysis of six independent sources of control matrix. The effect of environmental, physiological, or procedural variables on the matrix should be assessed. Each independent control matrix will be used to produce a standard curve, which will be compared to a standard curve produced under chemically defined conditions. The comparison of curves should exhibit parallelism and superimposability within the limits of analytical variation established for the chemically defined standard curve.

Accuracy (Recovery)

This parameter should be evaluated using at least three known concentrations of analyte freshly spiked in control matrix, one being at a point two standard deviations above the LoQ, one in the middle of the range of the standard curve ("midrange") and one at a point two standard deviations below the upper quantitative limit of the standard curve. The accuracy of the method, based upon the mean value of six replicate injections, at each concentration level, should be within 80% to 120% of the nominal concentration at each level (high, midrange, and LoQ).

Precision

This parameter should be evaluated using at least three known concentrations of analyte freshly spiked in control matrix, at the same points used for determination of accuracy. The CV of six replicates should be ±10% for concentrations at or above 0.1 ppm (0.1 μg/mL). A CV of ±20% is acceptable for concentrations below 0.1 ppm.

Analyte stability

Stability of the analyte in the biological matrix under the conditions of the experiment (including any period for which samples are stored before analyses) should be established. It is recommended that the stability be determined with incurred analyte in the matrix of dosed animals in addition to, or instead of, control matrix spiked with pure analyte. Also, the influence of three freeze-thaw cycles at two concentrations should be determined.

Stability samples at three concentrations should be stored with the study samples and analyzed through the period of time in which study samples are analyzed. These analyses will establish whether or not analyte levels have decreased during the time of analysis.

Analytical system stability

To ensure that the analytical system remains stable over the time course of the assay, the reproducibility of the standard curve should be monitored during the assay. A minimal

design would be to run analytical standards at the beginning and at the end of the analytical run.

QC samples
The purpose of QC samples is to ensure that the complete analytical method, sample preparation, extraction, cleanup, and instrumental analysis perform according to acceptable criteria. The stability of the drug in the text matrix for the QC samples should be known and any tendency for the drug to bind to tissue or serum components over time should also be known.

Drug-free control matrix, for example, tissue, serum, that is freshly spiked with known quantities of test drug, should be analyzed contemporaneously with test samples, evenly dispersed throughout each analytical run. This can be met by the determination of accuracy and precision of each analytical run.

Replicate and repeat analyses
Single rather than replicate analyses are recommended, unless the reproducibility and/or accuracy of the method are borderline. Criteria for repeat analyses should be determined prior to running the study and recorded in the method SOP.

Summary of samples to be run with each analysis
a. Accuracy estimate
b. Precision estimate
c. Analytical system stability
d. Analyte stability samples

R. Sampling Time Considerations
The total number of sampling times necessary to characterize the blood level profiles will depend upon the curvature of the profiles and the magnitude of variability associated with the BA data (including PK variability, assay error, and interproduct differences in absorption kinetics).

The sampling times should adequately define peak concentration(s) and the extent of absorption. The sampling times should extend to at least three terminal elimination half-lives beyond Tmax. The sponsor should consult with FDA prior to conducting the pivotal BE study if the assay is unable to quantify samples to three half-lives.

Maximum sampling time efficiency may be achieved by conducting a pilot investigation. The pilot study should identify the general shapes of the test and reference curves, the magnitude of the difference in product profiles, and the noise associated with each blood-sampling time (e.g., variability attributable to assay error and the variability between subjects, for parallel study designs, or within subjects, for crossover study designs). This information should be applied to the determination of an optimum blood-sampling schedule. Depending upon these variability estimates, it may be more efficient to cluster several blood samples rather than to have samples which are periodically dispersed throughout the duration of blood sampling.

S. Protein Binding
In general, product BE should be based upon total (free plus protein bound) concentrations of the parent drug (or metabolite, when applicable). However, if nonlinear protein binding is known to occur within the therapeutic dosing range (as determined from literature or pilot data), then sponsors may need to submit data on both the free and total drug concentrations for the generic and pioneer products.

Similarly, if the drug is known to enter blood erythrocytes, the protocol should address the issue of potential nonlinearity in erythrocyte uptake of the drug administered within the labeled therapeutic dosing range.

The BE protocol or completed study report should provide any information available from the literature regarding erythrocyte uptake and protein binding characteristics of the drug or drug class, including the magnitude of protein binding and the type of blood protein to which it binds.

T. Subject Number
Pilot studies are recommended as a means of estimating the appropriate sample size for the pivotal BE study. Estimated sample size will vary depending upon whether the data are analyzed on a log or linear scale. Useful references for sample size estimates include Hauschke et al., 1992.

U. Crossover and Parallel Design Considerations
A two-period crossover design is commonly used in blood level studies. The use of crossover designs eliminates a major source of study variability: between subject differences in the rates of drug absorption, drug clearance, and the volume of drug distribution.

In a typical two-period crossover design, subjects are randomly assigned to either sequence A or sequence B with the restriction that equal numbers of subjects are initially assigned to each sequence. The design is as follows:

	Sequence A	Sequence B
Period 1	Test	Reference
Period 2	Reference	Test

A crucial assumption in the two-period crossover design is that of equal residual effects. Unequal residual effects may result, for example, from an inadequate washout period. Another assumption of the crossover (or extended period) design is that there is no subject by formulation interaction. In other words, the assumption is that all subjects are from a relatively homogeneous population and will exhibit similar relative BA of the test and reference products. If there are subpopulations of subjects, such that the relationship between product BA is a function of the subpopulation within which they are being tested, then a subject by formulation interaction is said to exist.

A one-period parallel design may be preferable in the following situations:

- The drug induces physiological changes in the animal (e.g., liver microsomal enzyme induction), which persist after total drug clearance and alter the BA of the product administered in the second period.
- The drug has a very long terminal elimination half-life, creating a risk of residual drug present in the animal at the time of the second period dosing.
- The duration of the washout time for the two-period crossover study is so long as to result in significant maturational changes in the study subjects.
- The drug follows delayed or prolonged absorption (flip-flop kinetics), where the slope of the beta-elimination phase is dictated by the rate of drug absorption rather than the rate of drug elimination from one or both products.

Other designs, such as the two-period design with four treatment sequences (test/test, reference/reference, test/reference, and reference/test) or the extended period design may be appropriate depending on the circumstances. The use of alternative study designs should be discussed with

FDA prior to conducting the BE study. Pilot data or literature may be used in support of alternative study designs.

V. Duration of Washout Time for Crossover Study

For drugs which follow a one- or two-compartment open body model, the duration of the washout time should be approximately 10 times the plasma apparent terminal elimination half-life, to provide for 99.9% of the administered dose to be eliminated from the body. If more highly complex kinetic models are anticipated (e.g., drugs for which long withdrawal times have been assigned due to prolonged tissue binding), or for drugs with the potential for physiologic carryover effects, the washout time should be adjusted accordingly. The washout period should be sufficiently long to allow the second period of the crossover study to be applicable in the statistical analysis. However, if sequence effects are noted, the data from the first period may be evaluated as a parallel design study.

W. Fed BE Studies

Food-effect BA studies are usually conducted for new drugs and drug products during the IND period to assess the effects of food on the rate and extent of absorption of a drug when the drug product is administered shortly after a meal (fed conditions), as compared to administration under fasting conditions. Fed BE studies, on the other hand, are conducted for aNDAs to demonstrate their BE to the RLD under fed conditions. Food can influence the BE between test and reference products. Food effects on BA can have clinically significant consequences. Food can alter BA by various means, including:

- Delay gastric emptying.
- Stimulate bile flow.
- Change GI pH.
- Increase splanchnic blood flow.
- Change luminal metabolism of a drug substance.
- Physically or chemically interact with a dosage form or a drug substance.

Food effects on BA are generally greatest when the drug product is administered shortly after a meal is ingested. The nutrient and caloric contents of the meal, the meal volume, and the meal temperature can cause physiological changes in the GI tract in a way that affects drug product transit time, luminal dissolution, drug permeability, and systemic availability. In general, meals that are high in total calories and fat content are more likely to affect the GI physiology and thereby result in a larger effect on the BA of a drug substance or drug product. It is recommended to use high-calorie and high-fat meals during food-effect fed BE studies.

X. Food Effects on Drug Products

Administration of a drug product with food may change the BA by affecting either the drug substance or the drug product. In practice, it is difficult to determine the exact mechanism by which food changes the BA of a drug product without performing specific mechanistic studies. Important food effects on BA are least likely to occur with many rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances (BCS Class I) because absorption of the drug substances in Class I is usually pH- and site-independent and thus insensitive to differences in dissolution. However, for some drugs in this class, food can influence BA when there is a high first-pass effect, extensive adsorption, complexation, or instability of the drug substance in the GI tract. In some cases, excipients or interactions between excipients and the food-induced changes in gut physiology can contribute to these food effects and influence the demonstration of BE. For rapidly dissolving formulations of BCS Class I drug substances, food can affect Cmax and the time at which this occurs (Tmax) by delaying gastric emptying and prolonging intestinal transit time. However, we expect the food effect on these measures to be similar for test and reference products in fed BE studies.

For other immediate-release drug products (BCS Class II, III, and IV) and for all modified-release drug products, food effects are most likely to result from a more complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance. In these cases, the relative direction and magnitude of food effects on formulation BA and the effects on the demonstration of BE are difficult, if not impossible, to predict without conducting a fed BE study.

Y. Recommendations for Immediate-Release Drugs:

- For uncomplicated drugs in immediate-release dosage forms, BE must be demonstrated under fasted conditions. In addition to a BE study under fasting conditions, we recommend a BE study under fed conditions for all orally administered immediate-release drug products, with the following exceptions.
  - When both test products and RLDs are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I), or
  - when the Dosage and Administration section of the RLD label states that the product should be taken only on an empty stomach, or
  - when the RLD label does not make any statements about the effect of food on absorption or administration.
  - When the reference-listed product label does not make any statements about the effect of food on absorption or administration.
- For complicated drugs in immediate-release dosage forms, for example, narrow therapeutic range drugs (drugs with a steep dose—response curve, critical drugs), highly toxic drugs, and drugs known to have nonlinear PKs. BE must be demonstrated under both fasted and fed conditions.
- Nonlinear drugs. BE must be demonstrated under both fasted and fed conditions unless the nonlinearity occurs after the drug enters the systemic circulation and there is no evidence that the product exhibits a food effect.
- Drugs in modified-release dosage forms. BE must be demonstrated under both fasted and fed conditions.

Z. Recommendations For Modified-Release Products

In addition to a BE study under fasting conditions, a BE study under fed conditions should be conducted for all orally administered modified-release drug products. It is recommended that food-effect BA and fed BE studies be conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. A high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800–1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively. The caloric breakdown of the test meal should be provided in the study report.

For fasting administration, following an overnight fast of at least 10 hours, subjects should be administered the drug

product with 240 mL (8 fluid oz) of water. No food should be allowed for at least 4 hours post dose. Water may be allowed as desired, except 1 hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

For fed administration, following an overnight fast of at least 10 hours, subjects should start the recommended meal 30 minutes prior to the administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with 240 mL (8 fluid oz) of water. No food should be allowed for at least 4 hours post dose. Water may be allowed as desired, except 1 hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

1. Study Design

A sponsor may propose any study designs and data analyses. The scientific rationale and justification for these study designs and analyses should be provided in the study protocol. Sponsors may choose to conduct additional studies for a better understanding of the drug product and to provide optimal labeling statements for dosage and administration (e.g., different meals and different times of drug intake in relation to meals). In studying modified-release dosage forms, consideration should be given to the possibility that coadministration with food can result in *dose dumping*, in which the complete dose may be more rapidly released from the dosage form than intended, creating a potential safety risk for the study subjects.

2. General Design

A randomized, balanced, single-dose, two-treatment (fed vs. fasting), two-period, two-sequence crossover design is recommended for studying the effects of food on the BE of either an immediate-release or a modified-release drug product. The formulation to be tested should be administered following a test meal (fed condition). The treatments should consist of both test and reference formulations administered following a test meal (fed condition). An adequate washout period should separate the two treatments in food-effect BE studies.

3. Subject Selection

Fed BE studies can be carried out in healthy volunteers drawn from the general population. Studies in the patient population are also appropriate if safety concerns preclude the enrollment of healthy subjects. A sufficient number of subjects should complete the study to achieve adequate power for a statistical assessment of food effects. A minimum of 12 subjects should complete the fed BE studies.

4. Dosage Strength

In general, the highest strength of a drug product intended to be marketed should be tested in fed BE studies. In some cases, clinical safety concerns can prevent the use of the highest strength and warrant the use of lower strengths of the dosage form. For aNDAs, the same lot and strength used in the fasting BE study should be tested in the fed BE study. For products with multiple strengths in aNDAs, if a fed BE study has been performed on the highest strength, BE determination of one or more lower strengths can be waived based on dissolution profile comparisons.

5. Test Meal

The fed BE studies can be conducted using meal conditions that are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected. A high-fat (approximately 50% of total caloric content of the meal) and high-calorie (approximately 800–1000 calories) meal is recommended as a test meal for food-effect BA and fed BE studies. This test meal should derive approximately 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively. (An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 oz of hash brown potatoes and 8 oz of whole milk.) Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. The caloric breakdown of the test meal should be provided in the study report. If the caloric breakdown of the meal is significantly different from the one described here, the sponsor should provide a scientific rationale for this difference.

6. Administration

a. Fed Treatments

Following an overnight fast of at least 10 hours, subjects should start the recommended meal 30 minutes prior to administration of the drug product. Study subjects should eat this meal in 30 minutes or less; however, the drug product should be administered 30 minutes after start of the meal. The drug product should be administered with 240 mL (8 fluid oz) of water. No food should be allowed for at least 4 hours post dose. Water can be allowed as desired except for 1 hour before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

7. Sample Collection

Timed samples in biological fluid, usually plasma, should be collected from the subjects to permit characterization of the complete shape of the plasma concentration-time profile for the parent drug. It may be advisable to measure other moieties in the plasma, such as active metabolites. Consideration should be given to the possibility that coadministration of a dosage form with food can alter the time course of plasma drug concentrations so that fasted and fed treatments can have different sample collection times.

8. Data Analysis and Labeling

The following exposure measures and PK parameters should be obtained from the resulting concentration-time curves for the test and reference products.

- Total exposure, or area under the concentration-time curve ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$)
- Peak exposure (Cmax)
- Time to peak exposure (Tmax)
- Lag-time (t_{lag}) for modified-release products, if present
- Terminal elimination half-life
- Other relevant PK parameters

Individual subject measurements, as well as summary statistics (e.g., group averages, standard deviations, coefficients of variation) should be reported. An equivalence approach is recommended analyzing data using an average criterion. Log transformation of exposure measurements (AUC and Cmax) prior to analysis is recommended. The 90% CI for the ratio of population geometric means between test and

reference products should be provided for $AUC_{0\text{-inf}}$, $AUC_{0\text{-t}}$, and Cmax. For aNDA-fed BE studies, the RLD administered under fed condition serves as the reference treatment.

For an aNDA, BE of a test product to the RLD product under fed conditions is concluded when the 90% CI for the ratio of population geometric means between the test and RLD product, based on log-transformed data, is contained in the BE limits of 80% to 125% for AUC and Cmax. Although no criterion applies to Tmax, the Tmax values for the test and reference products are expected to be comparable based on clinical relevance. The conclusion of BE under fed conditions indicates that with regard to food, the language in the package insert of the test product can be the same as the reference product.

Parent Drug vs. Metabolites

The moieties to be measured in biological fluids collected in BA and BE studies are either the active drug ingredient or its active moiety in the administered dosage form (parent drug) and, when appropriate, its active metabolites [21 CFR 320.24(b)(1)(i)]. This guidance recommends the following approaches for BA and BE studies.

For BA studies (see section II.B), determination of moieties to be measured in biological fluids should take into account concentration and activity. *Concentration* refers to the relative quantity of the parent drug or one or more metabolites in a given volume of an accessible biological fluid, such as blood or plasma. *Activity* refers to the relative contribution of the parent drug and its metabolite in the biological fluids to the clinical safety and efficacy of the drug. For BA studies, the parent drug and its major active metabolite should be measured, if analytically feasible.

For BE studies, measurement of only the parent drug released from the dosage form, rather than the metabolite, is generally recommended. The rationale for this recommendation is that the concentration-time profile of the parent drug is more sensitive to changes in formulation performance than a metabolite, which is more reflective of metabolite formation, distribution, and elimination. The following are exceptions to this general approach.

- Measurement of a metabolite may be preferred when parent drug levels are too low to allow reliable analytical measurement in blood, plasma, or serum for an adequate length of time. The metabolite data obtained from these studies should be subject to a CI approach for BE demonstration. If there is clinical concern related to efficacy or safety for the parent drug, sponsors and applicants should contact the appropriate review division to determine whether the parent drug should be measured and analyzed statistically.
- Metabolite may be formed as a result of gut wall or other presystemic metabolism. If the metabolite contributes meaningfully to safety and efficacy, the metabolite and the parent drug should be measured. When the relative activity of the metabolite is low and does not contribute meaningfully to safety and efficacy, it does not need to be measured. The parent drug measured in these BE studies should be analyzed using a CI approach. The metabolite data can be used to provide supportive evidence of comparable therapeutic outcome.

Enantiomers vs. Racemates

For BA studies, the measurement of individual enantiomers may be important. For BE studies, this guidance recommends measurement of the racemate using an achiral assay. Measurement of individual enantiomers in BE studies is recommended only when all the following conditions are met.

- Enantiomers exhibit different pharmacodynamic characteristics.
- Enantiomers exhibit different PK characteristics.
- Primary efficacy and safety activity reside with the minor enantiomer.
- Nonlinear absorption is present (as expressed by a change in the enantiomer concentration ratio with a change in the input rate of the drug) for at least one of the enantiomers.

In such cases, BE criteria should be applied to the enantiomers separately.

Drug Products with Complex Mixtures as the Active Ingredients

Certain drug products may contain complex drug substances (i.e., active moieties or active ingredients that are mixtures of multiple synthetic and natural source components). Some or all the components of these complex drug substances cannot be characterized with regard to chemical structure or biological activity. Quantification of all active or potentially active components in pharmacokinetic studies to document BA and BE is neither necessary nor desirable. Rather, BA and BE studies should be based on a small number of markers of rate and extent of absorption. Although necessarily a case-by-case determination, criteria for marker selection include the amount of the moiety in the dosage form, plasma or blood levels of the moiety, and biological activity of the moiety relative to other moieties in the complex mixture. Where pharmacokinetic approaches are not feasible to assess the rate and extent of absorption of a drug substance from a drug product, in vitro approaches may be preferred. Pharmacodynamic or clinical approaches may be called for if no quantifiable moieties are available for in vivo pharmacokinetic or in vitro studies.

Long Half-Life Drugs

In a BA or PK study involving an oral product with a long half-life drug, adequate characterization of the half-life calls for blood sampling over a long period of time. For a BE determination of an oral product with a long half-life drug, a nonreplicate, single-dose crossover study can be conducted, provided an adequate washout period is used. If the crossover study is problematic, a BE study with a parallel design can be used. For either a crossover or parallel study, sample collection time should be adequate to ensure completion of GI transit (approximately 2–3 days) of the drug product and absorption of the drug substance. The Cmax, and a suitably truncated AUC, can be used to characterize peak and total drug exposure respectively. For drugs that demonstrate low intrasubject variability in distribution and clearance, an AUC truncated at 72 hours ($AUC_{0\text{–}72\,h}$) can be used in place of $AUC_{0\text{-t}}$ or $AUC_{0\text{-}\infty}$. For drugs demonstrating high intrasubject variability in distribution and clearance, AUC truncation warrants caution. In such cases, sponsors and applicants should consult the appropriate review staff.

First-Point Cmax

The first point of a concentration-time curve in a BE study based on blood and plasma measurements is sometimes the highest point, which raises a question about the measurement of true Cmax because of insufficient early sampling times. A carefully conducted pilot study may avoid this problem. Making collections at an early time point, between 5

and 15 minutes after dosing, followed by making additional sample collections (e.g., two to five) in the first hour after dosing may be sufficient for assessing early peak concentrations. If this sampling approach is followed, data sets should be considered adequate, even when the highest observed concentration occurs at the first time point.

Orally Administered Drugs Intended for Local Action

Documentation of product quality BA for NDAs, where the drug substance produces its effects by local action in the GI tract, can be achieved using clinical efficacy and safety studies or suitably designed and validated in vitro studies. Similarly, documentation of BE for aNDAs and for NDAs, as well as for aNDAs in the presence of certain postapproval changes, can be achieved by using BE studies with clinical efficacy and safety end points or suitably designed and validated in vitro studies, if the latter studies are reflective of important clinical effects or are more sensitive to changes in product performance compared with a clinical study. To ensure comparable safety, additional studies with and without food may help in understanding the degree of systemic exposure that occurs following administration of a drug product intended for local action in the GI tract.

Sprinkles

In aNDAs, BE of the test to the RLD is demonstrated in a single-dose crossover study. Both treatments should be sprinkled on one of the soft foods mentioned in the labeling, usually applesauce. The BE data should be analyzed using average BE and the 90% CI criteria should be used to declare BE. If there are questions about other foods, the design, or the analysis of such BE studies, the sponsors and/or applicants should contact the Office of Generic Drugs.

Special Vehicles

In aNDAs, BE of the test to the RLD is demonstrated in a single-dose crossover study. Both treatments should be mixed with one of the beverages mentioned in the labeling. Sponsors should provide evidence that BE differences would not be expected from the use of other listed vehicles. The BE data should be analyzed using average BE, and the 90% CI criteria should be used to declare BE.

Locally Acting GI Drugs

For drugs whose site of action is the GI tract, determination of BE is more complicated because local drug concentrations cannot be measured directly requiring evaluation of PKs, its relationship in vitro tests including dissolution and binding assays and correlation with clinical studies.

The PK studies for locally acting drugs provide safety data and whereas PK studies may not correlate with therapeutic effectiveness, the relationship with BE is not so straightforward. If a drug is acting locally and also absorbed in the systemic circulation, the PK studies would still reflect the dosage form factors even though the site of action is also local. The premise here remains same; any differences noted in the Cmax of AUC is due to differences in absorption rates and extent attributable to dosage form differences such as release of drug. However, when plasma levels can be connected to product effectiveness then we can determine the significance of differences in product performance. When the connection to efficacy is broken, we do not have a simple way to say what difference in PK is significant. In this sense, downstream PK is similar to a PD end point for which a dose-response curve needs to be established. Another concern about PK studies on locally acting drugs is that the drug may be able to reach the plasma without passing the site of action. An example is an inhalation product for which some of the dose is swallowed and potentially absorbed orally. An important distinction is between parallel and sequential absorption paths. In the inhalation example, the drug either goes to the lung or to the stomach or could appear in plasma at the same time by either path. In a locally acting GI drug the absorption process is sequential, so the drug absorbed from the intestine appears before the drug absorbed in the colon and thus can be distinguished.

The PK studies often fail for locally acting drugs because of the very low concentration observed in plasma and even at the site of local action. For example, mesalamine must reach the mucosal surface lining the GI tract to exert its pharmacological effect, which is dependent on the dissolution rate; for other dosage forms, which dissolve instantly, the rate-limiting factor would be the transit rate in the GI tract. The use of dissolution thus becomes an important tool to demonstrate BE. Some GI acting drugs are formulated to target different regions of the GI tract, often via coatings that lead to pH-dependent dissolution. Comparative dissolution testing at different pH could demonstrate that test and reference products are targeting the same region of the GI tract. Biowaivers for BCS Class I drugs formulated in rapidly dissolving immediate-release solid oral dosage forms are well established. Since a GI acting drug does not need to be absorbed, application of the scientific basis of the BCS would suggest that a high solubility drug in a rapidly dissolving formulation with no excipients that affect product performance may be eligible for a biowaiver.

Generally, studies that measure the concentration of drug in the small intestinal mucosa could provide more direct evidence of equivalent tissue concentration at the site of action. But those studies are difficult to conduct and interspecies correlations often add a lot of variability; as a result, there is a consensus developing that comparative clinical trails be conducted to demonstrate BE but only in those situations where other methods fail since not only are these expensive to conduct, these can often be insensitive to formulation differences—the purpose of the study.

Animal Drug BE Testing

A BE study may also be part of a NADA or supplemental NADA for approval of an alternative dosage form, new route of administration, or a significant manufacturing change, which may affect drug BA. Many requirements described earlier for human studies also apply to animal studies; various descriptions of experimental design and data handling are common to both. FDA has concluded that the tissue residue depletion of the generic product is not adequately addressed through BE studies. Therefore, sponsors of aNADA for drug products for food-producing animals will generally be asked to include BE and tissue residue studies [21 USC 360b(n)(1)(E)]. A tissue residue study should generally accompany clinical end-point and pharmacological end-point BE studies, and blood level BE studies that cannot quantify the concentration of the drug in blood throughout the established withdrawal period [21 USC 360b(n)(1)(A)(ii)]. BE studies (i.e., blood level, pharmacological end-point and clinical end-point studies) and tissue residue depletion studies should be conducted in accordance with GLP regulations (21 CFR Part 58). Whereas the focus of the guidance is BE

testing for aNADA approval, the general principles also apply to relative BA studies conducted for NADAs.

Reference Product

As a general rule, the proposed generic product should be tested against the original pioneer product. If the original pioneer product is no longer marketed, but remains eligible to be copied, then the first approved and available generic copy of the pioneer should be used as the reference product for BE testing against the proposed new generic product.

If several approved NADAs exist for the same drug product, and each approved product is labeled differently (i.e., different species and/or claims), then the generic sponsor must clearly identify which product label is the intended pioneer. BE testing should be conducted against the single approved product which bears the labeling that the generic sponsor intends to copy. The generic sponsor should consult with CVM regarding selection of the appropriate reference product before conducting the BE study.

REFERENCE

1. Hauschke D, Steinjans VW, Diletti M, Burke M (1992). Sample size determination for bioequivalence assessment using a multiplicative model. J Parm Biopharm 20:557–561.

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Bioequivalence Regulatory Review Process and Audit

BACKGROUND

The Food and Drug Administration (FDA) requires an applicant to provide detailed information to establish bioequivalency. Applicants may request a waiver from performing in vivo (testing done in humans) bioequivalence studies for certain drug products where bioavailability (the rate and extent to which the active ingredient or active moiety is absorbed from the drug product and becomes available at the site of action) may be demonstrated by submitting data such as (1) a formulation comparison for products whose bioavailability is self-evident, for example, oral solutions, injectables, or ophthalmic solutions where the formulations are identical or (2) comparative dissolution.

Alternatively, in vivo bioequivalence testing comparing the rate and extent of absorption of the generic versus the reference product is required for most tablet and capsule dosage forms. For certain products, a head-to-head evaluation of comparative efficacy based upon clinical endpoints may be required.

The Manual of Policies and Procedures of the CDER (Generic Drugs) (MAPP 5210.6) describes the following procedures for review of bioequivalence study protocols.

PROTOCOLS

When a protocol is received in the DBE, the PM assigns it randomly to the next available reviewer. All protocols received are entered in the protocol tracking system and assigned a control number. The protocol receipt date, firm name, drug name, reviewer assigned, and date of assignment are recorded. The reviewer searches the literature and the Agency's databases [e.g., Excalibur, WinBio, drug files (hard copy and electronic)]. If a protocol has been previously submitted and found acceptable by the Division, this should be used as a model in the preparation of responses to subsequent protocols for the same drug. The reviewer should state in the review whether other protocols for the same drug have been previously reviewed. If no other protocols have been reviewed for the product, a statement to that effect should be included in the review. The reviewer prepares a review with recommendations to the requestor. The review must have the concurrence of the team leader and Division Director. If the reviewer discovers discrepancies in bioequivalence criteria or appropriate study design in recommendations provided to industry in previous protocols or correspondence for the same drug product, the reviewer prepares a memorandum to the team leaders and Division Director. The memo should specify the name of the sponsor or CRO that received conflicting information/guidance in protocol responses. Abbreviated new drug applications (ANDAs) affected by this information should also be noted. Once the review is finalized and has the concurrence of the Division Director, it is forwarded to the PM. The PM or TIA drafts a letter based on the reviewer's recommendation. The PM ensures that all recommendations are provided to the firm. The letter will be routed through the team leader for corrections and endorsement, and to the Division Director for signature. Once the letter is signed by the Division Director, the PM or TIA enters into the protocol tracking system the date the review was finalized and the date the letter was issued. The protocol is then forwarded to the Document Room. Document Room personnel mail the letter and store the protocol in the designated area. The PM drafts letters to sponsors or CROs that have received outdated information to ensure that consistent information is provided to industry.

PRODUCTIVITY DOCUMENTATION

When the Document Room assigns an ANDA to the DBE, a description of the bioequivalence section is entered into the bioequivalence data entry screen in COMIS, using the study types below.

A. **Bioequivalence Studies**
   1. **Fasting Study** (STF). This includes replicate study designs and combined studies (e.g., combined fasting and multiple-dose studies where the same subjects are used).
   2. **Food Study** (STP).
   3. **Multiple-Dose Study** (STM).
   4. **Study** (STU). This category is generally used for a bioequivalence study with clinical endpoints, in vitro studies for metered-dose inhalers and nasal sprays, pilot and pivotal studies for vasoconstrictors, or any pharmacokinetic/pharmacodynamic study other than a standard bioequivalence study (such as 1–3 above).

B. **Dissolution Data** (DIS). This code is usually used when dissolution data are the only basis for approval. Examples are AA drugs and supplements for which changes in formulation or manufacturing require dissolution data only. In vitro release data for topical products may also be coded under DIS. *Note***:** Dissolution data submitted for the same strength drug that was the subject of a bioequivalence study are not separately coded. The dissolution information is considered part of the study.

C. **Other** (OTH):

   Study Amendment (STA). This category is for responses to deficiency comments. Whether the amendment contains dissolution data or addresses a deficiency such as incomplete information on analytical methods or a study, the submission should be coded as STA unless a new study is submitted for review. In that case, the appropriate code under BE studies should be selected. If an amendment to a previously submitted BE study is included with a new, not previously submitted BE study required to establish BE, then STA should be coded for

the amendment, and the new study should be coded separately. Retesting of subjects classified as outliers in the original submission should not be classified as a separate study, but as part of the original study. Frequently, the Division telephones sponsors to request information needed to finalize the review. These requests should be made for information the sponsor can respond to within 10 working days, and should be coded as STA. If the sponsor submits incorrect information or partial data, the submission should be coded as new correspondence (NC). Once the correct information is received, the submission should be coded as STA.

Waiver (WAI). This category is used for injectable, ophthalmic, otic, oral, and topical solutions.A formulation in the same concentration packaged in different sizes is not coded separately, but different concentrations of the same product are coded separately.

Dissolution Waiver (DIW). This code is used for lower strengths that can be approved based on proportionality of the formulation and an acceptable study on the highest strength or the strength of the reference listed drug.A dissolution waiver should be coded for each strength for which dissolution data are submitted, except the strength for which bioequivalence studies have been conducted.

Other (OTH). This category is used for correspondence or addenda revising the original review. The Division of Scientific Investigations (DSI) inspection reports may generate an addendum to the review. If a significant statistical analysis is needed based on the recommendation of the DSI, or if the issuance of a Form 483 (Inspectional Observations) indicates serious violations by the laboratory, then the review of the DSI report may be coded as OTH. If the DSI report is acceptable, the DSI report should be filed in the ANDA, and no addendum to the review is necessary. Addenda to the reviews are entered as US documents (FDA generated), because these reviews are not prompted by industry submissions, but are due to internal policy changes or inspection reports. Diskettes containing the data already coded in a previous submission will not be coded separately.

Methods Validation for Abbreviated New Drug Applications

A request for validation of the applicant's proposed regulatory analytical methods is sent by the review chemist to the Office of Regulatory Affairs (ORA) coordinator in the Division of Field Science (DFS) using form FDA 2871a. This action should be taken as soon as the need is identified and the test methods are determined to be adequate by the review chemist.

A copy of the methods, testing specifications, and composition statement is to be included with the request. The package is sent to DFS by current procedures.

Requests are processed and carried out as detailed in the Supplement to the Compliance Program on Preapproval Inspections CP7346.832.

The chemistry/microbiology review is included in the approval package, along with the bioequivalence and labeling reviews. Upon concurrence by the chemistry team leader, the package proceeds through the final administrative review channels. If, after administrative review, the application remains approvable (including an acceptable EER and office-level bioequivalence endorsement), the project manager determines the status of the methods validation process. The application can be approved with or without results of the methods validation, except under the circumstances noted below.

There was an undue delay in sample submission by the applicant.

There are problems identified in the course of methods validation by the servicing laboratory.

There is no commitment from the applicant to resolve any problems subsequently found by the FDA laboratory.

Any problem identified with the method or the product is evaluated by the review chemist for its significance. Any problem that potentially affects the quality of the drug product must be resolved before application approval. When approval is granted in the absence of a completed methods validation, the approval letter is revised to include the following statement as the last paragraph. *Validation of the regulatory methods has not been completed. It is the general policy of the OGD not to withhold approval until the validation is complete.*

The approval letter is endorsed by the chemistry reviewer and team leader as well as the division director. If the laboratory results are received during the administrative review process for approval and they reveal problems with the methods or the product, the approval of the application is delayed and the results transmitted to the applicant. The applicant is asked to address these issues as soon as possible in an amendment to the application. This amendment is given priority review in consultation, if necessary, with the servicing laboratory. If the amended methods are satisfactory to OGD and they address the concerns of the laboratory, the application can then be approved, provided all other aspects of the application are acceptable. Out-of-specification results on products already expired at the time of testing are evaluated for their significance and relevance. Any product failures must be satisfactorily resolved before application approval. Routine revalidation can be done after approval of the application. The review chemist can request testing at a second FDA laboratory to resolve conflicting results obtained by an applicant and by the FDA servicing laboratory. The team leader and the division director must concur with the request. For methods validation completed after an application is approved, any deficiencies identified are communicated promptly to the applicant. Generally, the response addressing the deficiencies can be submitted as a changes-being-effected supplement. If the methods validation is waived, this fact must be documented and filed in the ANDA.

Good Laboratory Practices

In the 1970s, FDA inspections of nonclinical laboratories revealed that some studies submitted in support of the safety of regulated products had not been conducted in accord with acceptable practice, and that accordingly data from such studies was not always of the quality and integrity to assure product safety. As a result of these findings, FDA promulgated the Good Laboratory Practice (GLP) Regulations, 21 CFR part 58, on December 22, 1978 (43 FR 59986). The regulations became effective June 1979. The regulations establish standards for the conduct and reporting of nonclinical laboratory studies and are intended to assure the quality and integrity of safety data submitted to FDA.

FDA relies on documented adherence to GLP requirements by nonclinical laboratories in judging the acceptability of safety data submitted in support of research and/or marketing permits. FDA has implemented this program of regular inspections and data audits to monitor laboratory compliance with the GLP requirements.

The objective of this program is

to verify the quality and integrity of data submitted in a research or marketing application,
to inspect (approximately every 2 years) nonclinical laboratories conducting safety studies that are intended to support applications for research or marketing of regulated products, and
to audit safety studies and determine the degree of compliance with GLP regulations.

Types of Inspections

1. Surveillance Inspections. Surveillance inspections are periodic, routine determinations of a laboratory's compliance with GLP regulations. These inspections include a facility inspection and audits of on-going and/or recently completed studies.
2. Directed Inspections. Directed inspections are assigned to achieve a specific purpose, such as:
   Verifying the reliability, integrity, and compliance of critical safety studies being reviewed in support of pending applications.
   Investigating issues involving potentially unreliable safety data and/or violative conditions brought to FDA's attention.
   Reinspecting laboratories previously classified OAI (usually within 6 months after the firm responds to a Warning Letter).
   Verifying the results from third party audits or sponsor audits submitted to FDA for consideration in determining whether to accept or reject questionable or suspect studies.

Inspections

1. The investigator will determine the current state of GLP compliance by evaluating the laboratory facilities, operations, and study performance.
2. Organization Chart—If the facility maintains an organization chart, obtain a current version of the chart for use during the inspection and submit it in the EIR.
3. Facility Floor-plan Diagram—Obtain a diagram of the facility. The diagram may identify areas that are not used for GLP activities. If it does not, request that appropriate facility personnel identify any areas that are not used for GLP activities. Use during the inspection and submit it in the EIR.
4. Master Schedule Sheet—Obtain a copy of the firm's master schedule sheet for all studies listed since the last GLP inspection or last 2 years and select studies as defined in 21 CFR 58.3(d). If the inspection is the first inspection of the facility, review the entire master schedule. If studies are identified as non-GLP, determine the nature of several studies to verify the accuracy of this designation. See 21 CFR 58.1 and 58.3(d). In contract laboratories determine who decides if a study is a GLP study.
   Identification of Studies
   a. Directed Inspections—Inspection assignments will identify studies to be audited.
   b. Surveillance inspections—Inspection assignments may identify one or more studies to be audited. If the assignment does not identify a study for coverage, or if the referenced study is not suitable to assess all portions of current GLP compliance, the investigator will select studies as necessary to evaluate all areas of laboratory operations. When additional studies are selected, first priority should be given to FDA studies for submission to the assigning Center.
5. Ongoing Studies—Obtain a copy of the study protocol and determine the schedule of activities that will be underway during the inspection. This information should be used to schedule inspections of on-going laboratory operations, as well as equipment and facilities associated with the study. If there are no activities underway in a given area for the study selected, evaluate the area based on on-going activities.
6. Completed Studies—The data audit should be carried out as outlined in part III, D. If possible, accompany laboratory personnel when they retrieve the study data to assess the adequacy of data retention, storage, and retrieval as described in part III, C 10.

The facility inspection should be guided by the GLP regulations. The following areas should be evaluated and described as appropriate.

1. Organization and Personnel (21 CFR 58.29, 58.31, 58.33)
   a. Purpose: To determine whether the organizational structure is appropriate to ensure that studies are conducted in compliance with GLP regulations, and to determine whether management, study directors, and laboratory personnel are fulfilling their responsibilities under the GLPs.
   b. Management Responsibilities (21 CFR 58.31)—Identify the various organizational units, their role in carrying out GLP study activities, and the management responsible for these organizational units. This includes identifying personnel who are performing duties at locations other than the test facility and identifying their line of authority. If the facility has an organization chart, much of this information can be determined from the chart.
2. Determine if management has procedures for assuring that the responsibilities in 58.31 can be carried out. Look for evidence of management involvement, or lack thereof, in the following areas:
   a) Assigning and replacing study directors.
   b) Control of study director workload (use the Master Schedule to assess workload).
   c) Establishment and support of the Quality Assurance Unit (QAU), including assuring that deficiencies reported by the QAU are communicated to the study directors and acted upon.
   d) Assuring that test and control articles or mixtures are appropriately tested for identity, strength, purity, stability, and uniformity.
   e) Assuring that all study personnel are informed of and follow any special test and control article handling and storage procedures.
   f) Providing required study personnel, resources, facilities, equipment, and materials.
   g) Reviewing and approving protocols and standard operating procedures (SOPs).
   h) Providing GLP or appropriate technical training.
3. Personnel (21 CFR 58.29)—Identify key laboratory and management personnel, including any consultants or

contractors used, and review personnel records, policies, and operations to determine if
   a. Summaries of training and position descriptions are maintained and are current for selected employees.
   b. Personnel have been adequately trained to carry out the study functions that they perform.
   c. Personnel have been trained in GLPs.
   d. Practices are in place to ensure that employees take necessary health precautions, wear appropriate clothing, and report illnesses to avoid contamination of the test and control articles and test systems.
4. If the firm has computerized operations, determine the following:
   a. Who was involved in the design, development, and validation of the computer system?
   b. Who is responsible for the operation of the computer system, including inputs, processing, and output of data?
   c. Whether computer system personnel have training commensurate with their responsibilities, including professional training and training in GLPs?
   d. Whether some computer system personnel are contractors who are present on-site full-time, or nearly full-time. The investigation should include these contractors as though they were employees of the firm. Specific inquiry may be needed to identify these contractors, as they may not appear on organization charts.
   e. Interview and observe personnel using the computerized systems to assess their training and performance of assigned duties.
5. Study director (21 CFR 58.33)
   a. Assess the extent of the study director's actual involvement and participation in the study. In those instances when the study director is located off-site, review any correspondence/records between the testing facility management and quality assurance unit and the off-site study director. Determine that the study director is being kept immediately apprised of any problems that may affect the quality and integrity of the study.
   b. Assess the procedures by which the study director
      i. assures the protocol and any amendments have been properly approved and are followed,
      ii. assures that all data are accurately recorded and verified,
      iii. assures that data are collected according to the protocol and SOPs,
      iv. documents unforeseen circumstances that may affect the quality and integrity of the study and implements corrective action,
      v. assures that study personnel are familiar with and adhere to the study protocol and SOPs, and
      vi. assures that study data are transferred to the archives at the close of the study.
6. EIR Documentation and Reporting—Collect exhibits to document deficiencies. This may include SOPs, organizational charts, position descriptions, and curriculum vitae (CVs), as well as study-related memos, records, and reports for the studies selected for review. **The use of outside or contract facilities must be noted in the EIR. The assigning Center should be contacted for guidance on inspection of these facilities.**
7. Quality Assurance Unit (QAU; 21 CFR 58.35)
   Purpose: To determine if the test facility has an effective, independent QAU that monitors significant study events and facility operations, reviews records and reports, and assures management of GLP compliance.
   QAU Operations—(21 CFR 58.35(b-d))—Review QAU SOPs to assure that they cover all methods and procedures for carrying out the required QAU functions, and confirm that they are being followed. Verify that SOPs exist and are being followed for QAU activities including, but not limited to, the following:
      a) Maintenance of a master schedule sheet.
      a) Maintenance of copies of all protocols and amendments.
      a) Scheduling of its in-process inspections and audits.
      a) Inspection of each nonclinical laboratory study at intervals adequate to assure the integrity of the study, and maintenance of records of each inspection.
      a) Immediately notify the study director and management of any problems that are likely to affect the integrity of the study.
      a) Submission of periodic status reports on each study to the study director and management.
      a) Review of the final study report.
      a) Preparation of a statement to be included in the final report that specifies the dates inspections were made and findings reported to management and to the study director.
8. Inspection of computer operations.
   a) Verify that, for any given study, the QAU is entirely separate from and independent of the personnel engaged in the conduct and direction of that study. Evaluate the time QAU personnel spend in performing in-process inspection and final report audits. Determine if the time spent is sufficient to detect problems in critical study phases and if there are adequate personnel to perform the required functions.
   b) *Note*: The investigator may request the firm's management to certify in writing that inspections are being implemented, performed, documented, and followed-up in accordance with this section [see 58.35(d)].
9. EIR Documentation and Reporting—Obtain a copy of the master schedule sheet dating from the last routine GLP inspection or covering the past 2 years. If the master schedule is too voluminous, obtain representative pages to permit headquarters review. When master schedule entries are coded, obtain the code key. Deficiencies should be fully reported and documented in the EIR. Documentation to support deviations may include copies of QAU SOPs, list of QAU personnel, their CVs or position descriptions, study-related records, protocols, and final reports.
10. Facilities (21 CFR 58.41 – 51)
    Purpose: Assess whether the facilities are of adequate size and design.
    Facility Inspection
      a) Review environmental controls and monitoring procedures for critical areas (i.e., animal rooms, test article storage areas, laboratory areas, handling of bio-hazardous material, etc.) and determine if they appear adequate and are being followed.
      b) Review the SOPs that identify materials used for cleaning critical areas and equipment, and assess the facility's current cleanliness.
      c) Determine whether there are appropriate areas for the receipt, storage, mixing, and handling of the test and control articles.

d) Determine whether separation is maintained in rooms where two or more functions requiring separation are performed.
e) Determine that computerized operations and archived computer data are housed under appropriate environmental conditions (e.g., protected from heat, water, and electromagnetic forces).

11. EIR Documentation and Reporting—Identify which facilities, operations, SOPs, etc., were inspected. Only significant changes in the facility from previous inspections need be described. Facility floor plans may be collected to illustrate problems or changes. Document any conditions that would lead to contamination of test articles or to unusual stress of test systems.
12. Equipment (21 CFR 58.61 – 63)
    Purpose: To assess whether equipment is appropriately designed and of adequate capacity and is maintained and operated in a manner that ensures valid results.
    Equipment Inspection—Assess the following:
    a) The general condition, cleanliness, and ease of maintenance of equipment in various parts of the facility.
    b) The heating, ventilation, and air conditioning system design and maintenance, including documentation of filter changes and temperature/humidity monitoring in critical areas.
    c) Whether equipment is located where it is used and that it is located in a controlled environment, when required.
    d) Nondedicated equipment for preparation of test and control article carrier mixtures is cleaned and decontaminated to prevent cross-contamination.
    e) For representative pieces of equipment check the availability of the following:
        i) SOPs and/or operating manuals.
        ii) Maintenance schedule and log.
        iii) Standardization/calibration procedure, schedule, and log.
        iv) Standards used for calibration and standardization.
    f) For computer systems, assess that the following procedures exist and are documented:
        i. Validation study, including validation plan and documentation of the plan's completion.
        ii. Maintenance of equipment, including storage capacity and backup procedures.
        iii. Control measures over changes made to the computer system, which include the evaluation of the change, necessary test design, test data, and final acceptance of the change.
        iv. Evaluation of test data to assure that data are accurately transmitted and handled properly when analytical equipment is directly interfaced to the computer.
        v. Procedures for emergency backup of the computer system (e.g., backup battery system and data forms for recording data in the event of a computer failure or power outage).
13. EIR Documentation and Reporting—The EIR should list which equipment, records, and procedures were inspected and the studies to which they are related. Detail any deficiencies that might result in contamination of test articles, uncontrolled stress to test systems, and/or erroneous test results.
14. Testing Facility Operations (21 CFR 58.81)
    Purpose: To determine if the facility has established and follows written SOPs necessary to carry out study operations in a manner designed to ensure the quality and integrity of the data.
    SOP Evaluation
    a. Review the SOP index and representative samples of SOPs to ensure that written procedures exist to cover at least all of the areas identified in 58.81(b).
    b. Verify that only current SOPs are available at the personnel workstations.
    c. Review key SOPs in detail and check for proper authorization signatures and dates, and general adequacy with respect to the content (i.e., SOPs are clear, complete, and can be followed by a trained individual).
    d. Verify that changes to SOPs are properly authorized and dated and that a historical file of SOPs is maintained.
    e. Ensure that there are procedures for familiarizing employees with SOPs.
    f. Determine that there are SOPs to ensure the quality and integrity of data, including input (data checking and verification), output (data control), and an audit trail covering all data changes.
    g. Verify that a historical file of outdated or modified computer programs is maintained. If the firm does not maintain old programs in digital form, ensure that a hard copy of all programs has been made and stored.
    h. Verify that SOPs are periodically reviewed for current applicability and that they are representative of the actual procedures in use.
    i. Review selected SOPs and observe employees performing the operation to evaluate SOP adherence and familiarity. EIR Documentation and Reporting - Submit SOPs, data collection forms, and raw data records as exhibits that are necessary to support and illustrate deficiencies.
15. Reagents and Solutions (21 CFR 58.83)
    Purpose: To determine that the facility ensures the quality of reagents at the time of receipt and subsequent use.
    Review the procedures used to purchase, receive, label, and determine the acceptability of reagents and solutions for use in the studies.
    Verify that reagents and solutions are labeled to indicate identity, titer or concentration, storage requirements, and expiration date.
    Verify that for automated analytical equipment, the profile data accompanying each batch of control reagents are used.
    Check that storage requirements are being followed.
16. Test and Control Articles (21 CFR 58.105 – 113)
    Purpose: To determine that procedures exist to assure that test and control articles and mixtures of articles with carriers meet protocol specifications throughout the course of the study, and that accountability is maintained.
    Characterization and Stability of Test Articles (21 CFR 58.105)—The responsibility for carrying out appropriate characterization and stability testing may be assumed by the facility performing the study or by the study sponsor. When test article characterization and stability testing is performed by the sponsor, verify that the test facility has received documentation that this testing has been conducted.

Verify that procedures are in place to ensure that
a) the acquisition, receipt and storage of test articles, and means used to prevent deterioration and contamination are as specified;
b) the identity, strength, purity, and composition, (i.e., characterization) to define the test and control articles are determined for each batch and are documented;
c) the stability of test and control articles is documented;
d) the transfer of samples from the point of collection to the analytical laboratory is documented;
d) storage containers are appropriately labeled and assigned for the duration of the study; and
f) reserve samples of test and control articles for each batch are retained for studies lasting more than 4 weeks.

Test and Control Article Handling (21 CFR 58.107)
a) Determine that there are adequate procedures for:
i. documentation for receipt and distribution;
ii. proper identification and storage; and
iii. precluding contamination, deterioration, or damage during distribution.
a. Inspect test and control article storage areas to verify that environmental controls, container labeling, and storage are adequate.
b. Observe test and control article handling and identification during the distribution and administration to the test system.
c. Review a representative sample of accountability records and, if possible, verify their accuracy by comparing actual amounts in the inventory. For completed studies verify documentation of final test and control article reconciliation.

17. Protocol and Conduct of Nonclinical Laboratory Study (21 CFR 58.120 – 130)
Purpose: To determine if study protocols are properly written and authorized, and that studies are conducted in accordance with the protocol and SOPs.
Study Protocol (21 CFR 58.120)
a) Review SOPs for protocol preparation and approval and verify they are followed.
b) Review the protocol to determine if it contains required elements.
c) Review all changes, revisions, or amendments to the protocol to ensure that they are authorized, signed, and dated by the study director.
d) Verify that all copies of the approved protocol contain all changes, revisions, or amendments.

18. Conduct of the Nonclinical Laboratory Study (21 CFR 58.130)—Evaluate the following laboratory operations, facilities, and equipment to verify conformity with protocol and SOP requirements for
Test system monitoring.
Recording of raw data (manual and automated).
Corrections to raw data (corrections must not obscure the original entry and must be dated, initialed, and explained).
Randomization of test systems.
Collection and identification of specimens.
Authorized access to data and computerized systems.

19. Records and Reports (21 CFR 58.185 – 195)
Purpose: To assess how the test facility stores and retrieves raw data, documentation, protocols, final reports, and specimens.
Reporting of Study Results (21 CFR 58.185)—Determine if the facility prepares a final report for each study conducted. For selected studies, obtain the final report, and verify that it contains the following:
a) Name and address of the facility performing the study and the dates on which the study was initiated and completed.
b) Objectives and procedures stated in the approved protocol, including any changes in the original protocol.
c) Statistical methods used for analyzing the data.
d) The test and control articles identified by name, chemical abstracts number or code number, strength, purity, and composition or other appropriate characteristics.
e) Stability of the test and control articles under the conditions of administration.
f) A description of the methods used.
g) A description of the test system used. Where applicable, the final report shall include the number of animals used, sex, body weight range, source of supply, species, strain and substrain, age, and procedure used for identification.
h) A description of the dosage, dosage regimen, route of administration, and duration.
i) A description of all circumstances that may have affected the quality or integrity of the data.
j) The name of the study director, the names of other scientists or professionals, and the names of all supervisory personnel, involved in the study.
k) A description of the transformations, calculations, or operations performed on the data, a summary and analysis of the data, and a statement of the conclusions drawn from the analysis.
l) The signed and dated reports of each of the individual scientists or other professionals involved in the study.
m) The locations where all specimens, raw data, and the final report are to be stored.
n) The statement prepared and signed by the quality assurance unit as described in section 58.35(b)(7).
i. The final report shall be signed and dated by the study director.
ii. Corrections or additions to a final report shall be in the form of an amendment by the study director. The amendment shall clearly identify that part of the final report that is being added to or corrected and the reasons for the correction or addition, and shall be signed and dated by the person responsible.

20. Storage and Retrieval of Records and Data (21 CFR 58.190)
Verify that raw data, documentation, protocols, final reports, and specimens have been retained.
Identify the individual responsible for the archives. Determine if delegation of duties to other individuals in maintaining the archives has occurred.
Verify that archived material retained or referred to in the archives is indexed to permit expedient retrieval. It is not necessary that all data and specimens be in the same archive location. For raw data and specimens retained elsewhere, the archives index must make specific reference to those other locations.
Verify that access to the archives is controlled and determine that environmental controls minimize deterioration.

Ensure that there are controlled procedures for adding or removing material. Review archive records for the removal and return of data and specimens. Check for unexplained or prolonged removals.

Determine how and where computer data and backup copies are stored, that records are indexed in a way to allow access to data stored on electronic media, and that environmental conditions minimize deterioration.

Determine to what electronic media such as tape cassettes or ultra high capacity portable discs the test facility has the capacity of copying records in electronic form. Report names and identifying numbers of both copying equipment type and electronic medium type to enable agency personnel to bring electronic media to future inspections for collecting exhibits.

21. Data Audit. In addition to the procedures outlined above for evaluating the overall GLP compliance of a firm, the inspection should include the audit of at least one completed study. Studies for audit may be assigned by the Center or selected by the investigator as described in part III, A. The audit will include a comparison of the protocol (including amendments to the protocol), raw data, records, and specimens against the final report to substantiate that protocol requirements were met and that findings were fully and accurately reported. For each study audited, the study records should be reviewed for quality to ensure that data are:

    Attributable—the raw data can be traced, by signature or initials and date to the individual observing and recording the data. Should more than one individual observe or record the data, that fact should be reflected in the data.

    Legible—the raw data are readable and recorded in a permanent medium. If changes are made to original entries, the changes

    a) must not obscure the original entry,
    b) indicate the reason for change, and
    c) must be signed or initialed and dated by the person making the change.

    Contemporaneous—the raw data are recorded at the time of the observation.

    Original—the first recording of the data.

    Accurate—the raw data are true and complete observations. For data entry forms that require the same data to be entered repeatedly, all fields should be completed or a written explanation for any empty fields should be retained with the study records.

22. General

    Determine if there were any significant changes in the facilities, operations, and QAU functions other than those previously reported.

    Determine whether the equipment used was inspected, standardized, and calibrated prior to, during, and after use in the study. If equipment malfunctioned, review the remedial action, and ensure that the final report addresses whether the malfunction affected the study.

    Determine if approved SOPs existed during the conduct of the study.

    Compare the content of the protocol with the requirements in 21 CFR

    Review the final report for the study director's dated signature and the QAU statement as required in 21 CFR 58.35(b)(7).

23. Protocol Versus Final Report—Study methods described in the final report should be compared against the protocol and the SOPs to confirm those requirements were met. Examples include, but are not limited to, the following:
24. Final Report Versus Raw Data—The audit should include a detailed review of records, memorandum, and other raw data to confirm that the findings in the final report completely and accurately reflect the raw data. Representative samples of raw data should be audited against the final report.
25. Samples—Collection of samples should be considered when the situation under audit or surveillance suggests that the facility had, or is having, problems in the area of characterization, stability, storage, contamination, or dosage preparation.
26. Inspectional Observations—A FDA 483 listing inspectional observations will be issued under this program. Findings should not be listed on the FDA 483 if in the opinion of the field investigator:

    The findings are problems that have been observed and corrected by the firm through its internal procedures.

    The findings are minor and are one-time occurrences that have no impact on the firm's operations, study conduct, or data integrity.

    1. Findings that are not considered significant enough to be listed on the FDA 483 may be discussed with the firm's management. Such discussions must be reported in the EIR. Analyzing Laboratories

FDA Audit Plans

When bioequivalence studies are submitted as part of an ANDA, the US FDA inspections include an audit of the studies submitted under the Compliance Program 7348.001. It is important to review these directives since it allows firms to prepare studies and have them ready for presentation in a format that is readily accessible and comprehensible. This applies to both domestic and international inspections. When the clinical and analytical portions of a study have been performed at separate locations, separate reports should be prepared and submitted for each site

PART I—BACKGROUND

The Bioequivalence Regulations (21 CFR 320) of January 7, 1977 and its amendments stated the requirements for submission of in vivo bioavailability and bioequivalence data as a condition of marketing a new (i.e., new chemical compound; new formulation, new dosage form, or new route of administration of a marketed drug) or generic drug. 21 CFR 320 also provided general guidance concerning the design and conduct of bioavailability/bioequivalence studies. However, it should be noted that bioequivalence studies conducted to support ANDAs involve testing of already approved drug entities and therefore, generally do not require an investigational new drug application (IND). However, sponsors of generic drugs need to file INDs when studies involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product [21 CFR 312.2(b)(iii)].

The FDA does not require bioequivalence studies on pre-1938 drug products. It is however the responsibility of the firm to assure that the studies are submitted in accordance with the most current guidelines as amended.

Bioequivalence studies involve both a clinical component and an analytical component. The objective of a typical

bioequivalence study is to demonstrate that the test and reference products achieve a similar pharmacokinetic profile in plasma, serum, and/or urine. Bioequivalence studies usually involve administration of test and reference drug formulations to 18 to 36 normal healthy subjects, but patients with a target disease may also be used. Formulations to be tested are administered either as a single dose or as multiple doses. Sometimes formulations can be labeled with a radioactive component to facilitate subsequent analysis. In a bioequivalence study, serial samples of biological fluid (plasma, serum, or urine) are collected just before and at various times after dose administration. These samples are later analyzed for drug and/or metabolite concentrations. The study data are used in subsequent pharmacokinetic analyses to establish bioequivalence.

In some situations, the clinical and analytical facilities for a study may be part of the same organization and therefore may be covered by one District. In other situations, the two facilities may be located in different Districts. For the purpose of this program, the District where the clinical facility is located will be referred to as the Clinical Component District, and the District where the analytical facility is located will be referred to as the Analytical Component District.

PART II—IMPLEMENTATION

Objective

1. To verify the quality and integrity of scientific data from bioequivalence studies submitted to the Center for Drug Evaluation and Research (CDER);
2. To ensure that the rights and welfare of human subjects participating in drug testing are protected; and
3. To ensure compliance with the regulations (21 CFR 312, 320, 50, and 56) and promptly follow-up on significant problems, such as research misconduct or fraud.

Program Management Instructions

A. Coverage

It is important to draw distinctions between a clinical laboratory, a clinical facility, and an analytical facility.A clinical laboratory generally uses blood and/or urine to conduct medical screening or diagnostic tests such as blood counts (CBC), liver function tests (ALT, AST) or kidney function (BUN, creatinine clearance, etc.) tests. Clinical laboratories are usually certified under programs based on the Clinical Laboratories Improvement Act (42 USC 263a) and are not routinely inspected by the FDA.A clinical laboratory may be visited during a bioequivalence study audit to confirm that reported screening or diagnostic laboratory work was indeed performed. The clinical facility and the analytical facility as described above are the laboratories that will be routinely inspected under this program.

1. Clinical Facilities
   Clinical facilities conduct bioequivalence studies (including screening, dosing, monitoring of subjects' safety, etc.) in order to obtain biological specimens (e.g., plasma, serum, urine) for analysis of drug and/or drug metabolite concentrations. Facilities that conduct bioequivalence studies in human research subjects for pharmacodynamic measurements (i.e., clinical or pharmacological effects) are also included.
2. Analytical Facilities
   Analytical facilities analyze biological specimens collected in bioequivalence studies and other human clinical studies for drug and/or metabolite concentrations to measure the absorption and disposition of the drug.
3. Clinical and Analytical Investigators
   The clinical investigator in a bioequivalence study is involved in the screening and dosing of human subjects, and will ordinarily be a physician. PhD clinical pharmacologists and PharmDs are acceptable if a physician is available to cover medical emergencies. The clinical investigator may also perform pharmacodynamic measurement(s) and evaluation activities of clinical or pharmacological endpoints. The analytical investigator in a bioequivalence study is the scientist in the analytical facility responsible for assay development and validation, and analyses of biological specimens, for example, Scientific Director or Laboratory Director.

B. Process

Facilities where bioequivalence studies are conducted are to be to include a review of the clinical and analytical testing procedures plus an audit of source data from one or more specified studies.

C. Assignments under this program are of two basic categories:

1. *Directed Data Audit*—Covers studies and/or facilities in which gross problems/inadequacies are suspected (including, but not limited to research misconduct, or fraud). Such assignments require rapid evaluation and resolution.
2. *Routine Data Audit*—Covers (1) pivotal studies under current review in the Divisions of Pharmaceutical Evaluation I (HFD-860), II (HFD-870), or III (HFD-880) in the Office of Clinical Pharmacology and Biopharmaceutics (HFD-850); and (2) bioequivalence studies supporting the approval of a generic product.

Assignments will be issued by the GLP and Bioequivalence Investigations Branch (GBIB, HFD-48) to the field. For each assignment, a scientific reviewer in GBIB with expertise in chemical assays, bioavailability/bioequivalence, biopharmaceutics, pharmacokinetics, or pharmacodynamics will (1) assist the field in coordinating and as necessary conducting the inspection; (2) provide technical guidance and on-site support to the field as necessary; and (3) serve as the liaison between the field investigator(s) and the Review Divisions in CDER.

For all inspections in which a Form FDA-483 is issued, a copy of the Form FDA-483 should be forwarded by facsimile to the GBIB contact or the Branch Chief of GBIB.

PART III—INSPECTIONAL

Operations

A. **Inspectional**

A complete inspection report under this compliance program consists of inspectional findings covering:

1. *Clinical testing*, which includes the adequacy of facilities and procedures utilized by the clinical investigator along with a data audit of the specific study(ies) identified by GBIB; and
2. *Analytical testing*, which includes the adequacy of the facilities, equipment, personnel, and methods and procedures utilized at the analytical facility including an audit of the method validation and analytical data for the study(ies) identified by GBIB.

A full narrative report of any deviations from existing regulations is required. Deviation(s) must be documented sufficiently to support legal or administrative action. For

example, any records containing data that are inconsistent with data submitted to FDA should be copied and the investigator should identify the discrepancy. Generally, serious violations will require more extensive documentation a discussion between the inspector and his supervisor and the appropriate Center contact prior to embarking on this type of coverage.

B. **Investigational**
If inspections of institutional review boards and/or clinical laboratories are indicated, the inspector is required to contact his supervisor and GBIB for guidance prior to initiating the inspection.

C. **Refusals**
If access to, or copying of records is refused for any reason, the inspector promptly contacts his supervisor so that the GBIB contact can be advised of the refusal. Send follow-up information via EMS to GBIB, and ORO contacts. The same procedure is followed when it becomes evident that delays by the firm constitute a de facto refusal.

If actions by the firm take the form of a partial refusal for inspection of documents or areas to which FDA is entitled under the law, inspector calls attention to 301(e) and (f) and 505(k)(2) of the FD&C Act; if the refusal persists, he telephones his supervisor and the GBIB contact for instructions.

If the proper course of action to deal with a refusal cannot be resolved expeditiously by GBIB or ORO, GBIB will notifies the Bioresearch Program Coordinator (HFC-230).

D. **Findings**
1. If the inspector encounters serious problems with the data, methodology, quality control practices, etc., he will continue with the originally assigned inspection, but contact GBIB for advice on possibly expanding the inspection. GBIB will determine if an in-depth inspection, involving additional bioequivalence studies, should be initiated.
2. If the inspector encounters questionable or suspicious records and is unable to review or copy them immediately and have reason to preserve their integrity by officially sealing them, the inspector contacts his supervisor immediately for instructions. Procedures exist for the inspector District to clear this type of action by telephone with the ORA/Bioresearch Program Coordinator (HFC-230). See *Inspection Operations Manual*, Section 453.5.
3. Issuance of a Form FDA-483, Inspectional Observations, is appropriate when (1) practice at the clinical site deviates from the standards for conduct of a clinical study as set forth in 21 CFR 312 and 320 and 361, (2) practice at the analytical site deviates from the standards of laboratory practices as set forth in 21 CFR 320, and (3) discrepancies have occurred between source data and reported data in the case report forms. Items that need to be checked for compliance to study standards are provided in Attachment A. Examples of noncompliance to study standards at the clinical and analytical sites are listed in part V of this guidance. Observed deficient practices should be discussed with the responsible officials.

PART IV—ANALYTICAL

Routine analytical work is anticipated for this compliance program. Collected study retention samples will be sent to the Division of Drug Testing and Applied Analytical Development, St. Louis, MO for screening. The sample size should be sufficient to allow the FDA laboratory to perform all of the release tests required in the ANDA, NDA, or supplemental applications five times. If the clinical investigator is not sure of the amount that constitutes the "five times quantity," the clinical investigator should contact the study sponsor. The clinical facility must provide a written assurance (e.g., an affidavit) that the retained samples are representative of those used in the specific bioavailability/bioequivalence study, and that they were stored under conditions specified in accompanying records.

PART V—REGULATORY/ADMINISTRATIVE STRATEGY

Clinical Testing

Examples of noncompliance are as follows:

1. Subjects not receiving the test or reference drug formulation according to the study randomization codes.
2. Biological samples compromised by improper identification, handling, or storage.
3. Failure to report adverse experiences, such as vomiting, and diarrhea, which may affect absorption and elimination of drugs.
4. Inadequate drug accountability records.
5. Inadequate medical supervision and coverage.
6. Significant problems/protocol deviations/adverse events not reported to the sponsor.
7. Failure to adhere to the inclusion/exclusion criteria of the approved protocol.
8. Inadequate or missing informed consent for participating subjects.
9. Any other situation in which the health and welfare of the subjects are compromised.

Analytical Testing

Examples of noncompliance are as follows:

1. Inconsistencies between data reported to FDA and at the site.
2. Inadequate or missing validation of assay methodology with respect to specificity (related chemicals, degradation products, metabolites), linearity, sensitivity, precision, and reproducibility.
3. Failure to employ standard, scientifically sound quality control techniques, such as use of appropriate standard curves and/or analyte controls that span the range of subjects' analyte levels.
4. Failure to include all data points, not otherwise documented as rejected for a scientifically sound reason, in determination of assay method precision, sensitivity, accuracy, etc.
5. Samples are allowed to remain for prolonged periods of time without proper storage.
6. Failure to maintain source data, for example, source data written on scrap paper and/or discarded in trash after transferring to analytical documents.
7. Lack of objective standard for data acceptance of calibration standards, quality controls, etc.
8. Unskilled personnel conducting analytical procedures.
9. No documentation of analytical findings.
10. Inadequate or no written procedures for drug sample receipt and handling.
11. Inadequate or missing standard operating procedures.

Note: The above are not all-inclusive lists of examples of clinical and analytical noncompliance.

Bioequivalence Inspection Report
PART I—FACILITIES AND PROCEDURES (Clinical and Analytical)

A. **Facilities** (Clinical and/or Analytical)
   1. Evaluate the general facilities for adequate space, work-flow patterns, separation of operations, etc.
   2. Comment on potential or actual problems, such as:
      1. adjacent clinic rooms housing concurrent studies;
      2. open windows allowing ingress of unauthorized food, drugs, etc., into clinic rooms;
      3. are dropped ceilings sealed or monitored to prevent storage of nonpermitted materials;
      4. other conditions that may compromise study security, contribute to the potential for sample mix-up, sample contamination/degradation, etc.
   3. Comment if the facilities do not appear adequate to support their normal workload.
   4. Are there written, dated, and approved standard operating procedures, readily available to all personnel in their work areas? Are working copies kept current?
   5. Are outdated procedures archived for future reference?
   6. Are visitors to the clinical facility permitted? How are visitors monitored to prevent passage of nonpermitted materials to the study subjects?
   7. Are off-site trips for smoking or other reasons monitored to prevent consumption of nonpermitted materials or passage of such materials to or from unauthorized persons?

B. **Personnel**
   1. Check the relevant qualifications, training, and experience of personnel. Assess staff's ability to perform assigned functions. Document any deficiencies that relate to the audited study(ies).

C. **Specimen Handling and Integrity**

   In the Clinic. Check and describe:
   1. Procedures for positive subject and sample identification so that study, drug, subject, sampling time, etc., are linked.
   2. Procedures for adherence to processing time, temperature, and light conditions as specified by analytical method.
   3. Storage conditions before and after processing, as well as during transit to the laboratory.
   4. Precautions against sample loss and mix-up during storage, processing and transit to the laboratory.

   In the Analytical Laboratory
   1. Determine if the analytical facility receives bioequivalence samples from other locations. If yes:
      a. Are there freight receipts for sending/receiving samples?
      b. Is a documented history of sample integrity available (e.g., the sample storage time and conditions prior to shipment)?
      c. Is the length of time in shipment recorded?
      d. Evaluate the type of transportation employed, and type of protection provided (e.g., shipped by air in insulated containers of dry ice). Report any questionable practices.
      e. What arrangement(s) can be made for receiving shipments outside of normal working hours?
      f. Are the conditions of the samples noted upon arrival at the analytical laboratory, along with the identity of the person(s) receiving the samples?
      g. Are there procedures and documentation to assure that the samples remained at the proper temperature during shipment and holding?
   2. Describe the storage equipment for bioequivalence samples until analysis (e.g., GE Freezer, chest type, Model #417, etc.)
   3. Evaluate the equipment and procedures (e.g., ultraviolet light protection) for storing and maintaining bioequivalence samples, prior to and during analysis.
      a. Compare storage capacity versus number of samples in storage.
      b. Examine set points for alarms and temperature controlling/recording devices.
      c. Review procedures for calibration and maintenance of alarms and controllers/recorders.
      d. Determine practices for monitoring, review, and storage of temperature records.
      e. Report any evidence of sample thawing.
      f. Check integrity of study samples.
      g. Determine if action plans are in place in case of power loss leading to abnormal storage conditions, that is, emergency procedures.
   4. Determine if samples are labeled and separated in storage and during analysis to prevent sample loss or mix-up between studies, subjects, and test/reference drug?
   5. Examine how sample identification is maintained through transfer steps during analysis.
   6. Is there accurate documentation to show how many freeze and thaw cycles the samples have been subjected to, including accidental thawing due to equipment failure(s)?

Electronic Records and Signatures

FDA published the Electronic Records; Electronic Signatures; Final Rule (21 CFR 11) on March 20, 1997. The rule became effective on August 20, 1997. Records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirement set forth in agency regulations must comply with 21 CFR 11. The following questions are provided to aid evaluation of electronic records and electronic signatures:

1. Are electronic data systems used to gather clinical (e.g., adverse experiences, concomitant medications) and analytical data (e.g., peak heights, peak areas of chromatograms)? Are such systems used to store, analyze, and/or calculate pharmacokinetic/pharmacodynamic modeling, or to transmit clinical and analytical data to the sponsor? If so, identify the system(s), and summarize the system(s)' capabilities. If electronic data systems are not used, omit coverage of the remainder of this section.
2. Determine the source(s) of data entered into the computer for accuracy, security, and traceability.
   a. Direct electronic transfer of on-line instrument data.
   b. Case report forms, analytical worksheets, or similar records requiring manual data entry.
   c. Chromatograms requiring evaluation prior to manual extraction of data.
   d. Other.
3. Determine the following:
   a. Who enters data and when?
   b. Who verifies data entry and when?
   c. Who has access to computer and security codes?
   d. How are data in computers changed? By whom? Audit trail?

4. Determine if the sponsor gets source data or tabulated, evaluated data.
5. Determine how data are transmitted to sponsor (hard copy, computer disk, fax, modem, etc.)
6. If the *sponsor* discovers errors, omissions, etc., in the final report, what contacts are made with the investigator; how are corrections effected, and how are they documented?
7. Determine how data are retained by the investigator? (Hard copy, electronic, etc.)
8. Determine if the firm has SOPs for validation of computer systems involved in storing, analyzing, calculating, modeling, and/or transmitting clinical and analytical data. Have the computer systems been validated according to the SOPs? Are results of the validations documented and available for audit? Summarize the validated capabilities of the computer systems with respect to their effect on the validity of the study data.

Clinical Data and Operations

General

Inspections of clinical facilities should include a comparison of the practices and procedures of the clinical investigator with the requirements of 21 CFR 312, 320.

Inspections should also include a comparison of the source data in the clinical investigator's files with the data submitted to the FDA. Original records should be reviewed, including medical records, dosing records, clinical laboratory test reports, adverse reaction reports, concomitant medications records, nurses' notes, etc.

Inspection Procedures

This part identifies the minimum information that must be obtained during an inspection to determine if the clinical investigator is complying with the regulations. Each FDA investigator should expand the inspection as facts emerge. The inspections should be sufficient in scope to determine the clinical investigator's general practices for each point identified, as well as the particular practices employed for the study(ies) under audit.

Study Responsibility and Administration

1. Determine if the clinical investigator was aware of the status of the test article(s), nature of the protocol, and the obligations of the clinical investigator.
2. Determine whether authority for the conduct of various aspects of the study was delegated properly so that the investigator retained control and knowledge of the study.
3. Determine if the investigator discontinued the study before completion. If so, provide reason.
4. Determine the name and address of any clinical laboratory performing clinical laboratory tests for qualifying and/or safety monitoring of study subjects.
   a. If any clinical laboratory testing was performed in the investigator's own facility, determine whether that facility is equipped to perform each test specified.
   b. Determine if individuals performing the clinical tests are adequately qualified.

Protocol

Obtain a copy of the written protocol. Unavailability should be reported and documented. If a copy of the protocol is sent with the assignment background material, it should be compared to the protocol on site. If the protocols are identical, a duplicate copy does not need to be obtained. The narrative should note that the protocols were identical. If the protocol has been accepted by a Review Division in CDER, a copy of the acceptance letter should be attached to the EIR. If the Agency has recommended the incorporation of additional material, method, or information into the protocol, verify that appropriate modifications were made.

1. Compare the written protocol and all Institutional Review Board (IRB) approved modifications against the protocol provided with the assignment package. Report and document any differences.
2. Determine if the approved protocol was followed with respect to:
   a. Subject selection (inclusion/exclusion criteria).
   b. Number of subjects.
   c. Drug dose form, strength and route of administration.
   d. Frequency of subject dosing, monitoring, and sampling.
   e. Washout period between study arms (test vs. reference drug)
   f. Other (specify)?
3. Determine whether all significant changes to the protocol were:
   a. documented by an approved amendment that is maintained with the protocol;
   b. dated by the investigator;
   c. approved by the IRB and reported to the sponsor before implementation except where necessary to eliminate apparent immediate hazard to human subjects.
   d. implemented after IRB approval.

   Note: Changes in protocol are not violations of protocol.

Subjects' Records

1. Describe the investigator's source data files in terms of their organization, condition, accessibility, completeness, and legibility.
2. Determine whether there is adequate documentation to assure that all audited subjects did exist and were alive and available for the duration of their stated participation in the study.
3. Compare the source data in the clinical investigator's records with the case reports completed for the sponsor. Determine whether clinical laboratory testing (including blood work, EKGs, X-rays, eye examinations, etc.), as noted in the case report forms, was documented by the presence of completed laboratory records among the source data.
4. Determine whether all adverse experiences were reported in the case report forms. Determine whether they were regarded as caused by or associated with the test article and if they were previously anticipated (specificity, severity) in any written information regarding the test article.
5. Concomitant therapy and/or intercurrent illnesses might interfere with the evaluation of the effect of the test article. Check whether concomitant therapy or illness occurred. If so, was such information included in the case report forms?
6. Determine whether the number and type of subjects entered into the study were confined to the protocol limitations and whether each record contains:
   a. Observations, information, and data on the condition of each subject at the time the subject entered into the clinical study;
   b. Records of exposure of each subject to the test article;
   c. Observations and data on the condition of each subject throughout participation in the investigation including time(s) of drug administration; dosing according to

preestablished, randomization schedules; results of laboratory tests; development of unrelated illness; bleeding times and any other specimen collections; wash-out periods for subjects; and other factors which might alter the effects of the test article; and

d. The identity of all persons and locations obtaining source data or involved in the collection or analysis of such data.

Other Study Records

Review information in the clinical investigator's records that would be helpful in assessing any under-reporting of adverse experiences by the sponsor to the agency. The following information will ordinarily be obtained from the sponsor and sent with the assignment:

a. The total number of subjects entered into the study;
b. The total number of dropouts from the study (identified by subject number);
c. The number of evaluable subjects and the number of nonevaluable subjects (the latter identified by subject number); and
d. The adverse experiences identified by subject number and a description of the adverse experience.

Compare the information submitted to the sponsor according to the clinical investigator's files with the information obtained from the sponsor, and document any discrepancies found.

Consent of Human Subjects

1. Obtain a copy of the consent form actually used.
2. Determine whether proper informed consent was obtained from *all* subjects *prior* to their entry into the study. Identify the staff who obtain and witness the signing of informed consent for study subjects.

Institutional Review Board

1. Identify the name, address, and chairperson of the Institutional Review Board for this study.
2. Determine whether the investigator maintains copies of all reports submitted to the IRB and reports of all actions by the IRB. Determine the nature and frequency of periodic reports submitted to the IRB.
3. Determine whether the investigator submitted reports to the IRB of all deaths and serious adverse experiences and unanticipated problems involving risk to human subjects (21 CFR 312.66).
4. Determine if the investigator submitted to and obtained IRB approval of the following *before* subjects were allowed to participate in the investigation:
   a. Protocol.
   b. Modifications to the protocol.
   c. Materials to obtain human subject consent.
   d. Media advertisements for subject recruitment.
5. Determine if the investigator disseminated any promotional material or otherwise represented that the test article was safe and effective for the purpose for which it was under investigation. Were the promotional material(s) submitted to the IRB for review and approval before use?

Sponsor

1. Did the investigator provide a copy of the IRB approved consent form to the sponsor?
2. Determine whether the investigator maintains copies of all reports submitted to the sponsor.
3. Determine if and how the investigator submitted any report(s) of deaths and adverse experiences to the sponsor.
4. Determine whether all intercurrent illnesses and/or concomitant therapy(ies) were reported to the sponsor.
5. Determine whether all case report forms on subjects were submitted to the sponsor shortly (within 6 months) after completion.
6. Determine whether all dropouts, and the reasons therefore were reported to the sponsor.
7. Did the sponsor monitor the progress of the study to assure that investigator obligations were fulfilled? Briefly describe the method (on-site visit, telephone, contract research organization, etc.) and *frequency* of monitoring. Do the study records include a log of on-site monitoring visits and telephone contacts?

Test Article Accountability

1. Determine whether unqualified or unauthorized persons administered or dispensed the test article(s).
2. What names are listed on the FDA-1571 (for Sponsor-Investigator) and FDA-1572 (for studies conducted under an IND)? Obtain a copy of all FDA-1572s.
3. Determine accounting procedures for test articles:
   A. Receipt date(s) and quantities.
   B. Dates and quantities dispensed.
   C. Quantities of bioequivalence testing samples retained (see section "Sample Collection" under part III).
4. Inspect storage area.
   a. Reconcile amounts of test article used with amounts received, returned, and retained. Report any discrepancy.
   b. If not previously sampled under CP 7346.832, collect samples of both the test and reference products for FDA analysis.
5. If test articles are controlled substances, determine if proper security is provided.

Records Retention

1. Determine who maintains custody of the required records and the means by which prompt access can be assured.
2. Determine whether the investigator notified the sponsor in writing regarding alternate custody of required records, if the investigator does not maintain them.
3. Be aware that records should be retained at the study site for the specified time as follows:
   a. Two years following the date on which the test article is approved by FDA for marketing for the purposes, which were the subject of the clinical investigation; or
   b. Two years following the date on which the entire clinical investigation (not just the investigator's part in it) is terminated or discontinued *by the sponsor*. If the investigator was terminated or discontinued, was FDA notified?

Abbreviated Report Format

For inspection of a clinical facility, abbreviated report is allowed if (1) there are no significant violations and no FDA Form 483 is issued, and (2) in cases where there are objectionable findings but the findings are not serious and clearly do not have any impact on data integrity and study outcomes. The following is a guideline for preparation of the abbreviated report:

1. Reason for inspection
   a. Identify the headquarters unit that initiated and/or issued the assignment.
   b. State the purpose of the inspection.

2. What was covered
   a. Identify the clinical study, protocol number, sponsor, NDA, ANDA, etc.
   b. Location of study.
3. Administrative procedures
   a. Report the name, title, and authority of the person to whom credentials were shown and FDA-482 Notice of Inspection was issued.
   b. Persons interviewed.
   c. Who accompanied the inspector during establishment inspection.
   d. Who provided relevant information.
   e. Identify the IRB.
   f. Prior inspectional history.
4. Individual responsibilities
   a. Identify study personnel and summarize their responsibilities relative to the clinical study (e.g., who screened the subjects, who administered the drugs, who supervised collection, identification, and processing of samples, etc.).
   b. A statement about (i) who obtained informed consent, (ii) how it was obtained, and (iii) was informed consent signed by each subject?
   c. Identify by whom the clinical study was monitored, and when, etc.
5. Inspectional findings
   a. A statement regarding the comparison of data on the case report forms to the source data at the investigator's site. Indicate the number of records compared and what was compared (patient charts, hospital records, lab slips, etc.), and specific information about any discrepancies.
   b. A statement indicating if the drug accountability records were sufficient to reconcile the amount of drug received, dispensed, returned, and retained.
   c. A statement about protocol adherence. Describe in detail any nonadherence.
   d. A statement concerning doses in accordance with preestablished, randomization schedules.
   e. The EIR should identify the IRB and state if it approved the study and was kept informed of the progress of the study.
   f. A statement on (i) follow-up activities in response to reports of adverse experiences (including death) if any occurred; (ii) whether there was evidence of under reporting of adverse experiences/events.
   g. Discussion of 483 observations, reference the exhibits/documentation collected.
6. Discussion with Management
   a. Discussion of 483 observations and non-483 observations.
   b. Clinical investigator's response to observations.

Remember that the above deals with abbreviated reports, not abbreviated inspections. All assignments issued for cause must have full reporting. The assignment EMS or memo will indicate the need for full reporting for any special inspection.

I. ANALYTICAL DATA AND OPERATIONS

Information required by this section must be obtained with the assistance of a qualified analyst from the field and/or a reviewer in GBIB with expertise in the type of analysis used in the bioequivalence study under review.

At random, compare the analytical source data with data provided in the inspection assignment for accuracy of transference and for scientific soundness/bearing on the validity of the study. Analytical source data are codes used to blind samples; data establishing the sensitivity, linearity, specificity, and precision of the analytical assay; data determining the stability of the drug in the biological specimen; all standard curves; blinded and unblinded spiked control samples; blanks; data on reagent preparation; instrumental readings; calculations; etc. The data comparison and the testing procedural review should include an evaluation of any discrepancies found.

A. Prestudy analysis
   If the analytical laboratory is involved in analysis of drug standards and products employed in the bioequivalence studies, determine if:
   1. Appropriate samples were analyzed by the laboratory to determine potency and content uniformity for tablets and capsules. Include a description of procedures used to prepare the sample(s) used in the study.
   2. If testing of the samples described above was not performed by the analytical laboratory, did the sponsor provide test results to the laboratory?
   3. For both the test and reference drug products studied, were the products' appearance, potency, dosage form (capsule, tablet, suspension, controlled release, etc.), lot numbers and expiration dates the same as that reported to FDA?

B. Protocol acceptance
   If the Review Division reviewed the protocol and recommended protocol modifications, verify that the modifications were incorporated into the protocol.

C. Equipment
   Check on the following with respect to both current equipment and practices and those in place at the time of the study:
   1. Does the laboratory have the same type, brand, and model (not serial) numbers of all major pieces of analytical equipment and instrumentation used in their testing procedures, as reported in the ANDA or NDA? (e.g., gas chromatographs, high-performance liquid chromatographs, ultraviolet spectrophotometers, colorimeter, fluorescence or atomic absorption spectrophotometer, pH meter, etc.). If not, describe the discrepancy and include its effect on the validity of the study data.
   2. Assess the general condition of the major pieces of equipment (e.g., gross mistreatment), which may render them inaccurate or unreliable. Examples: damaged gas chromatograph inlet port, dry pH meter electrodes, etc. Review maintenance and repair logs for indications of past problems.
   3. Are there written operating instructions for these major pieces of equipment, and are they available to the laboratory personnel?
   4. Are there written and scheduled calibration/standardization procedures, and preventative maintenance procedure for all analytical instruments employed in the study? Determine whether these calibration/standardization procedures are actually employed and documented? If not, describe the deficiencies and determine whether the instruments have been calibrated during the time of the study.
   5. Were specific instrument operating parameters documented during the study? If so, where?

D. Analytical methods validation—determine through data and procedural review if
   1. The analytical laboratory has scientifically sound data to support claims for the specificity of the assay employed in this study. Ascertain the laboratory's justification for noninterferences, both endogenous and exogenous (e.g., metabolites, solvent contamination, etc.) in measuring the analytes (drug, metabolites, etc.) studied.
   2. The analytical laboratory has data to support the claims for the linearity of the assay employed in this study.
   3. The laboratory analyst who analyzed the biological samples has generated data demonstrating the sensitivity of the assay using the same instrumentation as that employed in the bioequivalence study. The sensitivity of the assay (or limit of detection) may be defined as the lowest quantifiable limit that can be *reproducibly determined* for the measured analyte(s) being carried through the method.
   4. The laboratory analyst who analyzed the biological specimen has generated data demonstrating the precision of the assay using the instrumentation employed in the bioequivalence study. The data should be available for both standard and quality control samples and should include the consistency of precision of the standard and control samples carried through the assay procedure. Ascertain the laboratory's justification for the precision based on the separation procedure, instrumentation, and analyte concentration levels in the biological fluids.
   5. The laboratory has data to demonstrate drug recoveries (percent recovery) for the measured analyte(s). This should include both analyte extraction efficiency from the biological fluid *and* recovery of the analyte(s) carried through the analytical testing procedure.
   6. The analytical laboratory determined the stability of the drug both in the biological specimen and in the sample preparation medium under the same condition as in actual analysis of subject samples.
   7. The analytical laboratory showed that the storage procedures (e.g., freezing and number of freeze/thaw cycles) have no adverse effect on drug stability for the period of time the samples were stored, from subject dosing until last sample analysis.
   8. The water quality specified for sample and reagent preparation is consistently and readily available in the laboratory.

E. Sample analyses—determine if
   1. The analytical assay employed was the same as that specified in the ANDA or NDA.
   2. The assay parameters observed for the study's sample analysis are similar to those (e.g. specificity, precision, etc.) obtained during method validation. Review study subjects' source analytical data to check this; pay particular attention to analytical runs determined toward the end of analytical testing.
   3. Coding techniques were used to blind the analytical laboratory to the sample. Was the code available to the analytical chemist?
   4. The samples were analyzed in a randomized fashion or in some specific order. Were samples of test and reference products for the same subject analyzed at the same time under identical conditions with the same standard curve, same control, and same instrument?
   5. Standard curves are prepared each time a batch of unknown samples is assayed. If not, how often are standards run? Have all the standard curves run during the study been reported? How many standards are used to define each standard curve? (Should be 5–8, excluding blank.) Does the laboratory have scientifically sound procedures for acceptance or rejection of a standard point and/or a standard curve?
   6. The standard curve encompasses the concentration values reported. Were any values reported which were derived from points extrapolated on the standard curve?
   7. The laboratory has a scientifically sound SOP in place to guide the acceptance/rejection of data. Did the laboratory adhere to the SOPs in the reporting of repeated determinations, or was supervisory discretion used to accept/reject data points?
   8. Blinded or nonblinded spiked control samples have been included and reported with each run. Who prepared these samples? Were the controls made from a standard weight different from the standard weight used to prepare standards for the standard curve (i.e., two separate independent weighings for calibration standards and QC stock solutions)? Do the controls span the expected analyte concentration range (low, midrange, and high) found in the subjects' samples? Have all control values been reported individually, as opposed to averages?
   9. The control samples were processed and analyzed exactly the same as the unknown samples. Were the controls interspersed throughout the entire analytical run?
   10. The source of blank biological fluids. (Was each subject's zero hour serum used as the blank, pooled plasma, etc.?) Were interferences noted in the analytical source data for these samples? Specifications should be established to assure that blank biological fluids are as similar as possible to the biological matrix for the subject samples.
   11. The source of the drug standards used for the in vivo sample analysis. If not compendial standards, how was the quality and purity of the standard assured?
   12. All sample values were recorded and reported. If not, were reasons for rejection documented and justified? Were any samples rerun? When repeated determinations were made, were new standard curves and control samples run concurrently?
   13. The procedure employed for determining which value of a rerun sample is reported. Was this procedure scientifically sound and consistently followed? Was an established written procedure followed?
   14. The submitted chromatograms are representative of the quality of the chromatograms generated throughout the study.
   15. There are written procedures for preparing reagents used in these assays. Are reagents properly labeled with date of preparation, storage requirements, as well as chemist who prepared them? Were the original weighings for calibration standard and QC stock solutions checked and countersigned by a second party?
   16. Copies of the following chromatograms are available: (If not submitted by the applicant, the Field investigator or chemist should obtain copies.)
       a. Reagent blank
       b. Sample blank
       c. Internal standard
       d. A standard run
       e. A quality control run
       f. A set of chromatograms for one subject over the entire span of the study

F. For antibiotic analyses—determine:
   1. Are incubators available? Specify dimensions and type.
   2. Whether
      a. the bench tops are level;
      b. the room temperature is controlled and, if so, what are the temperature tolerances;
      c. agar, propagation cultures, and other necessary resources are available and properly monitored;
      d. zone readers are available, if so, specify type; and
      e. autoclaves are available and, if so, specify type and determine if the autoclave sterilization process has been validated.
   3. The room where these studies are conducted is "environmentally sterile" and what monitoring is done to determine the degree of "environmental sterility."
   4. Whether the samples were run properly through the incubator, that is, times and temperatures are controlled to desired specifications and properly documented.
   5. Whether the standards, controls and samples are incubated at the same time, in the same incubator.
   6. Whether the microorganisms used in the media are the same as described in the AADA.
   7. Whether a burner is used to heat the wire for transfer purposes.
   8. Whether calibrated zone readers were used for zone size determinations.
   9. Whether turbidimetric methodology was employed. Also, determine the type of spectrophotometry used.
   10. Whether the turbidimetric standardization procedure was the same as that specified in the AADA. If not, describe differences.
   11. Whether all samples were read in duplicate. Were all samples read by the same person? Did zone diameters or turbidimetric readings correlate with drug concentration levels?
   12. Are standard operating procedures in place to calibrate the incubator, autoclave, etc., used in antibiotic analysis? Are the SOPs readily available to laboratory personnel?

G. For radiometric analyses—in addition to the general guidance above, determine:
   1. How the specific activity of the radiochemical standards employed was determined.
   2. Whether all counts specified in records submitted to the Agency were actually counted for the time interval specified.
   3. Whether an inventory of all radiolabeled compounds is maintained by the laboratory.
   4. If the background level has been determined? If yes, by what method?
   5. For RIA methodology, determine if a commercial kit was used in the analysis. If so, report the type of kit, the expiration date and whether the laboratory validated the laccuracy, specificity, precision, sensitivity and linearity of the kit assay in relation to the reported study assay procedure.

H. Data handling and storage—determine:
   1. Whether bound notebooks and/or source data worksheets are used by the laboratory.
   2. If bound notebooks are used, are the pages filled in sequentially on a chronological basis? Does the analyst sign the notebook/worksheet daily? Does a supervisor initial the notebook/worksheet after checking it for accuracy?
   3. Whether the laboratory retains all source data, such as notebooks, worksheets, chromatograms, standard curves, etc. Is there justification for source data excluded from the study report, such as rejected runs, missing samples, etc.?
   4. Whether the analyst(s) sign and date all source data records.
   5. How long the source data is retained.
   6. Describe the maintenance and accessibility of laboratory source data (e.g., repeated determinations, rejected analytical runs, etc.). Document problems with data recording and verification, such as lack of dates and signatures, erasures, white-out, etc.

REFERENCES

1. FD & C Act Section 301 (e), 505 and 510
2. Code of Federal Regulations, Title 21: Part 11, "Electronic Records; Electronic Signatures," Part 50, "Protection of Human Subjects," Part 56, "Institutional Review Boards," Part 200.10, "Contract Facilities (Including Consulting Laboratories) Utilized as Extramural Facilities by Pharmaceutical Manufacturers," Part 207, "Registration of Producers of Drugs," Part 312, "Investigational New Drug Application," Part 314, "Applications for FDA Approval to Market a New Drug or An Antibiotic Drug," Part 314.125, "Refusal to Approve an Application or Abbreviated Antibiotic Application," Part 320, "Bioavailability and Bioequivalence Requirements," Part 361.1, " Radioactive Drugs for Certain Research Uses."
3. Compliance Program Guidance Manual (CPGM), CPGM 7348.811, "Clinical Investigators"
4. 21 CFR 11—Electronic Records. Electronic Signatures Regulation effective August 1997.
5. 21 CFR 58.1 – 58.219 Good Laboratory Practice Regulations effective June 1979, and amended effective October 1987
6. Good Laboratory Practice Regulations, Management Briefings, Post Conference Report, August 1979
7. Good Laboratory Practice Regulations, Questions and Answers, June 1981
8. "Guide to Inspection of Computerized Systems in Drug Processing," February 1983
9. "Software Development Activities, Technical Report" July 1987
10. "Guide For Detecting Fraud in Bioresearch Monitoring Inspections," April 1993
11. 21 CFR part 54, Financial Disclosure by Clinical Investigators
12. 21 CFR part 314, Applications for FDA Approval to Market a New Drug
13. 21 CFR part 320, Bioavailability and Bioequivalence Requirements
14. The Federal Food, Drug, and Cosmetic Act, Section 505(k)(2)
15. FDA Compliance Program Guidance Manual (CPGM), Compliance Program 7348.001 – Bioresearch Monitoring – In Vivo Bioequivalence

7

EU Guidelines to Good Manufacturing Practice

Basic Requirements for Active Substances Used as Starting Materials

1.1. Objective

These guidelines are intended to provide guidance regarding good manufacturing practice (GMP) for the manufacture of active substances under an appropriate system for managing quality. It is also intended to help ensure that active substances meet the requirements for quality and purity that they purport or are represented to possess.

In these guidelines "manufacturing" includes all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of active substances and the related controls. The term "should" indicates recommendations that are expected to apply unless shown to be inapplicable, modified in any relevant annexes to the GMP guide, or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance.

The GMP guide as a whole does not cover safety aspects for the personnel engaged in manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by other parts of the legislation.

These guidelines are not intended to define registration requirements or modify pharmacopoeial requirements and do not affect the ability of the responsible competent authority to establish specific registration requirements regarding active substances within the context of marketing/manufacturing authorizations. All commitments in registration documents must be met.

1.2. Scope

These guidelines apply to the manufacture of active substances for medicinal products for both human and veterinary use. They apply to the manufacture of sterile active substances only up to the point immediately prior to the active substance being rendered sterile. The sterilization and aseptic processing of sterile active substances are not covered, but should be performed in accordance with the principles and guidelines of GMP as laid down in Directive 2003/94/EC and interpreted in the GMP guide including its Annex 1.

In the case of ectoparasiticides for veterinary use, other standards than these guidelines, that ensure that the material is of appropriate quality, may be used.

These guidelines exclude whole blood and plasma, as Directive 2002/98/EC and the technical requirements supporting that directive lay down the detailed requirements for the collection and testing of blood; however, it does include active substances that are produced using blood or plasma as raw materials. Finally, these guidelines do not apply to bulk-packaged medicinal products. They apply to all other active starting materials subject to any derogations described in the annexes to the GMP guide, in particular Annexes 2 to 7 where supplementary guidance for certain types of active substance may be found. The annexes will consequently undergo a review but in the meantime and only until this review is complete, manufacturers may choose to continue to use Part I of the basic requirements and the relevant annexes for products covered by those annexes, or may already apply Part II.

Section 19 contains guidance that only applies to the manufacture of active substances used in the production of investigational medicinal products, although it should be noted that its application in this case, though recommended, is not required by community legislation.

An "Active Substance Starting Material" is a raw material, intermediate, or an active substance that is used in the production of an active substance and that is incorporated as a significant structural fragment into the structure of the active substance. An "Active Substance Starting Material" can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. "Active Substance Starting Materials" normally have defined chemical properties and structure.

The manufacturer should designate and document the rationale for the point at which production of the active substance begins. For synthetic processes, this is known as the point at which "Active Substance Starting Materials" are entered into the process. For other processes (e.g. fermentation, extraction, purification, etc.), this rationale should be established on a case-by-case basis. Table 7.1 gives guidance on the point at which the "Active Substance Starting Material" is normally introduced into the process. From this point on, appropriate GMP as defined in these guidelines should be applied to these intermediate and/or active substance manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the active substance. However, it should be noted that the fact that a manufacturer chooses to validate a process step does not necessarily define that step as critical. The guidance in this document would normally be applied to the steps shown in gray in Table 7.1. It does not imply that all steps shown should be completed. The stringency of GMP in active substance manufacturing should increase as the process proceeds from early steps to final steps, purification, and packaging. Physical processing of active substances, such as granulation, coating, or physical manipulation of particle size (e.g. milling, micronizing), should be conducted at least to the standards of these guidelines. These guidelines do not apply to steps prior to the first introduction of the defined "Active Substance Starting Material."

In the remainder of this guideline, the term active pharmaceutical ingredient (API) is used repeatedly and should be considered interchangeable with the term "Active Substance." The glossary in section 20 of Part II should only be applied in the context of Part II. Some of the same terms are already defined in Part I of the GMP guide and these therefore should only be applied in the context of Part I.

Table 7.1 Application of This Guide to API Manufacturing

Type of manufacturing	Application of this guide to steps (shown in gray) used in this type of manufacturing				
Chemical manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of intermediate(s)	Isolation and purification	Physical processing and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
API extracted from plant sources	Collection of plant	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/comminuting			Physical processing and packaging
Biotechnology: fermentation/cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing and packaging
"Classical" fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing and packaging

2. Quality Management

2.1. Principles

2.10 Quality should be the responsibility of all persons involved in manufacturing.

2.11 Each manufacturer should establish, document, and implement an effective system for managing quality that involves the active participation of management and appropriate manufacturing personnel.

2.12 The system for managing quality should encompass the organizational structure, procedures, processes and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality-related activities should be defined and documented.

2.13 There should be a quality unit(s) that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

2.14 The persons authorized to release intermediates and APIs should be specified.

2.15 All quality-related activities should be recorded at the time they are performed.

2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.

2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g. release under quarantine as described in section 10.20 or the use of raw materials or intermediates pending completion of evaluation).

2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects, and related actions (e.g. quality-related complaints, recalls, regulatory actions, etc.).

2.2. Responsibilities of the Quality Unit(s)

2.20 The quality unit(s) should be involved in all quality-related matters.

2.21 The quality unit(s) should review and approve all appropriate quality-related documents.

2.22 The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to

releasing or rejecting all APIs;
releasing or rejecting intermediates for use outside the control of the manufacturing company;
establishing a system to release or reject raw materials, intermediates, packaging, and labeling materials;
reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;
making sure that critical deviations are investigated and resolved;
approving all specifications and master production instructions;

approving all procedures impacting the quality of intermediates or APIs;
making sure that internal audits (self-inspections) are performed;
approving intermediate and API contract manufacturers;
approving changes that potentially impact intermediate or API quality;
reviewing and approving validation protocols and reports;
making sure that quality-related complaints are investigated and resolved;
making sure that effective systems are used for maintaining and calibrating critical equipment;
making sure that materials are appropriately tested and the results are reported;
making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate; and
performing product quality reviews (as defined in section 2.5).

2.3. Responsibility for Production Activities

The responsibility for production activities should be described in writing and should include but not necessarily be limited to

preparing, reviewing, approving, and distributing the instructions for the production of intermediates or APIs according to written procedures;
producing APIs and, when appropriate, intermediates according to preapproved instructions;
reviewing all production batch records and ensuring that these are completed and signed;
making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;
making sure that production facilities are clean and when appropriate disinfected;
making sure that the necessary calibrations are performed and records kept;
making sure that the premises and equipment are maintained and records kept;
making sure that validation protocols and reports are reviewed and approved;
evaluating proposed changes in product, process, or equipment; and
making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.4. Internal Audits (Self-Inspection)

2.40 In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.

2.41 Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

2.5 Product Quality Review

2.50 Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least

– a review of critical in-process control and critical API test results;
– a review of all batches that failed to meet established specification(s);
– a review of all critical deviations or nonconformances and related investigations;
– a review of any changes carried out to the processes or analytical methods;
– a review of results of the stability monitoring program;
– a review of all quality-related returns, complaints, and recalls; and
– a review of adequacy of corrective actions.

2.51 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

3. Personnel

3.1. Personnel Qualifications

3.10 There should be an adequate number of personnel qualified by appropriate education, training, and/or experience to perform and supervise the manufacture of intermediates and APIs.

3.11 The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.

3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

3.2 Personnel Hygiene

3.20 Personnel should practice good sanitation and health habits.

3.21 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.

3.22 Personnel should avoid direct contact with intermediates or APIs.

3.23 Smoking, eating, drinking, chewing and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.

3.24 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

3.2. Consultants

3.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.

3.31 Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

4. Buildings and Facilities

4.1. Design and Construction

4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.

4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.

4.12 Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.

4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

4.14 There should be defined areas or other control systems for the following activities:

- Receipt, identification, sampling, and quarantine of incoming materials, pending release or rejection;
- Quarantine before release or rejection of intermediates and APIs;
- Sampling of intermediates and APIs;
- Holding rejected materials before further disposition (e.g., return, reprocessing, or destruction);
- Storage of released materials;
- Production operations;
- Packaging and labeling operations; and
- Laboratory operations.

4.15 Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, and air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.

4.16 Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

4.2. Utilities

4.20 All utilities that could impact on product quality (e.g. steam, gases, compressed air, and heating, ventilation, and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.

4.21 Adequate ventilation, air filtration, and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.

4.22 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.

4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.

4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3. Water

4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.

4.31 Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.

4.32 If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms, and/or endotoxins should be established.

4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.

4.34 Where the manufacturer of a nonsterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

4.4. Containment

4.40 Dedicated production areas, which can include facilities, air-handling equipment, and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.

4.41 Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anticancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.

4.42 Appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another.

4.43 Any production activities (including weighing, milling, or packaging) of highly toxic nonpharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic nonpharmaceutical materials should be separate from APIs.

4.5. Lighting

4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

4.6. Sewage and Refuse

4.60 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

4.7. Sanitation and Maintenance

4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.

4.71 Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.

4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, intermediates, and APIs.

5. Process Equipment

5.1. Design and Construction

5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.

5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.

5.12 Production equipment should only be used within its qualified operating range.

5.13 Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.

5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids, or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.

5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.

5.16 A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

5.2. Equipment Maintenance and Cleaning

5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.

5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include

- assignment of responsibility for cleaning of equipment;
- cleaning schedules, including, where appropriate, sanitizing schedules;
- a complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;
- when appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;
- instructions for the removal or obliteration of previous batch identification;
- instructions for the protection of clean equipment from contamination prior to use;
- inspection of equipment for cleanliness immediately before use, if practical; and
- establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.

5.22 Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carryover of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.

5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent buildup and carryover of contaminants (e.g. degradants or objectionable levels of microorganisms).

5.24 Nondedicated equipment should be cleaned between production of different materials to prevent cross-contamination.

5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.

5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.

5.3. Calibration

5.30 Control, weighing, measuring, monitoring, and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.

5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.

5.32 Records of these calibrations should be maintained.

5.33 The current calibration status of critical equipment should be known and verifiable.

5.34 Instruments that do not meet calibration criteria should not be used.

5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

5.4. Computerized Systems

5.40 GMP-related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application.

5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.

5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.

5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There

should be controls to prevent omissions in data (e.g. system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.

5.44 Written procedures should be available for the operation and maintenance of computerized systems.

5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.

5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.

5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented, and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software, and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

5.48 If system breakdowns or failures would result in the permanent loss of records, a backup system should be provided. A means of ensuring data protection should be established for all computerized systems.

5.49 Data can be recorded by a second means in addition to the computer system.

6. Documentation and Records

6.1. Documentation System and Specifications

6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved, and distributed according to written procedures. Such documents can be in paper or electronic form.

6.11 The issuance, revision, superseding, and withdrawal of all documents should be controlled with maintenance of revision histories.

6.12 A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.

6.13 All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.

6.14 When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.

6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.

6.16 Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.

6.17 Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labeling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.

6.18 If electronic signatures are used on documents, they should be authenticated and secure.

6.2. Equipment Cleaning and Use Record

6.20 Records of major equipment use, cleaning, sanitization, and/or sterilization and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.

6.21 If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

6.3. Records of Raw Materials, Intermediates, API Labeling, and Packaging Materials

6.30 Records should be maintained including the following list:

- The name of the manufacturer, identity, and quantity of each shipment of each batch of raw materials, intermediates, or labeling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt.
- The results of any test or examination performed and the conclusions derived from this.
- Records tracing the use of materials.
- Documentation of the examination and review of API labeling and packaging materials for conformity with established specifications.
- The final decision regarding rejected raw materials, intermediates, or API labeling and packaging materials.

6.31 Master (approved) labels should be maintained for comparison to issued labels.

6.4. Master Production Instructions (Master Production and Control Records)

6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).

6.41 Master production instructions should include the following points

- The name of the intermediate or API being manufactured and an identifying document reference code, if applicable.
- A complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics.
- An accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included.

Variations to quantities should be included where they are justified.
- The production location and major production equipment to be used.
- Detailed production instructions, including the
- sequences to be followed;
- ranges of process parameters to be used;
- sampling instructions and in-process controls with their acceptance criteria, where appropriate;
- time limits for completion of individual processing steps and/or the total process, where appropriate; and
- expected yield ranges at appropriate phases of processing or time.
- Where appropriate, special notations and precautions to be followed, or cross references to these.
- The instructions for storage of the intermediate or API to assure its suitability for use, including the labeling and packaging materials and special storage conditions with time limits, where appropriate.

6.5. Batch Production Records (Batch Production and Control Records)

6.50 Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.

6.51 These records should be numbered with a unique batch or identification number, dated and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.

6.52 Documentation of completion of each significant step in the batch production records (batch production and control records) should include

- dates and, when appropriate, times;
- identity of major equipment (e.g., reactors, driers, mills, etc.) used;
- specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;
- actual results recorded for critical process parameters;
- any sampling performed;
- signatures of the persons performing and directly supervising or checking each critical step in the operation;
- in-process and laboratory test results;
- actual yield at appropriate phases or times;
- description of packaging and label for intermediate or API;
- representative label of API or intermediate if made commercially available;
- any deviation noted, its evaluation, investigation conducted (if appropriate) or reference to that investigation if stored separately; and
- results of release testing.

6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

6.6. Laboratory Control Records

6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:

- A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and where appropriate, the quantity and date the sample was received for testing.
- A statement of or reference to each test method used.
- A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents, and standard solutions.
- A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested.
- A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors.
- A statement of the test results and how they compare with established acceptance criteria.
- The signature of the person who performed each test and the date(s) the tests were performed.
- The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.

6.61 Complete records should also be maintained for

- any modifications to an established analytical method;
- periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;
- all stability testing performed on APIs; and
- out-of-specification (OOS) investigations.

6.7. Batch Production Record Review

6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.

6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of noncritical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).

6.72 All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.

6.73 The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

7. Materials Management

7.1. General Controls

7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.

7.11 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.

7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).

7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.

7.14 Changing the source of supply of critical raw materials should be treated according to section 13, "Change Control."

7.2. Receipt and Quarantine

7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals, and evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined, or tested as appropriate, and released for use.

7.21 Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.

7.22 If bulk deliveries are made in nondedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:

– Certificate of cleaning
– Testing for trace impurities
– Audit of the supplier

7.23 Large storage containers and their attendant manifolds, filling, and discharge lines should be appropriately identified.

7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

7.3. Sampling and Testing of Incoming Production Materials

7.30 At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in 7.32. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.

7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.

7.32 Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.

7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.

7.34 Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.

7.35 Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

7.4. Storage

7.40 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.

7.41 Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.

7.42 Materials should be stored under conditions and for a period that have no adverse effect on their quality, and should normally be controlled so that the oldest stock is used first.

7.43 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible and containers are appropriately cleaned before opening and use.

7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

7.5. Reevaluation

7.50 Materials should be reevaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

8. Production and In-Process Controls

8.1. Production Operations

8.10 Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.

8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:

– Material name and/or item code
– Receiving or control number

– Weight or measure of material in the new container
– Reevaluation or retest date if appropriate

8.12 Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.

8.13 Other critical activities should be witnessed or subjected to an equivalent control.

8.14 Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.

8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.

8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.

8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

8.2. Time Limits

8.20 If time limits are specified in the master production instruction (see 6.41), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps is determined by in-process sampling and testing.

8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

8.3. In-Process Sampling and Controls

8.30 Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-Process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.

8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).

8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).

8.33 In-Process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within preestablished limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.

8.34 Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.

8.35 In-Process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.

8.36 Out-of-specification (OOS) investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

8.4. Blending Batches of Intermediates or APIs

8.40 For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-Process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.

8.41 OOS batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.

8.42 Acceptable blending operations include but are not limited to

– blending of small batches to increase batch size and
– blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.

8.43 Blending processes should be adequately controlled and documented and the blended batch should be tested for conformance to established specifications where appropriate.

8.44 The batch record of the blending process should allow traceability back to the individual batches that make up the blend.

8.45 Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle-size distribution, bulk density, and tap density) that may be affected by the blending process.

8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.

8.47 The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

8.5. Contamination Control

8.50 Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.

8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.

8.52 Precautions to avoid contamination should be taken when APIs are handled after purification.

9. Packaging and Identification Labeling of APIs and Intermediates

9.1. General

9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labeling materials.

9.11 Packaging and labeling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.

9.12 Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

9.2. Packaging Materials

9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.

9.22 If containers are reused, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

9.3. Label Issuance and Control

9.30 Access to the label storage areas should be limited to authorized personnel.

9.31 Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).

9.32 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.

9.33 Obsolete and out-dated labels should be destroyed.

9.34 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.

9.35 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.

9.36 A printed label representative of those used should be included in the batch production record.

9.4. Packaging and Labeling Operations

9.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.

9.41 Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.

9.42 Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product, and storage conditions, when such information is critical to assure the quality of intermediate or API.

9.43 If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

9.44 Packaging and labeling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.

9.45 Packaged and labeled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.

9.46 Intermediate or API containers that are transported outside the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

10. Storage and Distribution

10.1. Warehousing Procedures

10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g. controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.

10.11 Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

10.2. Distribution Procedures

10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.

10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality.

10.22 Special transport or storage conditions for an API or intermediate should be stated on the label.

10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.

10.24 A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

11. Laboratory Controls

11.1. General Controls

11.10 The independent quality unit(s) should have at its disposal adequate laboratory facilities.

11.11 There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with section 6.6.

11.12 All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).

11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g. organic impurities, inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

11.14 Laboratory controls should be followed and documented at the time of performance. Any departures from the above-described procedures should be documented and explained.

11.15 Any OOS result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.

11.16 Reagents and standard solutions should be prepared and labeled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.

11.17 Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.

11.18 Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.

11.19 Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

11.2. Testing of Intermediates and APIs

11.20 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.

11.21 An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g. retention time), the range of each impurity observed, and classification of each identified impurity (e.g. inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH guideline Q6B.

11.22 The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.

11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

11.3. Validation of Analytical Procedures—See section 12.

11.4. Certificates of Analysis

11.40 Authentic Certificates of Analysis should be issued for each batch of intermediate or API on request.

11.41 Information on the name of the intermediate or API including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.

11.42 The Certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).

11.43 Certificates should be dated and signed by authorized personnel of the quality unit(s) and should show the name, address, and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the Certificate of Analysis should show the name, address, and telephone number of the repacker/reprocessor and a reference to the name of the original manufacturer.

11.44 If new Certificates are issued by or on behalf of repackers/reprocessors, agents, or brokers, these Certificates should show the name, address, and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.

11.5. Stability Monitoring of APIs

11.50 A documented, ongoing testing program should be designed to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.

11.51 The test procedures used in stability testing should be validated and be stability indicating.

11.52 Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.

11.53 Normally the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least 2 years, fewer than three batches can be used.

11.54 Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.

11.55 For APIs with short shelf lives, testing should be done more frequently. For example, for those biotechnological/biologic and other APIs with shelf lives of 1 year or less, stability samples should be obtained and should be tested monthly for the first 3 months, and at 3-month intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g. 9-month testing) can be considered.

11.56 Where appropriate, the stability storage conditions should be consistent with the ICH guidelines on stability.

11.6. Expiry and Retest Dating

11.60 When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g. published data, test results).

11.61 An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.

11.62 Preliminary API expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale and (2) the quality of the API represents the material to be made on a commercial scale.

11.63 A representative sample should be taken for the purpose of performing a retest.

11.7. Reserve/Retention Samples

11.70 The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.

11.71 Appropriately identified reserve samples of each API batch should be retained for 1 year after the expiry date of the batch assigned by the manufacturer, or for 3 years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for 3 years after the batch is completely distributed by the manufacturer.

11.72 The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

12. Validation

12.1. Validation Policy

12.10 The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval and documentation of each validation phase, should be documented.

12.11 The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include

- defining the API in terms of its critical product attributes,
- identifying process parameters that could affect the critical quality attributes of the API, and
- determining the range for each critical process parameter expected to be used during routine manufacturing and process control.

12.12 Validation should extend to those operations determined to be critical to the quality and purity of the API.

12.2. Validation Documentation

12.20 A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.

12.21 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g. retrospective, prospective, concurrent) and the number of process runs.

12.22 A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.

12.23 Any variations from the validation protocol should be documented with appropriate justification.

12.3. Qualification

12.30 Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:

- Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.
- Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.
- Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.
- Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected

together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4. Approaches to Process Validation

12.40 Process Validation (PV) is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.

12.41 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These approaches and their applicability are listed below.

12.42 Prospective validation should normally be performed for all API processes as defined in 12.12. Prospective validation performed on an API process should be completed before the commercial distribution of the final drug product manufactured from that API.

12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.

12.44 An exception can be made for retrospective validation for well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where

1. critical quality attributes and critical process parameters have been identified;
2. appropriate in-process acceptance criteria and controls have been established;
3. there have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and
4. impurity profiles have been established for the existing API.

12.45 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

12.5. Process Validation Program

12.50 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from 10 to 30 consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.

12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.

12.52 Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

12.6. Periodic Review of Validated Systems

12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

12.7. Cleaning Validation

12.70 Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment-cleaning procedures where residues are removed by subsequent purification steps.

12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labeled.

12.73 Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).

12.74 Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable, and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.

12.75 Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., nonsterile APIs used to manufacture sterile products).

12.76 Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these

procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

12.8. Validation of Analytical Methods

12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.

12.81 Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.

12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.

12.83 Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

13. Change Control

13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.

13.11 Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software.

13.12 Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units, and reviewed and approved by the quality unit(s).

13.13 The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. A classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g. as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.

13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.

13.15 After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.

13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.

13.17 Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the API.

14. Rejection and Reuse of Materials

14.1. Rejection

14.10 Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

14.2. Reprocessing

14.20 Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.

14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete and is considered to be part of the normal process. This is not considered to be reprocessing.

14.22 Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely impacted due to the potential formation of by-products and overreacted materials.

14.3. Reworking

14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for nonconformance should be performed.

14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.

14.32 Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

14.4. Recovery of Materials and Solvents

14.40 Recovery (e.g. from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.

14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that

solvents meet appropriate standards before reuse or commingling with other approved materials.

14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.

14.43 The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

14.5. Returns

14.50 Returned intermediates or APIs should be identified as such and quarantined.

14.51 If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.

14.52 Records of returned intermediates or APIs should be maintained. For each return, documentation should include

- name and address of the consignee;
- intermediate or API, batch number, and quantity returned;
- reason for return; and
- use or disposal of the returned intermediate or API.

15. Complaints and Recalls

15.10 All quality-related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.

15.11 Complaint records should include

- name and address of complainant;
- name (and, where appropriate, title) and phone number of person submitting the complaint;
- complaint nature (including name and batch number of the API);
- date complaint is received;
- action initially taken (including dates and identity of person taking the action);
- any follow-up action taken;
- response provided to the originator of complaint (including date response sent); and
- final decision on intermediate or API batch or lot.

15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.

15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.

15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.

15.15 In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

16. Contract Manufacturers (including Laboratories)

16.10 All contract manufacturers (including laboratories) should comply with the GMP defined in this guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.

16.11 Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.

16.12 There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.

16.13 The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.

16.14 Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.

16.15 Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.

16.16 Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

17. Agents, Brokers, Traders, Distributors, Repackers, and Relabellers

17.1. Applicability

17.10 This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute, or store an API or intermediate.

17.11 All agents, brokers, traders, distributors, repackers, and relabellers should comply with GMP as defined in this guide.

17.2 Traceability of Distributed APIs and Intermediates

17.20 Agents, brokers, traders, distributors, repackers, or relabellers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include

- identity of original manufacturer,
- address of original manufacturer,
- purchase orders,
- bills of lading (transportation documentation),
- receipt documents,
- name or designation of API or intermediate,
- manufacturer's batch number,
- transportation and distribution records,
- all authentic Certificates of Analysis, including those of the original manufacturer, and
- retest or expiry date.

17.2. Quality Management

17.30 Agents, brokers, traders, distributors, repackers, or relabellers should establish, document, and implement an effective system of managing quality, as specified in section 2.

17.3. Repackaging, Relabeling and Holding of APIs and Intermediates

17.40 Repackaging, relabeling, and holding of APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this guide, to avoid mix-ups and loss of API or intermediate identity or purity.

17.41 Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

17.4. Stability

17.50 Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.

17.5. Transfer of Information

17.60 Agents, brokers, distributors, repackers, or relabellers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.

17.61 The agent, broker, trader, distributor, repacker, or relabeller who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.

17.62 The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship between the authorized agents and the original API or intermediate manufacturer. (In this context "authorized" refers to authorized by the manufacturer.)

17.63 The specific guidance for Certificates of Analysis included in section 11.4 should be met.

17.7 Handling of Complaints and Recalls

17.70 Agents, brokers, traders, distributors, repackers, or relabellers should maintain records of complaints and recalls, as specified in section 15, for all complaints and recalls that come to their attention.

17.71 If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabellers should review the complaint with the original API or intermediate manufacturer in order to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.

17.72 Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabellers should include any response received from the original API or intermediate manufacturer (including date and information provided).

17.6. Handling of Returns

Returns should be handled as specified in section 14.52. The agents, brokers, traders, distributors, repackers, or relabellers should maintain documentation of returned APIs and intermediates.

Specific Guidance for APIs Manufactured by Cell Culture/Fermentation

18. General

18.10 Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for "classical" processes for production of small molecules and for processes using recombinant and nonrecombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.

18.11 The term "biotechnological process" (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma, or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high-molecular-weight substances, such as proteins and polypeptides, for which specific guidance is given in this section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.

18.12 The term "classical fermentation" refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g., irradiation or chemical mutagenesis) to produce APIs. APIs produced by "classical fermentation" are normally low-molecular-weight products such as antibiotics, amino acids, vitamins, and carbohydrates.

18.13 Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.

18.14 Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this guide starts at the cell culture/fermentation step, prior steps (e.g. cell banking) should be performed under appropriate process controls. This guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.

18.15 Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).

18.16 In general, process controls should take the following into account:

- Maintenance of the Working Cell Bank (where appropriate);
- Proper inoculation and expansion of the culture;
- Control of the critical operating parameters during fermentation/cell culture;
- Monitoring of the process for cell growth, viability (for most cell culture processes), and productivity where appropriate;

– Harvest and purification procedures that remove cells, cellular debris, and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;
– Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and
– Viral safety concerns as described in ICH Guideline Q5A Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin.

18.17 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities, and contaminants should be demonstrated.

18.1. Cell Bank Maintenance and Record Keeping

18.20 Access to cell banks should be limited to authorized personnel.

18.21 Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.

18.22 Records of the use of the vials from the cell banks and storage conditions should be maintained.

18.23 Where appropriate, cell banks should be periodically monitored to determine suitability for use.

18.24 See ICH Guideline Q5D Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products for a more complete discussion of cell banking.

18.2. Cell Culture/Fermentation

18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.

18.31 Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.

18.32 Personnel should be appropriately gowned and take special precautions handling the cultures.

18.33 Critical operating parameters (e.g., temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, e.g.) may not need to be monitored.

18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned and sanitized or sterilized.

18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.

18.36 There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.

18.37 Records of contamination events should be maintained.

18.38 Shared (multiproduct) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

18.3. Harvesting, Isolation, and Purification

18.40 Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.

18.41 Harvest and purification procedures that remove or inactivate the producing organism, cellular debris, and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.

18.42 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.

18.43 If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.

18. 44 Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

18.4. Viral Removal/Inactivation steps

18.50 See the ICH Guideline Q5A Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin for more specific information.

18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.

18.52 Appropriate precautions should be taken to prevent potential viral contamination from previral to postviral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air-handling units.

18.53 The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carryover (e.g., through equipment or environment) from previous steps.

19. APIs for Use in Clinical Trials

19.1. General

19.10 Not all the controls in the previous sections of this guide are appropriate for the manufacture of a new API for investigational use during its development. Section 19 provides specific guidance unique to these circumstances.

19.11 The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from preclinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that

APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

19.2. Quality

19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism of approval of each batch.

19.21 A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.

19.22 Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.

19.23 Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.

19.24 Process and quality problems should be evaluated.

19.25 Labeling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

19.3. Equipment and Facilities

19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use.

19.31 Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

19.4. Control of Raw Materials

19.40 Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.

19.41 In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

19.5. Production

19.50 The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.

19.51 Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

19.6. Validation

19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification assures API quality during this development phase.

19.61 Process validation should be conducted in accordance with section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

19.7. Changes

19.70 Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

19.8. Laboratory Controls

19.80 While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.

19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.

19.82 Expiry and retest dating as defined in section 11.6 applies to existing APIs used in clinical trials. For new APIs, section 11.6 does not normally apply in early stages of clinical trials.

19.9. Documentation

19.90 A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.

19.91 The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.

19.92 A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (or Drug Substance)—Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Air lock—An enclosed space with two or more doors, which is interposed between two or more rooms, for example, of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An air lock is designed for use either by people or for goods and/or equipment.

API Starting Material—A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

Authorized person—The person recognized by the national regulatory authority as having the responsibility for

ensuring that each batch of finished product has been manufactured, tested, and approved for release in compliance with the laws and regulations in force in that country.

Batch (or Lot)—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of subbatches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Batch Number (or Lot Number)—A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

Batch records—All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bioburden—The level and type (e.g. objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates, or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Bulk product—Any product that has completed all processing stages up to, but not including, final packaging.

Calibration—The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Clean area—An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Computer System—A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions. A process or operation integrated with a computer system.

Consignment (or delivery)—The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Contamination—The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a starting material or intermediate during production, sampling, packaging or repackaging, storage, or transport.

Contract Manufacturer—A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical—Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Critical operation—An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Cross-Contamination—Contamination of a material or product with another material or product. Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Deviation—Departure from an approved instruction or established standard.

Drug (Medicinal) Product—The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance—See Active Pharmaceutical Ingredient

Expiry Date (or Expiration Date)—The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Finished Product—A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.

Impurity—Any component present in the intermediate or API that is not the desired entity.

Impurity Profile—A description of the identified and unidentified impurities present in an API.

In-Process Control—Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate—A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Large-Volume Parenterals—Sterile solutions intended for parenteral application with a volume of 100 mL or more in one container of the finished dosage form.

Lot—See Batch

Lot Number—See Batch Number

Manufacture—All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Manufacturer—A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of pharmaceuticals.

Marketing Authorization (Product License, Registration Certificate)—A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling, and shelf life.

Master Formula—A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master Record—A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Material—A general term used to denote raw materials (starting materials, reagents, and solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother Liquor—The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It may be used for further processing.

Packaging—All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized would not normally be regarded as part of packaging.

Packaging Material—Any material intended to protect an intermediate or API during storage and transport. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical Product—Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Procedure—A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids—Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, etc.).

Process Control—See In-Process Control

Production—All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, and labeling and relabeling, to completion of the finished product.

Qualification—Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)—The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)—Checking or testing that specifications are met.

Quality Unit(s)—An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine—The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Raw Material—A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reconciliation—A comparison between the theoretical quantity and the actual quantity.

Recovery—The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

Reference Standard, Primary—A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be used to prepare secondary reference standard.

Reference Standard, Secondary—A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing—Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process, and not reprocessing.

Retest Date—The date when a material should be reexamined to ensure that it is still suitable for use.

Reworking—Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

Self-contained Area—Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well-established procedures, controls, and monitoring. This includes physical barriers as well as separate air-handling systems but does not necessarily imply two distinct and separate buildings.

Signature (Signed)—See definition for signed.

Signed (Signature)—The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent—An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification—A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Standard Operating Procedure (SOP)—An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance, and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting Material—Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Validation—A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity, or system actually leads to the expected results (see also qualification).

Validation Protocol—A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected—The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical—The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

8

Preapproval Inspections

I. INTRODUCTION

A preapproval inspection is a visit by regulatory authority inspectors (generally from the District officer of FDA) to review the compliance, in terms of adequacy and accuracy of the information included in a regulatory submission (Compliance Program Guidance Manual, Program 7346.832). The preapproval inspection program has evolved over the years in response to the fraudulent submissions to the U.S. Food and Drug Administration (FDA) by the generic drug industry.

A. Background

The Food, Drug, and Cosmetic Act provides that the FDA may approve a new drug application (NDA) or an abbreviated new drug application (ANDA) only if the methods used in, and the facilities and controls used for, the manufacture, processing, packing, and testing of the drug are found adequate to ensure and preserve its identity, strength, quality, and purity. The applicant is required to submit information in the NDA/ANDA to the Center for Drug Evaluation and Research (CDER), which contains among other things a method of analysis and details as to how the firm proposes to manufacture—and control the manufacture—of the product that is the subject of the application. This information is reviewed by CDER scientists (chemists, microbiologists, etc.) to determine whether the specifications in the application meet the FDA's standards. The CDER's role in the preapproval process is to review data submitted to the agency as part of premarket NDAs and generic drug applications and to establish specifications for the manufacture and control of the resulting drug product on the basis of the submitted data.

The investigator's role is to ensure current good manufacturing practice (cGMP) compliance, verify the authenticity and accuracy of the data contained in these applications, and report any other data that may affect the firm's ability to manufacture the product in compliance with GMPs. This program is designed to provide close inspectional and analytical attention to the authenticity and accuracy of data in applications and to provide information regarding facilities. Such coverage is necessary to ensure that applications are not approved if the applicant has not demonstrated an ability to operate with integrity and in compliance with all applicable requirements.

B. Objective

The objective of the compliance program is to ensure that establishments involved in the manufacturing, testing, or other manipulation of new drug dosage forms and new drug substances are audited

1. through on-site inspections for compliance with cGMPs;
2. for conformance with application commitments;
3. to ensure data is authentic and accurate; and
4. through laboratory testing of products, including evaluations of the adequacy of analytical methodology.

Both foreign and domestic establishments are covered by this program. Such coverage is intended to be consistent to the extent possible. This program provides guidance for establishment inspections and related investigations and for laboratory evaluations of methods of analysis proposed by applicants in NDA and ANDA submissions.

Before any application is approved by the CDER, a determination will be made of whether all establishments that will participate in the manufacture, packaging, or testing of the finished dosage form or new drug substance are in compliance with cGMP and application commitments. This determination may be made by conducting preapproval inspections. Method validations, method verifications, and forensic analyses will be performed to confirm the authenticity of the preapproval product and to ensure that it can be accurately assayed with the proposed regulatory methods. Postapproval inspections will monitor and enforce what is submitted in an application. "Application" means NDA, ANDA, antibiotic drug application, or abbreviated antibiotic drug application (AADA) and their supplements. CDER will request inspections in accordance with preestablished criteria. Optional preapproval inspections may be requested where circumstances warrant. The scope of preapproval inspections, compared with the responsibilities assigned to CDER scientists, is set forth below:

- Biobatch manufacturing: Inspection to determine the establishment's compliance with cGMP requirements, including a data audit of the specific batches on which the application is based (e.g., pivotal clinical, bioavailability, bioequivalence, and stability) is a field office responsibility. CDER scientists are responsible for the review and evaluation of the records and data submitted in the application, including the components, composition, batch instructions, in-process and finished product test points, and specifications established for the resulting drug product.
- Manufacture of drug substance or substances: Inspection to determine cGMP compliance of the establishment is a Field responsibility. CDER chemists are responsible for the scientific review and evaluation of the records and data associated with the manufacture of the active drug substance submitted in the application or of a properly referenced Type II Drug Master File (DMF). The review will include starting materials, key intermediates, reagents, and solvents. CDER reviewers are also responsible for the review of process validation required for the manufacturing of biotechnological and certain natural substances.
- Excipients manufacture: The manufacture of novel excipients may be provided in an application or supporting DMF. Typically, these excipients are noncompendial and are used in specialized dosage forms and drug delivery systems. CDER chemists are responsible for the scientific reviews and evaluation of the records and data associated with the manufacture of these novel excipients. The review will include starting materials, key intermediates, reagents, and

solvents. cGMP inspections by the Field usually will be performed on request from CDER.

- Raw materials (cGMP controls): Inspection of the establishment for the drug substance and review of data on raw materials to determine compliance with cGMP requirements is a Field responsibility.
- Raw materials (tests, methods, and specifications): Audit of the data submitted for CDER review in the application is a Field responsibility. CDER chemists are responsible for the scientific review of the associated data, evaluations of the adequacy of the submitted data, and ultimate approval of the tests, methods, and specifications established for the raw materials in the application.
- Composition and formulation of finished dosage form: Audit of the data submitted for CDER review in the application is a Field responsibility. CDER reviewers are responsible for the scientific review of the composition and formulation to determine, qualitatively and quantitatively, the acceptability of the information submitted in the application.
- Container/closure system or systems: CDER is responsible for the scientific review of the container/closure system or systems to be used to package the drug product as indicated in the application. The Field may audit this data.
- Labeling and packaging controls: Inspection to determine the establishment's compliance with cGMP requirements and audit of the data submitted for CDER review in the application are Field responsibilities.
- Labeling and packaging materials: CDER reviewers are responsible for the scientific review of the labeling and packaging components associated with the drug product.
- Laboratory support of methods validation: On CDER request, Field laboratory analysts will conduct laboratory validation of the analytical methods proposed by the applicant. CDER laboratories may participate in certain instances abbreviated antibiotic drug application [(AADA) validations, etc.]. CDER chemists are responsible for the review and acceptance/rejection of the analytical methods based on the laboratory results and the established specifications. Contacts between field laboratory analysts and the applicant will include the CDER chemist.
- Product (cGMP) controls: Inspection of the establishment to determine compliance with cGMP requirements, and review and audit of the data furnished to CDER in the application, are Field responsibilities. CDER scientists will request information on sterile processes, for example, laboratory controls for environmental monitoring, sterile fill operations, and evaluation and reduction of microbial contamination, to be submitted to the application for CDER review.
- Product tests, methods, and specifications: Audit of the data submitted for CDER review in the application is a Field responsibility. CDER is responsible for the scientific review of the associated data and for the ultimate approval of the tests, methods, and specifications established for the drug product in the application. The Field will advise the center when it finds a questionable specification.
- Product stability: Inspection of the establishment to determine compliance with cGMP requirements and to conduct an audit of the data furnished to CDER in the application is a Field responsibility. This requirement applies to both the relevant preapproval batches, as discussed above, and the proposed commercial batches. CDER application review chemists are responsible for review of the proposed drug product stability protocol, specifications, and evaluation of the data submitted in support of the expiration dating period proposed for the drug product in the application.
- Comparison of the relevant preapproval batch or batches and proposed commercial production batches: CDER chemists are responsible for the comparison of the formulation, manufacturing instructions, and associated in-process and finished product tests and specifications established for the relevant preapproval batch or batches with the proposed commercial production batch to determine the acceptability of the firm's proposed scale-up procedure. The Field will compare the process used to make the preapproval batches with the actual process used to manufacture the validation batches. Significant differences in these processes will be evaluated by CDER's Office of Compliance, to determine whether the differences constitute fraud, and by the reviewing officers, to determine whether differences in the processes will affect the safety and effectiveness of the resulting product.
- Facilities, personnel, and equipment qualification: Review of the information and inspection of the establishment to determine compliance with cGMP requirements is a Field responsibility.
- Equipment specification or specifications: Audit of the data submitted for CDER review in the application is a Field responsibility. CDER scientists are responsible for the review of equipment specifications furnished to the center in the application.
- Packaging and labeling (cGMP controls): Review of the controls information and inspection of the establishment to determine compliance with cGMP requirements is a Field responsibility.
- Process validation: Inspection of the establishment to determine compliance with cGMP requirements and adherence to application requirements is a Field responsibility. CDER may request data to support validation of sterile processing operations; for example, environmental monitoring, equipment validation, sterile fill validation, and associated sterile operations.
- Reprocessing: Inspection of the establishment to determine compliance with cGMP requirements and to conduct an audit of the data submitted to the center in the application is a Field responsibility. CDER application review chemists are responsible for review of reprocessing protocols proposed in the application. All reprocessing procedures must be validated, or scientific data must be available to justify the reprocessing procedure. The Field will audit the validation of these procedures.
- Ancillary facilities: Ancillary facilities (contract testing laboratories and contract packagers and labelers) will be inspected to determine compliance with cGMP requirements at the discretion of CDER. The name, address, and function of each ancillary facility will be indicated in the drug application, and CDER will review biological and immunological test methods and results submitted. These facilities shall also provide a certification in the drug application regarding compliance with the conditions of approval of the application.

C. Triggering of Inspections

There are two types of events that trigger inspection: categories that will regularly prompt an inspection request, and categories in which the district office may elect to perform an inspection at their discretion for elements of applications—filed or otherwise.

The following categories will regularly prompt a preapproval or cGMP:

1. New molecular entities (includes finished drug product and the active pharmaceutical ingredient)
2. Priority NDAs
3. First application filed by an applicant
4. For-cause inspection
5. For original applications, if the current cGMP status is unacceptable or greater than 2 years
6. For certain preapproval supplements, such as site change or major construction, if the cGMP status is unacceptable
7. Treatment IND inspections (information is available to CDER indicating that an inspection of a clinical supplies manufacturer is warranted to protect the health of patients)

D. Inspections/Audits

1. Manufacturing Process

i. Drug Product (Dosage Form)

In many cases, clinical production or trial runs of a new drug are produced in facilities other than the ones used for full-scale production. The facilities and controls used for the manufacture of the batch or batches are audited. For a generic drug product, the biobatch or biobatches are required to be manufactured in production facilities, using production equipment, by production personnel, and the facility is to be in conformance with cGMPs. Accurate documentation is essential so that the production process can be defined and related to the batch or batches used for the early clinical, bioavailability, or bioequivalence studies of new drug or generic drug products. Generic product biobatches are ANDA batches that are compared to the originator/reference product to establish their equivalence. NDA biobatches are NDA batches comparing the product planned for marketing with that studied during clinical trials to establish their equivalence. The batch records submitted in the application must be audited as part of the inspection to ensure that the proposed production process is the process that was used for the manufacture of the bio/stability batches. Some manufacturers have historically made small batches that were used for biostudies and stability studies and misrepresented them as larger batches in submissions. Documentation sometimes has included research and development notebooks or batch records. Inventory records or receiving records of drug substances have been found to be of value in documenting the accountability of drug substances used in the early batches.

ii. Drug Substance (Bulk Drug Chemical)

The *Guide to Inspection of Bulk Pharmaceutical Chemical Manufacturing* (http://www.fda.gov/ora/inspect_ref/igs/bulk.html) and Compliance Program 7356.002F (http://www.fda.gov/cder/dmpq/compliance_guide.htm) covering bulk pharmaceutical chemicals (BPCs) provide details of inspections covering bulk drug chemical manufacturing processes.

2. Reprocessing

The GMP regulations require reprocessing procedures to be written, and it is customary but not required that NDAs/ANDAs contain procedures covering foreseeable deviations from physical specifications (e.g., color, capped tablets, deviations from hardness specifications, etc.). If the NDA/ANDA contains a reprocess provision, the applicant must produce scientific data to establish that the procedure will result in a product that is equivalent to the original product.

3. Laboratory

Laboratory equipment and procedures must be qualified and validated. Every NDA/ANDA inspection will include both an evaluation of laboratory controls and procedures and an audit of some of the raw data used to generate results. These data may be located in research and development test logs. The authenticity and accuracy of data used in the development of a test method should be established. (See the *Guide to Inspection of Pharmaceutical Quality Control Laboratories*, July 1993.)

4. Components

The supplier and source of the active drug substance used in the manufacturing of the biobatch or clinical batch should be identified. When the manufacturer changes suppliers of drug substance from that supplier used for the manufacture of the biobatch or clinical batches, then the application should include data demonstrating that the dosage forms produced from the drug substances from the two different suppliers are equivalent in terms of conformance with established specifications, including those stated in the application. The data used to determine the adequacy of the physical specifications established for the subsequent suppliers or suppliers of the drug substance should be established.

5. Building and Facilities

The addition of any new drug to a production environment must be carefully evaluated as to its effect on other products already under production and as to changes that will be necessary to make to the building and facility. Construction of new walls, installation of new equipment, and other significant changes must be evaluated for their effect on the overall compliance with GMP requirements. For example, new products, such as cephalosporins, would require that the firm demonstrate through appropriate separation and controls that cross-contamination cannot occur with regard to other products being made in the same facility. In addition, facilities that may already be operating at full capacity may not have adequate space for additional products.

6. Equipment

New products, particularly potent drug products, can present cleaning problems in existing equipment. Manufacturers must validate their cleaning processes for the new drug/dosage form.

7. Packaging and Labeling Controls

Packaging and labeling control procedures must be adequately written. Poor label control and accountability for other products may have an adverse effect on the firm's ability to ensure that the new drug will always be properly labeled. The label and packaging controls should take into account considerations of past label mix-ups and recalls.

II. REGULATORY/ADMINISTRATIVE STRATEGY

A. General

The plant should be in substantial compliance with GMP regulations and should have the necessary facilities and equipment in place to manufacture the specific product in the pending application. Some significant problems include, but are not limited to

- Application misrepresents data or conditions relating to preapproval batches; there are other inconsistencies or

discrepancies raising significant questions about the validity of records
- Preapproval batches are not made in accordance with GMPs
- There is a failure to report adverse findings or test data without adequate justification: If applications are withheld because of significant cGMP noncompliance, and the GMP deficiencies also apply to commercially marketed products, then action must be taken to ensure that the deficiencies are corrected

B. Process Validation

Approvals are not generally withheld on the basis of a lack of complete, full-scale, multiple-batch process validation. Although the agency does not require the manufacturer to fully validate the manufacturing process and control procedures of the commercial batch production before approval, the CDER will require that certain data be filed to demonstrate that a plant's sterilization and aseptic fill process has been qualified. These filing issues are under the control of the CDER's reviewing divisions. Because complete process validation is not required before approval, it is not required to audit complete process validation for sterile and nonsterile processes until the application has been approved. However, if the plant has already validated the process before the preapproval inspection, the validation is evaluated during the preapproval inspection. The inspection team lists deficiencies in the validation process on the FDA-483 and advises the plant official that complete validation must be completed before shipment. Applicants and sponsors must be able to justify filed specifications with scientific data. In other words, the sponsor should have conducted sufficient research on the test batches to establish specifications for the manufacturing and control procedures listed in the application. These data form the basis for the review and evaluation of the application, and these specifications form the basis of the validation protocol that may be developed following the approval of the application. The final step in the product development process is validation that the process will perform consistently. Companies are expected to validate the process using the specifications listed in the filing. Process validation requirements for the manufacture of BPCs differ somewhat from those involving dosage forms. The *Guide to Inspection of BPCs* issued in 1991 states that BPC manufacturers are expected to adequately determine and document that significant manufacturing processes perform consistently. The type of BPC, the range of specifications, and other factors determine the extent of the process development and documentation required. The documentation system required for early process steps must provide a chain of documentation, and although it need not be as comprehensive as in the later parts of the process, the manufacturer is required to identify and control the key steps in the process. Though many BPC manufacturers have recently initiated validation programs, not all BPCs can be validated simultaneously. Therefore, the inspections do not recommend taking any legal action where a firm has an adequate program in place, including reasonable milestones. Regulatory actions are recommended where there is a lack of validation and where there is evidence of a significant number of failed batches.

C. Key Elements

The key elements of an inspection are to ensure that the facility is capable of fulfilling the application commitments to manufacture, process, control, package, and label a drug product following GMP; the adequacy and accuracy of analytical methods submitted, to ensure that these methods are proper for the testing proposed; correlation between the manufacturing process for clinical trial material, bioavailability study material, and stability studies and submitted process; that the scientific data support full-scale production procedures and controls; that only factual data have been submitted; and that the protocols are in place to validate the manufacturing process.

The CDER, which governs the preapproval inspections, can additionally require preapproval inspections in the case of drugs with narrow therapeutic range, where new chemical entities are involved, where drugs are difficult to manufacture, in the case of drugs that represent a new dosage form for the application, where it is the first approval for the company, in the case of a poor GMP track record, and where generic versions of one of the 200 most prescribed drugs is involved (see Table 8.1).

D. Strategies for Preinspection

Preinspection preparation involves developing both short-term and long-term strategies. The short-term strategy may comprise

- Determining the state of cGMP compliance of all of the manufacturing and development facilities listed in the NDA for the product under review: This should be carried out by the quality assurance division of the firm.
- Compiling all relevant regulatory documents for use by the FDA inspectors at the potential inspection sites: This should be done by the regulatory affairs group of the firm; the efforts also include a summary of the commitments made to the FDA.
- Identification of key batch records: These documents are then compared with the commitments that are contained in the Regulatory Commitment Document (see above). Any discrepancies identified are resolved, and explanations are documented when appropriate. This is done by the product development group in collaboration with the quality control and regulatory affairs departments.
- The history of analytical methods used to control the product is prepared: The analytical development department prepares a chronological history of the various analytical methods used during the product development. This includes justifications for any changes made in the methods during the development process and a comparison of the methods used to release clinical batch vis-à-vis the commercial batches.
- Transfer of analytical methods to the site or sites where they are used: This is the responsibility of the analytical development division. Raw data supporting a successful transfer should be readily available to the inspectors.
- Scale-up ensuring that installation qualification, operational qualification, performance qualification (IQ/OQ/PQ) activities are properly conducted: These include cleaning validation, process validation, sterilization validation, and so forth, according to established corporate procedures.
- The development report has two main sections, one that addresses the dosage form and one that deals with the bulk drug substance: The product development scientist compiles the experimental evidence to demonstrate bioequivalency for the first clinical trial lot through those lots that will be used for launch. The report further includes a description of the current process along with a description of the chemical/physical characteristics, purity, related substances, specifications, and stability of the drug substance.

Table 8.1 Active Pharmaceutical Ingredients from the Top 200 Prescription Drugs in 2002

Acetaminophen+codeine	Fluconazole	Omeprazole
Acyclovir	Fluoxetine	Oxybutynin
Albuterol	Fluticasone	Oxycodone
Alendronate	Folic acid	Oxycodone+APAP
Allopurinol	Fosinopril	Pantoprazole
Alprazolam	Furosemide	Paroxetine
Amitriptyline	Gabapentin	Penicillin VK
Amlodipine	Gemfibrozil	Phenytoin
Amlodipine/benazepril	Glimepiride	Pioglitazone
Amoxicillin	Glipizide	Potassium chloride
Amoxicillin+clavulanate	Glyburide	Pravastatin
Amphetamine mixed salts	Glyburide+metformin	Prednisone
Aspirin	Human insulin 70/30	Promethazine
Atenolol	Human insulin NPH	Promethazine+codeine
Atorvastatin	Hydrochlorothiazide	Propoxyphene N+APAP
Azithromycin	Hydrocodone+APAP	Propranolol
Benazepril	Hydroxyzine	Quetiapine
Bisoprolol+hydrochlorothiazide	Ibuprofen	Quinapril
Budesonide	Insulin lispro	Rabeprazole
Bupropion hydrochloride	Ipratropium+albuterol	Raloxifene
Buspirone	Irbesartan	Ramipril
Captopril	Isosorbide mononitrate S.A.	Ranitidine
Carbidopa+levodopa	Lansoprazole	Risedronate
Carisoprodol	Latanoprost	Risperidone
Carvedilol	Levofloxacin	Rofecoxib
Cefprozil	Levonorgestrel+ethinyl estradiol	Rosiglitazone maleate
Celecoxib	Levothyroxine	Salmeterol
Cephalexin	Lisinopril	Salmeterol+fluticasone
Cetirizine	Lisinopril+HCTZ	Sertraline
Ciprofloxacin	Loratadine	Sildenafil Citrate
Citalopram	Loratidine+pseudoephedrine	Simvastatin
Clarithromycin	Lorazepam	Spironolactone
Clindamycin	Losartan	Sumatriptan
Clonazepam	Losartan+hydrochlorothiazide	Tamoxifen
Clonidine	Meclizine	Tamsulosin
Clopidogrel	Medroxyprogesterone	Temazepam
Conjugated estrogens+medroxyprogesterone	Metaxalone	Terazosin
Conjugated estrogens	Metformin	Tetracycline
Cyclobenzaprine	Methylphenidate extended release	Timolol maleate
Desloratadine	Methylprednisolone	Tolterodine
Desogestrel+ethinyl estradiol	Metoclopramide	Topiramate
Diazepam	Metoprolol	Tramadol
Diclofenac	Metronidazole	Tramadol+acetaminophen
Digoxin	Minocycline	Trazodone
Diltiazem	Mirtazapine	Triamcinolone
Divalproex	Mometasone	Triamterene+HCTZ
Doxazosin	Montelukast	Trimethoprim+sulfamethoxazole
Doxycycline	Mupirocin	Valacyclovir
Enalapril	Naproxen	Valdecoxib
Esomeprazole	Nifedipine	Valsartan
Estradiol	Nitrofurantoin	Valsartan+HCTZ
Ethinyl estradiol+norethindrone	Norethindrone+ethinyl estradiol	Venlafaxine
Famotidine	Norgestimate+ethinyl estradiol	Verapamil
Fenofibrate	Nortriptyline	Warfarin
Fexofenadine	Nystatin	Zolpidem
Fexofenadine+pseudoephedrine	Olanzapine	

The long-term strategy of preparing for a pre-NDA approval inspection generally comprises

- Incorporating drug development process in the preparation to allow the FDA to review the documents from the earliest stages of development.
- Establishing measures of cGMP for the production and distribution of clinical trial material; this may be different from the commercial production systems and addresses the issues of stability guidelines developed by the analytical laboratory in consultation with the quality assurance, the policy on the management of deviations (fully justified), batch disposition of clinical trial lots, change documentation—which is another critically important part of a quality system for product development, process validation, training, management notification—which sets the standard for notification of corporate research management in the event that a quality issue occurs with clinical trial materials.

E. International Inspection

The FDA inspections are conducted in the same manner for both domestic and international firms, but in practice there are legal and logistic reasons for the FDA to follow different procedures when scheduling and conducting international inspections for the purpose of verifying integrity of information submitted and ascertaining compliance with the cGMP regulations. There are four differences between domestic and international inspections: international inspections are nearly always scheduled in advance, language barriers pose unique challenges during international inspections, international inspections are typically of shorter duration than domestic inspections that are conducted for the same purpose, and international firms are reinspected less often than are domestic facilities.

When inspecting domestic firms, the FDA has the responsibility over all products manufactured, and thus inspections are often extended to include other products as well. At foreign facilities, the FDA generally has interest only in products that will be marketed in the United States, and it is likely that the firm inspected may only be marketing a handful of products in the United States, though it may have a large presence. In addition, most international inspections are completed within a fixed duration, as the inspection may be heading for similar audits in the region elsewhere and it is not often possible to make last-minute changes to itinerary. In domestic audits, the inspectors routinely interrupt the audit and return later to complete it; such is not the case with the foreign inspections.

Unless a firm has previous experience with such audits, it is highly recommended that the firm assign responsibilities for PAI readiness, determine the PAI schedule, anticipate FDA needs, verify application integrity, and verify GMP compliance on their own before the visit.

Whereas the regulatory submissions must be in English, the FDA expects that raw data and original records may be in the native language, and this is acceptable: there is no need to translate documents that are created in the native language. In fact, it is ill-advised to convert documents, as this may result in errors that can unnecessarily create confusion in the inspection. However, the summary documents as requested by the FDA may be translated before the arrival of inspectors. Where attachments were included in the regulatory submissions, these should be available with proper certification for their authenticity.

Foreign inspections almost always follow a preset routine, despite individual style, which depends on the qualification of the inspector (whether he or she is a microbiologist or a chemist, for example).

Summary documents are critical to a successful start of the audit; the FDA would rely heavily on the development reports, particularly as they pertain to early development phases of development, scale-up, and the development of analytical methods. Information contained in the development report is also useful for the firm's management to present overviews to the FDA about key development activities at the start of an inspection. Well-written, comprehensive reports may be sufficient for the purpose of the inspection without the FDA getting into inquiry about the raw data. Because the FDA is short of time in foreign inspections, they are more likely to accept the report in lieu of a larger number of support documents; as a result, the importance of a well-written, comprehensive development report is the most important tool for foreign firms. A lack of reports or incomplete reports will almost always cause the FDA inspectors to inquire about the raw data—something that should be avoided, if at all possible. Raw data always spells trouble in every inspection. An unnoticed peak in the active pharmaceutical ingredient (API) thin layer chromatography (TLC), a missing signature, numbers changed without crossing it out, and so forth, are some of the common occurrences that raise flags as the audit gets deeper.

Next to the preparation of the development report, the most important thing for the foreign firm to do is to "break ice" with the FDA inspectors. Almost always there are cultural and etiquette differences that must be overcome immediately. Although there is no need for an elaborate protocol, the firm is expected to inform the FDA inspectors about the matters indigenous to the region, such as traffic problems, hotel accommodation, food availability, and most important, any local customs that may adduce a behavior with which the inspectors may not be familiar. It is also a good idea to start the meeting with the inspectors by expressing a desire to be apprised of any findings as they occur, as it is easier to rebut or explain the situation at that moment. These situations often arise as a result of different systems of document keeping, document routing, and personnel management.

Where deficiencies are found, the firm should attempt to rectify them during the visit while keeping the FDA inspectors informed of the changes made to overcome the objections. Know that the FDA personnel are expected to report corrective actions in the Environmental Impact Report (EIR). When it is not possible to complete the corrective actions before the FDA leaves the premises, it is in the firm's best interest to report steps that have already been taken toward initiating a corrective action plan. In addition, the FDA is concerned about the steps taken to prevent recurrence of such problems and the evaluations made to determine whether the objectionable conditions may apply to other areas of the facility, as well as the steps taken by the company to determine the cause of specific objections found by the FDA. Also, falsification of documentation that a corrective action has been taken when it may not have been can land the firms in deep trouble in the follow-up inspections. The FDA becomes suspicious when the firm provides evasive or inconsistent answers, shows unexpected body language or behavior in responding, or an inconsistent response is received from different employees. It is important, therefore, that the firm go through a mock-up exercise involving all those employees who may eventually end up talking to the FDA inspectors.

At the end of inspection, the FDA conducts an exit discussion with management to deliberate on the inspection findings. Should there be any GMP-related deviations or other objectionable conditions, they will leave with the company a written list of observations (FDA-483) and will provide management with the opportunity to discuss the FDA findings. The purpose of the FDA-483 is to list objectionable conditions and practices found by the FDA investigator; it is not intended to report any favorable or acceptable conditions that may have been observed during the inspection. Each of the FDA-483s issued is subjected to further review by FDA management in the field offices or at headquarters units to determine the validity and significance of each item. It is imperative that personnel completely understand the reason or reasons that the FDA considers a condition or practice to be objectionable before the inspection team departs. As mentioned earlier, it is in the best interest of the FDA as well that issues are closed before their departure, as the inspectors may not be able to return soon, and it will create a substantial burden on the firm if the approval is withheld; this is a significant benefit in international inspections of which the firms should take full advantage.

Management should verbally respond to the inspection findings during the discussion of the FDA-483. Each item should be discussed individually, and the company personnel should provide additional explanations where appropriate and should state their intentions for items where they have made or intend to make improvements. When companies have initiated corrective actions, it is imperative that the FDA be informed of the actions taken (especially corrections that have already been completed). The company should request that the FDA team report in their EIR the corrections that have been accomplished. If the FDA has had the opportunity to verify the corrections, it would be appropriate to ask them to comment on the adequacy of the actions taken by the company (i.e., Were they satisfied with the corrective actions, or should the firm consider further actions?).

To demonstrate to the FDA that corrective actions have been taken, firms should provide to the FDA team the copies of documents that show corrections such as revised standard operating procedures (SOPs), change control records for facility improvements, training documentation, and results of analytical testing. In those situations in which the firm may need some time to decide appropriate corrective actions, it is advisable to inform the FDA team that a written response will be provided within a reasonable period (ideally within 2 weeks). It is extremely important to stick to this timeline, as it takes about 2 weeks for the inspector to file his or her EIR: It is most beneficial, strategically, to have the response of the firm be recorded in the EIR. The firm, however, should not make promises that it knows cannot be fulfilled, such as requiring substantial financial outlay that the firm may not be able to afford, or giving a timeline that is too restrictive or unrealistic. The firms should not risk creating a credibility problem in the follow-up visits. The FDA encourages an open discussion of each item listed on the FDA-483, and the FDA team should be able to defend its observations. If management believes that an item listed on the FDA-483 is incorrect or does not accurately reflect the true conditions found by the FDA investigator, this should be discussed in sufficient detail until the issue can be resolved to mutual satisfaction. If the observation is an error caused by misunderstandings, it is essential that there be full discussions to ensure that the FDA has accurate and complete information. This is why it was earlier recommended that the firm develop an open communication with the FDA, finding out the deviations as they are discovered rather than in the end-of-visit reporting. If the FDA has all of the relevant information and facts, but the FDA team has reached the conclusion that the firm's practices or conditions are unacceptable, then the FDA-483 observation will remain. The FDA does routinely alter its FDA-483; however, where disputes remain on how the FDA has interpreted a finding vis-à-vis the position firm takes, it is important to identify which data were used by the FDA that formed the basis of their decision; these data should then be verified, and if it is discovered that discrepancies occurred that were unintentional, the FDA inspectors should be informed as soon as possible after they leave the firm's premises.

When the FDA team has not found objectionable conditions, they will terminate the inspection (an FDA-483 will not be issued). In such cases, the company will not receive anything in writing from the FDA team. The firm, however, reserves the right to request the FDA to issue a statement to this effect and to ask for an exit discussion.

However, one should be extremely careful about engaging the FDA inspectors in discussions that are superfluous, to prevent any inadvertent disclosure that might change their opinion about the inspection.

The Application Integrity Policy (AIP) is a formal administrative program that the FDA uses to deal with fraud, scientific misconduct, or other instances in which wrongful acts have been committed or are suspected. The AIP, introduced in 1990 as consequence of the generic drug scandal, was formerly called the "fraud policy." The AIP is invoked when the integrity of data or information in applications filed with the FDA has been compromised or questioned. Examples of actions that may prompt investigations include submission of false or fraudulent data, making untrue statements to the FDA officials, offering illegal gratuities, and other actions that subvert the integrity of an application. The primary enforcement options that are available to the FDA under the AIP program include withholding of approvals, product recalls, and civil and criminal penalties. However, note that the FDA may not have a legal jurisdiction over a foreign establishment, and thus the penalties are mainly the rejection of application and banning the firm from submitting future applications.

F. Product Stability Data

One of the most widely cited observations in the FDA audits is the lack of or inadequate data to support the stability of the product. This applies to domestic as well as international audits, though more problems arise in international audits, where the firm may have used a different climatic zone for testing the product. A robust stability program includes study of loss of active ingredient (potency), increase in concentration of active ingredient, alteration of bioavailability, loss of content uniformity, decline in microbiological status, increase in possibly toxic decomposition product, loss of pharmaceutical elegance, and modification in any other factor of functional relevance (e.g., loss of adhesion strength in a transdermal). The stability data that should available at the time of preapproval inspection include

- Adequate test method: The assays of the active component should be stability-indicating; that is, they can be separated from the degradation products and other components of the formulation. Furthermore, the degradation products should be quantitated and all methods should be validated not only at the beginning of the testing but also through the testing period.
- Characterization of drug substance: Where a reference standard is used in an ANDA, this aspect is set aside. However, where a new chemical entity (NCE) is involved, a large volume of data would generally be required to establish the degradation profile of the new drug, especially if this happens to be a macromolecule; when the testing requires evaluation by a biological response, the difficulties in validating the test method rise exponentially. Where an entirely new stability-indicating assay is established, it is necessary to demonstrate that the procedure is indeed stability-indicating by forced degradation studies. For protein drugs, incomplete knowledge of the molecule makes it difficult to demonstrate the stability-indicating nature of the assay.
- Calibration of equipment: This is a routine requirement, and the FDA inspectors may not review these data if they find that the firm is in general good compliance with the cGMP. However, these data should be updated and current at all times.
- Assay validation parameters: The common parameters that require attention include accuracy, limit of detection, limit of quantification, linearity, precision, range, recovery, robustness, sample stability (on storage and during

assay), specificity and selectivity, and systems suitability. Two additional parameters that may need special attention are transferability and comparability. This applies to both chemical and physical testing where used. Because stability-indicating methods evolve over time, revalidation is critical. Partial revalidation is required whenever significant changes are made either in the method itself or in the material analyzed, which could reasonably be expected to affect the results obtained (e.g., changes in equipment or suppliers of critical supplies).

- Preformulation studies (bulk drug substance): Stability data of the bulk drug substance alone or in model test systems is required, and most companies find this to be weakest point of their presentation to the FDA.
- SOPs: During the PAI, the FDA investigators routinely examine the SOPs that relate to the development and operation of the stability program to ascertain the strengths and weaknesses of the program, as well as ensuring compliance with the SOPs. Firms should understand that there are no official guidelines on how to write an SOP, what methods to use, and who should be responsible for doing it. What the FDA looks for is that, given an approved SOP, the firm adheres to its own guidance. Should doubts arise that the firm is not following its own guidelines, suspicion grows about the firm's overall ability to comply with the cGMP regulations.
- Room temperature and accelerated test data: For products that will be labeled to require storage at controlled room temperature, long-term studies at 25°C ± 2°C with 60% relative humidity (RH; ± 5%) with at least 12 months of data are needed. Accelerated studies at 40°C ± 2°C and 75% ± 5% RH with at least 6 months of data are also normally required. However, the ICH does allow for a less rigorous accelerated test if the 40°C test cannot be passed. When "significant change" occurs during the 40°C accelerated study, an intermediate test, such as 30°C ± 2°C and 60% RH ± 5% for 12 months, can be used. Significant change is defined as a 5% loss of potency, exceeding pH limits, dissolution failure, and failures of physical specifications (hardness, color, etc.). If products are to be labeled with instructions for storage at a temperature of less than 25°C, then the accelerated studies can be performed at a temperature less than 40°C; however, the conditions should be at least 15°C above those used for long-term evaluation. Products for which water loss may be more important, such as liquids or semisolids in plastic containers, it can be appropriate to replace high-RH conditions by lower RH, such as 10% to 20%. If, during clinical trials, a number of different formulations have been used that differ in either formulation or processing variables from the product intended for the market, it may be appropriate to "build bridges" between the various formulations if there is reason to believe that the changes in the formulation or processing variables are such that might reasonably be expected to significantly modify stability. The FDA SUPAC (scale-up and postapproval changes) Guideline should be consulted about the importance of such changes.
- Contract laboratory stability testing: Where contract work is involved, complete details about the facility conducting the testing should be available. The FDA may choose to visit that facility as well, unless it is an approved facility that has undergone several FDA inspections in the past.

Developing stability data for an ANDA product generally requires fewer laboratory studies than those required with an NCE. The primary goal of an ANDA should be to mimic the stability profile of the innovator product, barring any intellectual property issues that might prevent the generic manufacturer from formulating a similar product. (Of course, there is nothing to prevent an ANDA sponsor from trying to formulate a product with a longer shelf life than that of the innovator, and this idea has been considered by some companies.) The formulation of generic products requires developing a source of API—a DMF source—that is substantially identical in its stability profile to the innovator API; where reference standards are not yet available, this may create serious problems. In addition, it is often difficult to obtain impurities in sufficient quantity to validate the test methods. As a result, much effort is needed in making this part of the stability profile appear as comprehensive as possible. Firms often use bracketing, or matrixing—a form of partial factorial experimental design—to reduce their experimental load, and it is well accepted; however, before adopting this method, the firm is advised to consult with the FDA, as the power of test required may change with the type of API involved. Also, normalization of stability results is not usually desirable, and the plots of percentage of label claim as a function of time should not be normalized so that all batches originate at 100% of label claim. In considering batch-to-batch variability in three or more batches, the FDA is interested in both intercepts and slopes. The arguments often adduced by European companies that the slope is more important in establishing shelf life are not acceptable to the FDA. The FDA also considers delay in testing of samples a serious issue in the stability profiling in addition to the calibration and validation of the stability chambers. Know that the FDA takes a hard-line approach when it comes to the conduct of stability testing. Firms often are greatly surprised by how important the FDA considers these "nuts and bolts" issues, such as crowded stability chambers with poor air circulation, lack of proper calibration, and evidence that the temperature fluctuation is not more than 2°C.

G. Validation of Processes

Next to the problems frequently recorded in stability profiles of drug products is the lack of or inadequacy of the documents that affirm that the process used for the manufacture of a biobatch of the commercial batch was fully validated. Validation is a requirement of both the development stage and the final batches. Process validation is defined as establishing documented evidence, which provides a high degree of assurance, that a specific process will consistently produce a product meeting its predetermined specifications and quality characteristics. To provide the FDA with sufficient documentation, firms should prepare a flow diagram of the process in a logical flow, identifying various unit operations. Firms are required to perform validation of three formal batches.

The general principles of process validation involve prospective process validation (also called premarket validation), retrospective process validation, revalidation, and concurrent process validation. Prospective process validation is the most important for an FDA pre-NDA approval inspection of a NCE or API in a dosage form or delivery system.

Prospective validation is conducted before the distribution of either a new product or an existing product made under a revised manufacturing process where such revisions may affect product specifications or quality characteristics (attributes). This involves documenting critical step analysis, in which the unit operations are challenged during the process qualification stage to determine, using either "worst case" analysis or a fractional factorial design, critical process variables that may affect overall process performance.

During formal, three-batch, prospective validation, critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should fall well within finished product specifications.

Retrospective validation involves using the accumulated in-process production and final product testing and control (numerical) data to establish that the product and its manufacturing process are in a state of control. Valid in-process results should be consistent with the drug products' final specifications and should be derived from previous acceptable process average and process variability estimates, where possible, and determined by the application of suitable statistical procedures, that is, quality control charting, where appropriate. The retrospective validation option is selected when manufacturing processes for established products are considered to be stable and when, on the basis of economic considerations and resource limitations, prospective qualification and validation experimentation cannot be justified.

Before undertaking either prospective or retrospective validation, the facilities, equipment, and subsystems used in connection with the manufacturing process must be qualified in conformance with cGMP requirements.

Concurrent validation is conducted under a protocol during the course of normal production. The first three production-scale batches must be monitored as comprehensively as possible. The evaluation of the results is used in establishing the acceptance criteria and specifications of subsequent in-process control and final product testing. Some form of concurrent validation, using statistical process control techniques (quality control charting), may be used throughout the product manufacturing life cycle.

Revalidation is required to ensure that changes in-process or in the process environment, whether introduced intentionally or unintentionally, do not adversely affect product specifications and quality characteristics. Firms should put a quality assurance system (change control) in place that requires revalidation whenever there are significant changes in formulation, equipment, process, and packaging that may affect product and manufacturing process performance. Furthermore, when a change is made in a raw material supplier, the supplier of API should be apprised of the critical requirements of impurities. Revalidation is often required in following conditions:

- Change in an API or a key excipient, or primary packaging.
- Change or replacement in a critical piece of equipment.
- Significant change in processing conditions that are known to affect either subsequent unit operations or product quality.
- Change in a location, site, or support system (e.g., utilities).
- Significant change in batch size from what was validated and that affects the operation of or selection of manufacturing equipment.
- Where several batches fail sequentially.

Process performance requalification studies before revalidation assignments are currently required for sterile products only; some of these issues can be covered in the yearly filings. However, firms are urged to review the most current SUPAC guidelines for the specific type of product manufactured.

An important document that all firms must have is the validation master plan, which enables creation of an overview of the validation effort. This plan should be put together early in the drug development process and updated on a regular basis as the drug product enters various stages of development. The plan is basically a layout of how the various activities will be performed against a predetermined timeline [perhaps using Gantt or Program Evaluation and Review Technique (PERT) chart format]. Of significance are the critical paths in the plan and how they are linked to objective achievement.

The validation program generally follows the following order:

- Selection of raw materials and components
- IQ/OQ of facilities, equipment, and systems
- Performance and process qualification stages
- Protocol-driven, three-batch, formal process validation

Running these in series and in parallel, much time can be conserved. The three stages with respect to equipment qualification are sometimes referred to as Equipment Validation, comprising IQ, which ensures that a piece of equipment has been correctly calibrated and installed in accordance with the equipment manufacturer's recommendations (proper voltage, amperage, clearance from wall, exhaust requirements, etc.). It is important to understand that IQ is also required for all utility systems. In most instances, once the installation is complete, IQ cannot be performed retroactively, such as in the case of heating, ventilation, and air-conditioning or water systems; the FDA considers this phase of planning crucial in evaluating the readiness for compliance with GMP regulations. The next phase is OQ, comprising procedures and documentation that show that the facility, support system, or piece of equipment performed as intended throughout all anticipated operating ranges under a suitable load. In this phase the systems or equipment are challenged to the limits of operation. The final phase is PQ, which demonstrates that the facility, support system, or piece of equipment performed according to a predefined protocol and achieved process reproducibility and product acceptability.

Given below is a proposed outline for a prototype validation protocol:

1. Purpose of the entire validation and prerequisites
2. Description of the entire process and subprocesses, including flow diagram and critical step analysis
3. Validation protocol approvals
4. IQ and OQ, including blueprints or drawings
5. Qualification report or reports for each subprocess
   a. Purpose
   b. Methods/procedures
   c. Sampling and testing procedures, release criteria; for example, reporting function
   d. Calibration of test equipment used; for example, test data
   e. Summary of results
   f. Approval and requalification procedure
6. Product qualification, test data from prevalidation batches
7. Product validation, test data from three formal validation batches
8. Evaluation and recommendations (including revalidation/requalification requirements)
9. Certification (approval)
10. Summary report with conclusions

The validation protocol and report may also include the product stability data or a summary and documentation concerning cleaning and analytical validation.

The pilot-production program is generally a result of cooperation between the development laboratories and the manufacturing department. Technology transfer documentation applies to processes as well as to the systems being

qualified and validated and their testing standards and testing methods. This documentation is important, particularly where an NDA is involved.

The concept of validation should be incorporated during every phase of product and process development:

1. Preformulation studies incorporate API qualification and evaluation of key excipients. Studies should incorporate studies of combinations of API and excipients and a rationale developed for the levels of various excipients chosen. Interactions between the API and excipients are expected and should not form the basis of altering the choice so long as data can be collected to show that the API is available through the shelf life.
2. Once a selection of ingredients is made, the work is transferred to the formulation laboratory to establish preliminary product design as well as prototype formulations. If the product manufactured at this level is to be used in humans, the manufacturing should be done at a GMP level.
3. Once a laboratory batch (often called 1¥) has been determined to be both physically and chemically stable based on accelerated, elevated-temperature testing (i.e., 1 month at 45°C or 3 months at 40°C or 40°C/80% RH), the next step is to scale the product and its process to a (10¥) pilot-laboratory-size batch or batches. The pilot-laboratory-size batch represents the first replicated scale-up of the designated formula. The size of the pilot-laboratory batch will usually range between 10 and 100 kg, 10 and 100 L, or 10,000 and 100,000 U. These pilot-laboratory batches are often used in clinical trials and bioequivalency studies. According to the FDA, the minimum requirement for a biobatch is 100,000 U. The pilot-laboratory batches are usually prepared in small pilot equipment within a designated cGMP-ready facility. Process-development (process-qualification) or process-capability studies are normally started in this important stage of the scale-up sequence. To evaluate the critical control parameters and their unit operation, constraint analysis techniques followed by fractional factorial designs are often used to challenge the tentative control limits (so-called "worst-case analysis") established for the process at this intermediate stage.
4. A pilot production is at about a 100¥ level; in general, the full-scale batch and the technology transfer at this stage should comprise preformulation information, product development report, and product stability and analytical methods reports. This is the time to finalize the batch production documentation for the 100¥ level. The objectives of prevalidation trials at this stage are to qualify and optimize the process in full-scale production equipment and facilities. These studies should not be rushed, as they are followed by a formal validation cycle, and rushing the prevalidation protocols may result in costly errors later on.
5. The formal validation is often completed after the PAI, where three-batch process validation will be conducted in accordance with the protocol approved during the preapproval inspection. The primary objective of the formal process validation exercise is to establish process reproducibility and consistency. Such validation must be completed before entering the market. The formal validation studies continue through packaging and labeling operations (in whole or in part), so that machinability and stability of the finished product can be established and documented in the primary container-closure system.

H. Change Control

Changes in the processes, systems, and formulations are inevitable. However, procedures for change control should be in place before, during, and after the completion of the formal validation program—to ensure that the process continues in a validated, operational state even when small noncritical adjustments and changes have been made to the process. These changes should be critically reviewed by the validation or CMC committee. The change control system allows innovation and process improvements, making it more flexible without prior formal review on the part of the NDA- and ANDA-reviewing function of the FDA. The supplemental procedures with respect to the Chemistry and Manufacturing Control sections of NDAs and ANDAs are covered through annual SUPAC review documentation procedures, with change control procedures providing assurance that process validation will remain more proinnovative.

1. Cleaning Validation

According to section 211.67 Equipment Cleaning and Maintenance of cGMP regulations, equipment and utensils should be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunction or contamination that would alter the safety, identity, strength, quality, or purity of the drug product. This includes materials used in clinical trials as well as the commercial drug product. Written SOPs must ensure that cleaning and maintenance of equipment in both product development laboratories and manufacturing facilities is strictly adhered to. Records should be kept of maintenance, cleaning, sanitizing, and inspection. These records are likely to be requisitioned by the FDA during the course of the preapproval inspection. The objective of cleaning validation of equipment and utensils is to reduce the residues of one product below established limits so that the residue of the previous product does not affect the quality and safety of the subsequent product manufactured in the same equipment. Some of the equipment design considerations include type of surface to be cleaned (stainless steel, glass, plastic), use of disposables or dedicated equipment and utensils (bags, filters, etc.), use of stationary equipment (tanks, mixers, centrifuges, presses, etc.), use of special features (clean-in-place systems, steam-in-place systems), and identification of the difficult-to-clean locations on the equipment (so-called "hot spots" or critical sites). It is important to realize that the FDA has tightened significantly the cleaning validation policies, particularly if there are biological products involved; the therapeutic proteins and peptides are specifically the target of FDA inspection.

The cleaning procedures define in certain terms the amounts and the specific type of cleaning agents or solvents used, and the procedure includes complete details about what is to be cleaned and how it is to be cleaned. As always, the methods focus on the worst-case conditions, such as the higher-strength, least soluble, most difficult-to-clean formulations manufactured within the facility that may be alternated. Cleaning procedures should identify the time between processing and cleaning, cleaning sequence, equipment dismantling procedure, need for visual inspection, and provisions for documentation.

The analytical methods chosen to validate the cleaning process may include the HPLC, TLC, spectrophotometry, TOC (total organic carbon), pH, conductivity, gravimetric, and so forth. The sampling techniques chosen may include direct surface sampling, using swabs and gauze or rinsing, depending on the residue limit to be established on the basis of the sampling site, type of residue sought, and equipment

configuration (critical sites vis-à-vis large surface area) consideration. The analytical and sampling methods should be challenged in terms of specificity, sensitivity, and recovery. The residue limits to validate the cleaning must be practical, achievable, and verifiable, and they must ensure safety. The potency of the selected drug and the presence of degradation products, cleaning agents, and microorganisms should be taken into consideration.

As a general rule, use these limits: not more than 10 ppm, not more than 0.001 of the dose of any product will appear in the maximum daily dose of another product, and no physical or chemical residue will be visible on the equipment after cleaning procedures have been performed.

2. Analytical Methods Validation

Nothing is more critical to a successful PAI than an elegant presentation of analytic methods validation in the eyes of the FDA investigators. Not only does this tell the investigators about the assurance provided for the correct testing of the product, but this also reflects on the overall understanding of the firm on compliance with the cGMP. Analytical methods go to the heart of a validated process for drug product manufacture. To establish what is tested and what the amounts involved are may appear a simple process at the outset, yet there remain many elaborate steps that will ensure that every time an analysis is performed, the test results can be relied on. Analytical methods that form the technical package for a product include not only the API but also inert excipients, the impurities in both, the residue from previously used materials and operations, the composition of in-process blends and compositions, and obviously the finished product before its release. To ascertain that the methods used are qualified for each of these phases of testing, a large volume of data is generally collected at all stages of product development, for scale-up and final manufacturing batches, and at all stages of validation and stability protocol development.

While validating a production process, several steps were listed as they pertained to each of the components of manufacturing: equipment, process conditions, personnel, and so forth. These key elements multiply rapidly when it comes to analytical methods validation. Take, for example, HPLC—the most commonly used method of analysis. A typical analytical method would involve use of columns, pumps, heaters, detectors, controllers, samplers, sensors, recorders, computers, reagents, standards, and operators—put together as a system. Each of these components and systems needs independent validation, followed by a validation of the system. Note that when this equipment is used to manufacture a product such a therapeutic proteins wherein HPLC techniques are used for the purification purpose, then all additional requirements of a manufacturing system also apply, including, but not limited to, the requirement that the equipment be of a sanitary kind. This limits the choice for manufacturers, and these considerations should be taken into account in the first selection of equipment.

The suitability of analytic method must be clearly demonstrated. This involves developing data on accuracy, precision, and linearity over the range of interest; that is, 80% to 120% of label potency. Data demonstrating the specificity, sensitivity, and ruggedness of the method and the limits for degradation products or impurities should be included. It is also important to study degradation products and impurities, which should be adequately identified and characterized. Data collected must demonstrate recovery of actives and lack of interference from other components, reagents, and standards. In addition, data characterizing day-to-day, laboratory-to-laboratory, analyst-to-analyst, and column-to-column variability should be developed to supplement reproducibility and ruggedness information. The validated analytical method should be stability-indicating. Recognition by an official compendium will often simplify the requirements listed above, but it still requires a verification process. Biological assay methods as well as the identification and analysis of microorganisms should be held to similar but reasonable standards in conformance with the limitation of biological testing.

3. Computer System Validation

New to the industry is the requirement that all electronically kept records be validated in accordance with the CFR (title 21, volume 1, part 11 revised April 1, 2003 requirement. This is particularly true of instances in which the systems are custom-designed and, furthermore, where computer-controlled automated processes are used. There remain many misconceptions about makes up computer validation. The CFR guideline as listed below should be well understood:

PART 11—ELECTRONIC RECORDS; ELECTRONIC SIGNATURES

Subpart A—General Provisions

Sec. 11.1 Scope.

(a) The regulations in this part set forth the criteria under which the agency considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper.

(b) This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.

(c) Where electronic signatures and their associated electronic records meet the requirements of this part, the agency will consider the electronic signatures to be equivalent to full handwritten signatures, initials, and other general signings as required by agency regulations, unless specifically excepted by regulation(s) effective on or after August 20, 1997.

(d) Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with sec. 11.2, unless paper records are specifically required.

(e) Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.

Sec. 11.2 Implementation.

(a) For records required to be maintained but not submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that the requirements of this part are met.

(b) For records submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that:
  (1) The requirements of this part are met; and
  (2) The document or parts of a document to be submitted have been identified in public docket No. 92S-0251 as being the type of submission the agency accepts in electronic form. This docket will identify specifically what types of documents or parts of documents are acceptable for submission in electronic form without paper records and the agency receiving unit(s) (e.g., specific center, office, division, branch) to which such submissions may be made. Documents to agency receiving unit(s) not specified in the public docket will not be considered as official if they are submitted in electronic form; paper forms of such documents will be considered as official and must accompany any electronic records. Persons are expected to consult with the intended agency receiving unit for details on how (e.g., method of transmission, media, file formats, and technical protocols) and whether to proceed with the electronic submission.

Sec. 11.3 Definitions.

(a) The definitions and interpretations of terms contained in section 201 of the act apply to those terms when used in this part.
(b) The following definitions of terms also apply to this part:
  (1) Act means the Federal Food, Drug, and Cosmetic Act [secs. 201-903 (21 U.S.C. 321-393)].
  (2) Agency means the Food and Drug Administration.
  (3) Biometrics means a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.
  (4) Closed system means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.
  (5) Digital signature means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.
  (6) Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.
  (7) Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.
  (8) Handwritten signature means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.
  (9) Open system means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.

Subpart B—Electronic Records

Sec. 11.10 Controls for closed systems.

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

(a) Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.
(b) The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.
(c) Protection of records to enable their accurate and ready retrieval throughout the records retention period.
(d) Limiting system access to authorized individuals.
(e) Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.
(f) Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.
(g) Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.
(h) Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.
(i) Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.
(j) The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.
(k) Use of appropriate controls over systems documentation including:
  (1) Adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance.
  (2) Revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

Sec. 11.30 Controls for open systems.

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from

the point of their creation to the point of their receipt. Such procedures and controls shall include those identified in sec. 11.10, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

Sec. 11.50 Signature manifestations.

(a) Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:
  (1) The printed name of the signer;
  (2) The date and time when the signature was executed; and
  (3) The meaning (such as review, approval, responsibility, or authorship) associated with the signature.

(b) The items identified in paragraphs (a)(1), (a)(2), and (a)(3) of this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

Sec. 11.70 Signature/record linking.

Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

Subpart C—Electronic Signatures

Sec. 11.100 General requirements.

(a) Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.

(b) Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.

(c) Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.
  (1) The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857.
  (2) Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.

Sec. 11.200 Electronic signature components and controls.

(a) Electronic signatures that are not based upon biometrics shall:
  (1) Employ at least two distinct identification components such as an identification code and password.
    (i) When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual.
    (ii) When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.
  (2) Be used only by their genuine owners; and
  (3) Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone other than its genuine owner requires collaboration of two or more individuals.

(b) Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.

Sec. 11.300 Controls for identification codes/passwords.

Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:

(a) Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.

(b) Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).

(c) Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.

(d) Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.

(e) Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

To understand fully the importance of computer validation, one must realize that computers can perform the functions humans used to. Instructions such as SOPs are needed to instruct humans as to what functions to perform and in what order. When computers are used, these instructions are programmed. Computer systems are extensions of the processes that they are designed to control or monitor; as a result, all computer-controlled manufacturing is subject to validation. With exponential increase in PLC-based manufacturing systems, the FDA has begun to place strict requirements on computer validation. A computer system consists of hardware, that is, physical and calibration devices, sensors, input/output devices, transducers, or equipment, and its companion software, which is used to generate records, instructions, or data. Source codes and supporting software documentation used in drug process control is considered to be part of the master production and control records under cGMP interpretation. The computer systems may comprise

- computer-integrated manufacturing,
- analytical instrumentation and automated laboratory practices,

- computer-controlled electronic signature systems,
- computer-integrated packaging operations,
- laboratory information-management systems,
- computer systems for good clinical practice, and
- computer-assisted medical devices.

The categories listed above require qualification and validation documentation. It is advisable that process automation and companion computer-integrated manufacturing operations not be initiated until sufficient prospective and concurrent validation studies have been completed.

The requirements for hardware validation are identical to those of any other equipment in use, comprising the OQ/IQ/PQ cycle, except that in the PQ, it is the test of software used. The software validation comprises functional testing, in which defined inputs produce outputs that meet expectations or specifications; a thorough examination of source codes, database designs, programming standards, control methods, and support documentation; or a quality-assurance program that includes alternate plans, contingency practices, record retrieval, and security practices

I. Documentation Standards

The cliché of the three Ds—documents, documents, and more documents—is apt for FDA PAI inspections. Historically, the regulatory agencies have relied heavily on cross-checking documents to ascertain the state of compliance with the cGMP regulations. The documents of critical importance are the batch records that contain detailed information about the batch history. It is often difficult for a firm to "fudge" these documents, although many have tried. What is important to understand here is that the entire batch record is cross-checked with the purchase requisitions, delivery documents, testing documents, and final release documents. It is almost impossible to create a system that would fool the FDA inspectors. The firms are advises that a low level of due diligence will expose the trial of doing paperwork. Included in the batch records are the date of manufacture, the identity of major equipment and lines used, specific identification of each batch of component or in-process material used, weights and measures of components used in the course of processing, in-process and laboratory control results, inspection of the packaging and labeling area before and after use, a statement of the actual yield and a statement of the percentage of theoretical yield at appropriate phases of processing, complete labeling control records, including specimens or copies of all labeling used, description of drug product containers and closures, any sampling performed, identification of the persons performing and directly supervising or checking each significant step in the operation, any deviation report resulting from an investigation made according to 21 CFR 211.192, and results of examinations made in accordance with 21 CFR 211.134 (packaging and labeling inspections).

Change control is the procedural system through which changes are reviewed, justified, documented, approved, and implemented in conformance with regulatory and corporate requirements. To support a strong change control system, the firms must have a series of documents available that includes a summary of all changes made to date that affect the manufacturing process being considered for approval; individual reports that are written to review, justify, approve, and implement specific changes that affect the manufacturing process being considered for approval; any change control reports for facilities, manufacturing processes, and cleaning processes; or analytical laboratory methods that are related to the NDA/ANDA process being submitted. As it is a routine that changes are made in the development timeline, a rigid change control system may not work all the time. It is therefore recommended that the firms must have available for the FDA investigators a history of changes made, along with justification for the changes. It is important for the firms to know that the investigators arriving at the site may not have a copy of the filing made to the FDA, such as the CMC section of the application. Firms are advised to have a "third" copy available. The requirements of the CMC section are given below; these requirements also apply to supplements, except that the information required in the supplement is limited to that needed to support the change being submitted.

1. Batch production record
2. Specifications and test procedures for each component and for the drug product
3. Names and addresses of the sources of the active and noncompendial inactive components and of the container closure system for the drug product
4. Results of any test performed on the components used in the manufacture of the drug product and on the drug product
5. Name and address of each contract facility involved in the manufacture, processing, packaging, or testing of the drug product and identification of the operation performed by each contract facility
6. Proposed or actual master production record, including a description of the equipment to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product must be provided for all initial NDAs; ANDAs must contain a proposed or actual master production record

1. Development History Report

A historic summary of the development of the product serves many purposes. The foremost purpose is to apprise the investigators of the scope of inspection. The investigators learn more about the product from the history of its development than from the analysis report of the finished product. This shows the awareness of the firm about the development process. This document should include a description of the API, the formulation, and the analytical methods. These sections should be clearly marked or presented in separate binders. The summary section should highlight how the biobatch is linked to the full-scale batch with respect to validation and scale-up of production. This section also offers an opportunity for the firm to address the issues that it considers critical.

2. Deviation Records

Deviations are inevitable, whether they occur in the production or the testing of the product; obviously, a broader standard is used during development than in full-scale production. The important thing is that all deviations should be recorded, a justification should be provided for the decision to deviate, and a description of its potential effect on the quality of product should be provided. Of most significance to the FDA is the reason for entering into a deviation: Is it because the process was not adequately characterized or validated? Or was it because of inevitable circumstances, such as a breakdown in the system? A logbook describing deviations is one way the firm may show to the FDA is diligence in ensuring compliance with the cGMP regulations. Nothing makes the FDA more suspicious than a blank log stating that there were no deviations. In addition, these log reports offer an excellent medium for internal QA audits. Firms need to understand

that the purpose of cGMP compliance is ensuring the quality and safety of the product, not necessarily adhering to a particular process or composition. Obviously, the requirements of validation make it necessary that any deviation converted into regular practice must be properly validated.

3. Installation, Operational, and Performance Qualification

The IQ/OQ/PQ documents pertaining to all manufacturing equipment, analytical equipment, or systems should be available for inspection. In many instances, firms consider their development laboratories as not needing to be as rigidly compliant for these documentation requirements as their manufacturing facilities are. This creates serious problems at PAI if the development laboratory produces a biobatch. Furthermore, the process or method transfer becomes a serious problem if unqualified equipment or processes are used in the development cycle. Firms are strongly urged to treat their development laboratory as if they were cGMP-compliant facilities.

4. Organizational Chart

Organizational charts establish that an adequate number of personnel are available to perform and supervise the manufacture, processing, packaging, or holding of a drug product (21 CFR 211.25), that a proper chain of responsibility has been established in supervisors of manufacturing processes, and that there is appropriate separation of responsibilities for manufacturing operations and the quality unit. These charts should be available for both the development organizations and the commercial manufacturing organizations.

5. Products List

To evaluate how the product submitted may be affected by the manufacturing of other products in the same premises, a complete list of all products manufactured should be provided to the PAI team on the first day of inspection. The FDA considers cross-contamination issues critical; should there be a serious objection raised, the PAI team will refuse to continue the audit. Firms are strongly urged to review the cGMP guidelines and the guidance documents provided by the FDA: Some basic rules about the cephalosporins, penicillins, hormones, and biological products are well known; however, when in doubt, do not hesitate to write the FDA to seek clarification before beginning the production of a new product. It is noteworthy that a single batch of a forbidden entity in the premises may render the premises unsuitable forever if proper validation could not be performed. For example, if a penicillin or cephalosporin product is manufactured on the premises, this premises can no longer be used for any other product, as it would be difficult to prove the absence of contaminants.

6. Drawings

Site plan drawings should be available for facilities used in clinical trial material production as well as for those at which commercial products will be produced. These drawings quickly show how the facility is constructed and controlled and include the floor plan, which shows the proper segregation of areas by walls, airlocks, and doors; these plans are useful to demonstrate people and equipment flow, showing that clean personnel and equipment do not cross paths with dirty personnel and equipment. Also, there should be a broader facility and grounds plan showing the relative position and location of various buildings in the facility. This is particularly useful where multiple building are used to finish the product or to test it, as the security of the batch in transit and the possibility of contamination are key issues to be resolved. In addition, drawings of the utility systems, such as the heating, ventilation, and air-conditioning systems and water systems, should be available. Firms are advised that they may request the FDA to review these drawings before the visit, perhaps at the time of installation, to make sure that the basic guidelines are adhered to.

7. Stability Data

Some of the most significant data that the PAI team confirm is the stability profile of the product; most likely the raw data would be examined if the presentation of the summary data appears flawed.

8. SOPs

SOPs relevant to basic systems and operations should be provided in a neatly arranged folder starting with the master validation plan, product, personnel, and process management. A comprehensive index should be attached.

9. Training Records

It is a cGMP requirement (21 CFR 211.25 a, b) that personnel have education, training, or experience that enables them to perform their assigned task. These training records should include the training curriculum for each individual, as well as the list of completed courses. These records should be made available for all personnel who manufacture, process, package, test, or release clinical trial materials and the commercial product. Firms are strongly reminded that in most inspections the FDA finds this to be one of the weakest areas. For example, some of the common FDA citations for training violations include lack of formal training documentation, lack of training in GMP regulations on an ongoing basis, lack of a formal job function training program, lack of a system for evaluating or monitoring employees to ensure that training was effective, no provision for retraining individuals on a periodic basis to ensure that employees remain familiar with the requirements applicable to them, no provision for training employees on recently revised procedures, and no provision for ensuring that employees were trained before they perform job functions. Training records should also include details about how the new employees are trained to follow the company's SOPs, rules, and other regulations. The SOP reading and understanding records, therefore, form vital evidence that the FDA examines to ensure that all employees have received adequate training in performing their tasks. Awareness and understanding of what is considered critical depends on the role the employee plays; for example, compliance with good laboratory practices or good clinical practice may be relevant to some, but not all, employees. Safety training, job function training, and documentation training are additional requirements.

10. Validation Records

Validation protocols may include test parameters, product characteristics, production equipment specifications and settings, and decision points on what constitutes acceptable test results. Three types of validation protocols should be available during the PAI: cleaning, manufacturing process, and analytical methods. Any data associated with a completed protocol should also be made available. Also, if there had been any retrospective validation, these data should also be available.

11. Technology Transfer and Scale-Up

The goal of technology transfer and scale-up is to show, through process control, that any modifications made from conception to implementation have been appropriately

evaluated and documented and that the product is safe, pure, and effective. The technology transfer master plan comprises three components: the documents, the writing style, and the illustration of equivalents. The development stage documents are often abbreviated, and the files are not necessarily as complete as in the case of full-scale production; also in addition, the language used often differs as the audience changes from a scientist to a line worker. It is important also to show how the equivalent processes were selected; for example, when using a small dryer, how can the use of large fluid bed dryer be labeled as equivalent?

12. Quality Policy

The quality policy is a global document for the company that covers such issues as recalls, employee training and certification, and overall impact analysis of product and process changes. Customer expectations, materials specifications, and laws and regulations may also affect the number of personnel needed and the way quality functions are subdivided into manageable work units. Of importance for inclusion in the quality systems description are the documenting controls, including clearance and issuance of production records, procedures, specifications, and so forth; internal and vendor audits; sampling, examination, and approval of materials, including packaging and labeling (often administered by the laboratory component of the department); Material Review Board representatives; verifying yields and other critical production data through production record audits; finished product release; accompanying FDA investigators and external auditors; administering or contributing to cGMP, safety, or other required training programs; ensuring the investigations of product failures, process deviations, laboratory out-of-specification findings, and consumer complaints; monitoring approval and implementation of corrective action plans and change controls; on-site verification of the performance of critical production operations such as clearing labeling equipment and lines; review and approval of the product development records and documents transferring a product from development to commercial production; validation/qualification protocols and summary reports acceptance; and annual cGMP review. In addition, some functions are delegated to the engineering group to complete, and these include statistical process control and trend analyses; calibration of instruments and equipment, including out-of-specification follow-up; and analysis of reports of extraordinary maintenance and preventative maintenance failures.

13. Vendor Approval

The ISO 9001 and ISO 9002 Quality Standards require manufacturers to select vendors on the basis of their ability to meet purchase specifications. By ISO 9004 definition, this includes meeting regulatory requirements and safety standards. The FDA's cGMP regulations 21 CFR 211.84(a) through (e) require a manufacturer to test and approve or reject components, drug product containers, and closures. 21 CFR 211.84(d)(2) requires the manufacturer to test each component for conformity with written specifications for purity, strength, and quality or to accept the supplier's report of analysis. 21 CFR 211.84(d)(3) requires the manufacturer to test containers and closures for conformance with all appropriate written procedures or to accept the supplier's report of analysis. Reports showing compliance with firm's vendor approval policy are required at the time of PAI.

14. Outside Contractors

When any work is contracted out, whether in manufacture or testing phase, the FDA will hold the firm where the deviation or deviations occurred responsible for violations of the cGMP regulations (21 CFR 210 and 211) that pertain to those services. However, the contractor and the application holder will be held jointly responsible for processes performed by the contractor to the extent that each party contributed to the violations. Performance of each party will be considered in determining whether one or both parties are subject to regulatory action for failure to comply with cGMPs. It is in the best interest of the applicant to perform due diligence in the selection of any contractor, as well as to audit the contractors to ensure they meet the regulatory requirements and the contractual commitments.

9

Formulation Factors in Uncompressed Dosage Forms

I. RELATIVE HUMIDITY

Relative humidity in the filling and storage areas is more important for powders than for other dosage forms because of the large specific surface area (area/weight), which can result in significant moisture uptake. The gelatin capsule shells are also susceptible to moisture and degradation at high moisture. In addition, at very low moisture, gelatin in capsules can become very brittle; therefore, an appropriate humidity level must be maintained.

II. SURFACE AREA

The large surface area of powders provides greater opportunity for the production of static electricity during the friction of flow and handling. Make sure all equipment is well grounded or else significant segregation and impeded flow of powder can result. Monodisperse systems of particles of regular shape, such as perfect cubes or spheres, can be described completely by a single parameter; however, when either nonuniform size distribution or anisometric shapes exist, any single parameter is incapable of totally defining the powder. In addition to a value for the average particle size, often we use frequency histograms to help describe the powder. We also use other measures of powder characteristics such as angle of repose and bulk or tap density. Lastly, we use compressibility and the powder's ability to undergo plastic deformation.

III. SIEVE ANALYSIS

Dry sieving allows the fractionation of relatively coarse powders and granules. Sieves are stacked (*nested*) with the largest apertures at the top and the smallest at the bottom. A sample of powder is placed on the top sieve and shaken for a fixed time period at a given amplitude and pulse frequency.

The weight of powder on each sieve can then be calculated and the particle size distribution obtained. Particles must have a two-dimensional profile smaller than the sieve aperture in order to pass through a particular sieve. A *mean sieved diameter* is calculated. Because the weight of particles on each sieve is determined, the mean sieved diameter represents a *mass distribution.*

A mesh number denotes the size of the apertures in each sieve. The mesh number is the number of wire strands (of constant diameter) per inch used to weave the square mesh pattern. The side length of the aperture in microns is inversely related to the mesh number.

Whereas the specifications of starting materials are specified, the powders often form aggregates during storage; a point of use check of aggregation is needed. It is a good idea to sift all ingredients through specified sieves prior to adding them to mixing of blending vessels. For most raw materials, sifting through a No. 60 sieve (250 mm) is desirable; however, passing materials through finer sieves can generate electrostatic charges. Wet mass is passed through a No. 8 (2.38 mm) sieve and dried granules are passed through a No. 16 (1.19 mm) mesh sieve. Lubricants should be sieved through No. 60 mesh, except for magnesium stearate, which should not be shifted through an opening smaller than the opening in a No. 35 mesh. This is necessary to avoid building up electrical charges. A conversion chart for sieve sizes from U.S. Mesh to inches and microns (or millimeters) is presented next.

U.S. Mesh	Inches	Microns	Millimeters
3	0.2650	6730	6.730
4	0.1870	4760	4.760
5	0.1570	4000	4.000
6	0.1320	3360	3.360
7	0.1110	2830	2.830
8	0.0937	2380	2.380
10	0.0787	2000	2.000
12	0.0661	1680	1.680
14	0.0555	1410	1.410
16	0.0469	1190	1.190
18	0.0394	1000	1.000
20	0.0331	841	0.841
25	0.0280	707	0.707
30	0.0232	595	0.595
35	0.0197	500	0.500
40	0.0165	400	0.400
45	0.0138	354	0.354
50	0.0117	297	0.297
60	0.0098	250	0.250
70	0.0083	210	0.210
80	0.0070	177	0.177
100	0.0059	149	0.149
120	0.0049	125	0.125
140	0.0041	105	0.105
170	0.0035	88	0.088
200	0.0029	74	0.074
230	0.0024	63	0.063
270	0.0021	53	0.053
325	0.0017	44	0.044
400	0.0015	37	0.037

IV. PARTICLE SIZE DISTRIBUTION

Sieving is a common method for establishing the distribution of particle size in a powder sample. It is a simple method that works well for powders in the size ranges used most often in the pharmaceutical industry. Sieves are limited in that they cannot be made with very small openings. The current lower limit is 43 mm, which corresponds to a No. 325 sieve. The sieve number or mesh number refers to the number of openings per linear inch. You can easily calculate the opening

size in millimeters. For example, a No. 2 sieve has an opening of 9.52 mm, while a No. 200 sieve has an opening of 0.074 mm.

A frequency histogram is a useful tool in understanding the nature of a sample of powder. It is a bar graph with the size range on the x-axis and the number or weight of each segment of the powder on the y-axis. The particle size distribution can be determined by a sample of coarse powder using a nest of sieves shaken in a sonic sifter:

1. Using at least a three-decimal-place electronic balance, record the weight of each empty sieve and the collection pan. Also record the sieve size.
2. Arrange the sieves in a sequential nest: smallest mesh number (largest aperture) at the top, largest mesh number (smallest aperture) at the bottom. Add the collection pan to the bottom of the nest.
3. Add approximately 5 g of accurately weighed coarse powder to the top sieve, and cover with the rubber cap.
4. Shake the sample for 5 minutes with a sieve "amplitude" greater than 3.
5. Reweigh each sieve and the collection pan. Calculate the weight and percentage of powder on each sieve and in the collection pan. Then calculate the cumulative weight percentage of powder that is finer than the aperture.
6. Use the probability paper to calculate the mean diameter and standard deviation; alternately, calculate the geometric mean and standard deviation for the coarse and fine powder particles.

V. POWDER FLOW PROPERTIES

During many pharmaceutical production processes, it is necessary to transfer large quantities of powder from one location to another in a controlled manner, for example, in powder blending, powder filling into containers (e.g., dusting powders), powder flow into capsules, and powder filling into the dies of a tablet press.

One method of assessing flow properties is the *Angle of repose,* which is another measure of the nature of the powder. It estimates the adhesive force between the particles. Uniform glass beads, which will show good flow properties, have an angle of repose of 23 degrees. As the adhesive force between the particles increases, the angle increases. In rare cases, it can exceed 90 degrees.

Powder is allowed to flow freely through a funnel onto the center of an upturned petri dish of known radius. When the powder reaches the side of the petri dish, the height of the cylindrical cone is determined. From the petri dish radius (r, cm) and cone height (h, cm), the angle of repose (between the petri dish and base of the powder cone) can be calculated. *Flow rate* can also be determined by measuring how fast a powder flows through an aperture. Free-flowing powders exhibit a high flow rate and a smaller angle of repose. Angle of repose and flow rate depend on particle size, shape, and surface roughness. Flow properties are frequently enhanced by the use of *glidants.*

Several commercial instruments are available to evaluate angle of repose. Follow the instructions from the supplier of instrument and test methods. A simple method is given in the following list:

1. Measure the external diameter of a petri dish; position the bottom of a funnel or paper cone approximately 5 to 15 cm above the center of the upturned petri dish using a ring stand. Be sure, a piece of paper is under the petri dish so you can pick up the powder and reuse the powder for all your replicates.
2. Slowly pour the *coarse powder* sample into the funnel, tapping the funnel as necessary to ensure that powder flows through the hole.
3. Continue this process until the bottom of the powder pile just begins to fall over the edge of the petri dish.
4. Measure the height of the pile using a ruler.
5. If the powder is lumpy, sieve it before beginning the experiment.
6. Repeat step 2 until you consistently obtain the same answer.
7. Calculate the mean height of the coarse powder pile and the mean angle of repose (ϕ).
   Note: Remember that Tan ϕ = Opposite/Adjacent; therefore, Tan $\phi = 2\,h/D$.
8. Repeat steps 2 and 3 using both *fine powder* and *fine powder with glidant,* if the purpose is to select an appropriate glidant.
9. Plot angle of repose (x-axis) against Carr's index (y-axis).

VI. REAL, TAPPED, AND BULK DENSITY

Bulk or *tapped density* is a measure of the degree of packing or, conversely, the amount of space between the particles in the powder. Bulk density is determined by placing a sample of powder of known weight in a graduated cylinder. Tap density is determined by tapping the powder in the graduate until it no longer settles.

Many methods are also used to determine the true density of the powder (e.g., helium pycnometer or gas adsorption). Dividing the true density by the bulk or tap density yields a number that is related to the amount of space in the powder. If the particles are sphere, the value is approximately 0.53, while irregular shaped particles can have values of 0.74 or more.

The *real density* of a powder sample is the weight per unit volume of the material with no air spaces between particles. Therefore, if a material has a true density of 1 g/cm^3, 100 g of material will occupy 100 mL, assuming individual particles fit together exactly. In practice, most powders do not fit together very well. Therefore, if one fills a graduated cylinder to 100 mL with a powder, the weight of powder required may only be 70 g. This apparent density is known as the *bulk* or *expanded density* (0.7 g/cm^3). If the 100-mL cylinder is subsequently tapped, the particles slide past each other and become consolidated. The 70 g of particles that once occupied 100 mL may now only occupy 80 mL. They have an apparent *packed* or *tapped* density (g/cm^3) of 0.875 g/cm^3. Carr's index is a measure of interparticulate forces. If the interparticulate forces are high, powders will have a low bulk density because bridging will occur between particles. This results in a large Carr's index and a large change in volume caused by tapping. If the interparticulate forces are low, particles will have little affinity for one another and will compact spontaneously. Under these circumstances, Carr's index is small and little change in apparent density is induced by tapping. Porosity is the volume ratio occupied by air spaces (voids) between particles of a powder sample.

VII. SOLID HANDLING

A sample of powder is the most complex physical system. No two particles are identical. The properties of the powder

are dependent on both the chemical and physical nature of the component and the nature of the interactions between the particles in the powder.

The ability of a powder to pack is dependent on the shape, size, and porosity of the particle.

VIII. MIXING OF POWDERS

Three primary mechanisms are responsible for mixing:

1. convective movement of relatively large portions of the powder;
2. shear failure, which primarily reduces the scale of segregation; and
3. diffusive movement of individual particles.

Large-scale mixers
- Rotating shell
- Fixed shell

Vertical impeller
- Fluid bed

Small-scale mixing
- Mortar and pestle
- Spatula and surface
- Paper bag

Extemporaneous techniques for mixing
- Geometric dilution
- Uniform particle size

Trituration

Sieving
- Pulverization by intervention

Levigation

IX. ORAL POWDERS

Oral powders include headache powders, dusting powders (such as antifungal powders), powders to be reconstituted (such as antibiotics), and insufflations, which are powders intended to be blown into a body cavity such as in the ear or nose. Powder mixtures as a means of measuring small quantities of powders are called triturations.

X. CAPSULES

Capsules are solid dosage forms in which one or more medicinal ingredients and/or inert substances are enclosed within a small shell or container generally prepared from a suitable form of gelatin. Some of the best sources of information about capsules are the companies that manufacture capsule shells. For example, Capsugel® (http://www.capsugel.com/contact.html) provides a lot of very useful information.

What goes into the capsule plays a role in proper capsule selection. Although the industry-leading Coni-Snap® (http://www.capsugel.com/products/conisnap.html) capsule is extremely versatile for many formulations, other capsule types are used specifically with liquids or with materials with unique moisture retention properties.

The amount of active ingredient per dose has a direct bearing on the proper size capsule to use. Because capsules usually require less excipients and additives, it is easier to get a more potent dosage without having to use a large-size capsule.

For broad-based appeal, the Coni-Snap capsule is a proven winner; however, for targeting select consumer segments, such as vegetarians, Vcaps (http://www.capsugel.com/products/vcaps.html) capsules, which are of plant origin, may better meet customer needs.

Very often, strict governmental regulations are placed on products that are being consumed by the public for health reasons. In most cases, pharmaceutical applications (http://www.capsugel.com/services/rx_dpstdy.html) face different regulatory constraints than do dietary supplements (http://www.capsugel.com/services/ds_dpst_dy.html). Capsule shell manufacturers are well acquainted with Regulatory Information and Certification (http://www.capsugel.com/services/regulatory.html) and can alert you to important areas of consideration.

Adding to the complexity to the aforementioned regulatory issue, different countries have varying regulations that need to be considered. For example, regarding the issue of color selection (http://www.capsugel.com/services/color.html), countries have their own specific lists of colorants that can be legally used for capsules.

The appearance of the capsule itself is an important consideration. Colors are known to impact user perception, and the printing of logos on the capsule can increase brand recognition. Because capsules have a long and successful history as the dosage form of choice for pharmaceutical applications (http://www.capsugel.com/services/rx_dpstdy.html) as well as for dietary supplement applications (http://www.capsugel.com/services/dsproduct.html), many options are available for locating capsule-filling-machinery (http://www.capsugel.com/equipment/ index.html).

XI. FDA CLASSIFICATION OF CAPSULE TYPES

Capsule 600	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin.
Capsule, coated 602	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; additionally, the capsule is covered in a designated coating.
Capsule, coated, extended release 611	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; in addition, the capsule is covered in a designated coating, which releases a drug (or drugs) in such a manner to allow at least a reduction in dosing frequency as compared with the same drug (or drugs) presented as a conventional dosage form.
Capsule, coated pellets 603	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; the drug itself is in the form of granules to which varying amounts of coating have been applied.
Capsule, delayed release 620	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin, which releases a drug (or drugs) at a time other than promptly after administration. Enteric-coated articles are delayed-release dosage forms.

Capsule, delayed-release pellets 621	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; the drug itself is in the form of granules to which enteric coating has been applied, thus delaying release of the drug until its passage into the intestines.
Capsule, extended release 610	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin, which releases a drug (or drugs) in such a manner to allow a reduction in dosing frequency as compared with the same drug (or drugs) presented as a conventional dosage form.
Capsule, film coated, extended release 612	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container or "shell" made from a suitable form of gelatin; in addition, the capsule is covered in a designated film coating, which releases a drug (or drugs) in such a manner to allow at least a reduction in dosing frequency as compared with the same drug (or drugs) presented as a conventional dosage form.
Capsule, gelatin coated 605	A solid dosage form in which the drug is enclosed within either a hard or soft soluble container made from a suitable form of gelatin; through a banding process, the capsule is coated with additional layers of gelatin so as to form a complete seal.
Capsule, liquid filled 606	A solid dosage form in which the drug is enclosed within a soluble, gelatin shell that is plasticized by the addition of a polyol, such as sorbitol or glycerin, and is therefore of a somewhat thicker consistency than that of a hard shell capsule; typically, the active ingredients are dissolved or suspended in a liquid vehicle.

XII. FDA CLASSIFICATION OF POWDERS

Powder (PWD 110)	An intimate mixture of dry, finely divided drugs or chemicals that may be intended for internal or external use.
Powder, dentifrice (PWD DENT 115)	A powder formulation intended to clean and polish the teeth, and may contain certain additional agents.
Powder, for solution (PWD F/SOL 833)	An intimate mixture of dry, finely divided drugs or chemicals that, upon the addition of suitable vehicles, yield a solution.
Powder, for suspension (PWD F/SUSP 834)	An intimate mixture of dry, finely divided drugs or chemicals that, upon the addition of suitable vehicles, yield a suspension (a liquid preparation containing the solid particles dispersed in the liquid vehicle).
Powder, metered (PWD MET 841)	A powder dosage form that is situated inside a container, which has a mechanism to deliver a specified quantity.

XIII. INHALERS AND LUNG DELIVERY

Key factors that contribute to the aerodynamic properties of aerosol particles are found in Stokes' law. These factors may be monitored or controlled to optimize drug delivery to the lungs. Predictions of the aerodynamic behavior of therapeutic aerosols can be derived in terms of the physical implications of particle slip, shape, and density. The manner in which each of these properties has been used or studied by pharmaceutical scientists to improve lung delivery of drugs is readily understood in the context of aerosol physics. Additional improvement upon current aerosol delivery of particulates may be predicted by further theoretical scrutiny (Crowder TM et al 2002).

The history of inhaler development in modern times can be traced to the metering valve and propellants (metered dose inhalers, pMDI) used in the treatment of asthma in the 1950s. This was followed closely by somewhat primitive dry powder inhalers (DPIs) in the 1970s. Throughout this period, nebulizers were employed to deliver drugs in aqueous solution. In the past decade, research and development in the field has broadened. This may be explained, in part, by the demise of the Kyoto Treaty on Global Warming (1997), which has refocused activities in the area of alternative propellant formulation. More significantly, there has been an increase in research into alternative approaches to powder and solution formulation and stability. This review is intended to reflect the interest and growth that has occurred in the field of pharmaceutical inhalation aerosol technology in the last 4 years (Crowder TM et al, 2001).

The field of inhalation science is expanding rapidly as scientists are designing delivery systems for proteins and peptides using nanoparticle inhalation systems; the quick absorption through lung surface offers an excellent administration route.

XIV. PROBLEMS IN POWDER HANDLING

Powder materials exhibit a number of technological challenges with their manufacture, storage, transportation, mixing, dusting, characterization, packing, crushing, and milling.

Symptoms of a nonoptimized product system utilizing a powder include unacceptable rehydration, dissolution, and solubility rate/reproducibility of the powder mixture; degradation, loss of drug activity, and reduction of product shelf life; drug mixture heterogeneity both before and during use; clogging of spray nozzle; and loss of delivered drug. The following can have a significant impact on the performance of a product using a powder:

- Utilization of the appropriate binders and adhesives
- Disintegrating agents
- Fillers
- Lubricants
- Wetting agents/surfactants
- Glidants
- Flavoring and sweetening agents

Typical powder dispersion problems include the following:

- Chemical and morphological heterogenity of the surface
- Dissolution or isomorphous substitution of constituent components (metals)
- Dependency of the surface and solution (dissolved or added) ion species

A number of interrelated physicochemical properties, such as pH (acidity), pI (ionic strength), pe (redox), and pc

(concentration) influence the properties of the dispersion beside of the pressure and temperature.

XV. CAPSULATION EQUIPMENT

Significant advances have been made within the recent years in automating and validating capsule filling equipment. For example, the German packaging company, Bosch Packaging Technology recently introduced a new generation of capsule-filling machines. A main feature of the models GKF 701, GKF 1400, and GKF 2500 ASB 100% is the dosing station on the slide-gate principle, which, according to the company, ensures low-loss processing, even for difficult powders. The machine is controlled by an industrial personal computer (PC), using software that complies with the FDA 21 CFR part 11 federal regulations. In response to harmful dust that occurs in all areas of pharmaceutical production, Bosch has developed a containment system for its standard blister machine TLT 1400. The system, which produces 400 blisters per minute, protects the operator while processing toxic contents, according to the company. (No endorsement of any manufacturer or product is intended here.) Major suppliers of capsule-filling equipment include Farmatic, Hofliger and Karg, macofar, mGw, and Zanasi.

XVI. CAPSULE FINISHING

Capsules coming off the filling line require dedusting and polishing. These can be done by pan polishing, cloth dusting, and brushing. Commercial equipment to do this includes Rotosort™, Erwek Deduster™ and the equipment from Seidenader™. Imprinting on capsules serves many purposes including ready identification. The choice of ink is important.

XVII. MODIFIED-RELEASE PRODUCTS

The capsulation process offers many advantages for designing modified-release products. The simple process of loading the drug onto nonpareil sugar beads and then coating them with a variety of release profiles offers the opportunity of not only separating the incompatible components, but also mixing granules that provide different release profiles, from instant release to step release to prolonged release. Equipment is available to fill several beads simultaneously into capsules, thus assuring dosing accuracies. (If granules with different coatings are mixed, segregation is likely because of the differences in their density.) Coated granules, if compressed, lose their release profiles.

XVIII. CLINICAL TEST SUPPLIES AND PLACEBOS

Encapsulation is the preferred form of drug delivery in preparing placebos and clinical test supplies wherein small runs are planned.

XIX. COATED PARTICLES

Use of hard gelatin capsules allows for the preparation of coated particles to provide modified release or stability; these particles are prepared generally by the method described in section XVII; however, the possibilities of creating innovative dosage forms using different size of particles makes this dosage form highly desirable for many unstable drugs.

XX. MIXING MECHANISMS

Mixing solids involves a combination of one or more mechanisms of convection, shear, and diffusive mixing. Convection mixing is achieved by the transport of solids such as by blades or screws. Shear mixing results from the forces within the particulate mass; slip planes are set up. This can take place singularly or as a laminar flow. When shear occurs between regions of different composition and parallel to their interface, it reduces the scale of segregation by thinning the dissimilar layers. Shear occurring in a direction normal to the interface of such layers is also effective because it reduces segregation. The diffusive mixing is the random motion of particles.

XXI. SEGREGATION MECHANISMS

Particulate solids tend to segregate by virtue of differences in the size, density, shape, and other properties; it can happen during mixing or subsequent storage handling as well. It is important to note that powders that are difficult to flow do not segregate easily because of high interparticulate adhesion; however, because powders must be rendered flowable for the purpose of filling capsules or in bottles or sachet, the segregation phenomenon because very important. Note that often after the addition of magnesium stearate, it is advisable to mix the product only for a limited time because electrical charges on the particles may cause segregation. Often, additives are included in formulations to reduce the tendency of segregation; these components have polarity similar to the components of the formulation. A variety of mixers are designed to counter the segregation during mixing. Regardless of the formulation or equipment used, however, the formulator must conduct a validation study to assure that the product before filling is not segregated and that detailed Manufacturing Directions consequently include conditions such as humidity, mixing speeds, mixing times, and grounding of equipment. It is often said that longer mixing causes unmixing; this occurs because of segregation as well as abrasion of particles, which alters the particle size distribution profile.

XXII. MIXING EQUIPMENT

Batch mixing is the most common practice using twin-shell, cubic, and cylindrical tumbling mixers on a common shaft. The speed of rotation (generally 30–100 rpm) for these mixers is crucial to good mixing. Other mixers of the same type take the shape of cylinders, cubes, or hexagonal cylinders. The stationary container mixers do not depend on gravity for tumbling as for the preceding mixers; these are useful for mixing sticky, wetted, or plastic mass where shear force is needed to impart mixing. Stationary container mixers include the ribbon blender and the helical flight mixer.

Large mixers produce continuous mixing; large mixers are less consistent in producing uniform mixing and are more useful in the stages, where such consistency is not critical.

Selection of equipment depends on the measure of mixing degree required. Manufacturing process validation should include a definition of segregation where large-scale segregation is not present. A large volume of data on the statistics of "degree of mixing" is available where samples are drawn from the mix at various times, and the samples must be of a sufficiently large size to contain enough particles. Perfect mixtures, in statistical terms, are random mixtures. In capsules where pellets of different types are included, these considerations become critical. Let us take the example of a binary mixture, where n is the number of particles in the sample and p is the fraction of particles of interest. For example, if a capsule contains 30% of type A pellets, then the average number is 150 in a 500-pellet capsule with standard deviation of:

$$\sigma = \tilde{A}(\text{average})(1 - p)$$

Thus, for the preceding composition, a deviation of 10.2 counts for 150 pellets occurs in each capsule when there is perfect mixing; in this instance, each capsule must be individually sampled because large bulk samples would not reveal the variations.

XXIII. MILLING

Mixing of powders is easier if all components are of the same dimension in particle size. Granulation of powders is done to provide a more uniform particle size; this is a common practice in tablet, capsule, and powder suspension formulations. Milling of granulated mass produces uniform particle size, where dyes are used, milling provides a more uniform mixing and spread of dyes. Lubricants act by coating the particles and require the presence of a certain amount of fines. Size distribution profiles are routinely prepared as part of the development pharmaceutics process, especially where high-speed filling machines are used. Frequency and cumulative plots are made to validate the process. Probability function values found in statistics books should be consulted when designing a robust evaluation program. Particles are measured either microscopically or by weight fractions through a stack of sieves. A sedimentation method is also used for particles in the range of 1 to 200 mm to obtain a size–weight distribution. Other methods include adsorption, electrical conductivity, light and X-ray scattering, permeametry, and particle trajectory.

During the process of milling or comminution, the particles undergo transformation based on the strain applied, which produces stress, and size reduction begins with the opening of new cracks. If the force applied is not sufficient, then the particle returns to its original state from a stressed state and does not yield. The type of mill used is important, such as a cutter, fluid energy, hammer, or roller, because each provides a special pattern of comminution. For example, it is useful for fibrous material, but not for friable material; it produces a product size of 20 to 80 mesh. The fluid energy mill can produce 1- to 30-mm-particles, and is more suitable for soft and sticky materials. The most common mill is the hammer mill, which is useful for abrasive materials and produces 4- to 325-mesh particles. In a hammer mill, it matters whether the blades are forward or reversed.

REFERENCES

1. Crowder TM, Rosati JA, Schroeter JD, et al (2002). Fundamental effects of particle morphology on lung delivery: Predictions of Stokes' law and the particular relevance to dry powder inhaler formulation and development. Pharm Res 19:239–245.
2. Crowder TM, Louey MD, Sethuraman VV, et al (2001). An odyssey in inhaler formulations and design. Pharm Technol 25(7):99–113.

10

Bioequivalence Testing Protocols

To receive approval for an ANDA, applicants generally must demonstrate, among other things, that their product has the same active ingredient, dosage form, strength, route of administration and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. BE drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 USC 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320.

The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-specific BE studies, the U.S. FDA will be issuing product-specific BE recommendations (www.fda.gov/cder/ogd/index.htm). Given below are the current recommendations for the products of relevance to this specific volume of the book:

Acitretin Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 25 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Pregnant female subjects should be excluded from the bioequivalence studies. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 25 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure*: All-trans-acitretin and 13-*cis*-acitretin in plasma. Since acitretin undergoes extensive presystemic metabolism and interconversion by isomerization to 13-*cis*-acitretin, measurement of all-trans-acitretin and 13-*cis*-acitretin in plasma is recommended. The pharmacokinetic parameters for all-trans-acitretin should meet the current bioequivalence criteria. The 13-*cis*-acitretin data will be used as supportive evidence. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax. *Bioequivalence based on (90% CI)*: All-trans-acitretin. *Waiver request of in vivo testing*: 10 mg based on (i) acceptable bioequivalence studies on the 25-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Amlodipine Besylate; Benazepril Hydrochloride Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 10 mg/40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Female subjects should be excluded from the bioequivalence studies, if they are pregnant. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 10 mg/40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure*: Amlodipine, benazepril, and active metabolite benazeprilat in plasma. *Bioequivalence based on (90% CI)*: Amlodipine and benazepril. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax. *Waiver request of in vivo testing*: 2.5 mg/10 mg, 5 mg/10 mg, 5 mg/20 mg, 5 mg/40 mg, and 10 mg/20 mg, based on (i) acceptable bioequivalence studies on the 10-mg strength/40-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Amprenavir Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: Single dose of 200 mg (4×50 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: Single dose of 200 mg (4 × 50 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluids)*: Amprenavir in plasma. *Bioequivalence based on (90% CI)*: Amprenavir. *Waiver request of in vivo testing*: Not applicable.

Anagrelide Hydrochloride Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 1 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 1 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Anagrelide in plasma. *Bioequivalence based on (90% CI)*: Anagrelide. *Waiver request of in vivo testing*: 0.5 mg based on (i) acceptable bioequivalence studies on the 1-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Aprepitant Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Singledose, two-way crossover in vivo. *Strength*: 125 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 125 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Aprepitant in plasma. *Bioequivalence based on (90% CI)*: Aprepitant. *Waiver request of in vivo testing*: 40 mg and 80 mg based on (i) acceptable bioequivalence studies on the 125-mg strength, (ii) proportionally similar to the

125-mg strength, and (iii) acceptable in vitro dissolution testing.

Atazanavir Sulfate Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Atazanavir in plasma. *Bioequivalence based on (90% CI)*: Atazanavir. *Waiver request of in vivo testing*: 100 mg, 150 mg, and 200 mg based on (i) acceptable bioequivalence studies on the 300-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Atomoxetine Hydrochloride Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 60 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: 60 mg is studied, because higher doses may cause unacceptable side effects in normal healthy subjects. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 60 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluid)*: Atomoxetine in plasma. *Bioequivalence based on (90% CI)*: Atomoxetine. *Waiver request of in vivo testing*: 5, 10, 18, 25, 40, 80, and 100 mg based on (i) acceptable bioequivalence studies on the 60-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. The 5-mg strength of Strattera(tm) is currently not marketed. If a firm is interested in seeking approval for this strength, please submit a citizen petition requesting the U.S.FDA make a determination that this particular strength was not withdrawn for reasons of safety or effectiveness, or check the Federal Register for a previously submitted citizen petition. Submission of the citizen petition to the FDA should be done prior to an ANDA submission.

Balsalazide Disodium Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 2250-mg dose (3 × 750 mg). *Subjects*: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 2250-mg dose (3 × 750 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluid)*: Balsalazide and mesalamine in plasma. *Bioequivalence based on (90% CI)*: Balsalazide and mesalamine. *Waiver request of in vivo testing*: Not applicable. In vitro dissolution testing under the following conditions should be submitted to support documentation of bioequivalence. *Apparatus and rotation speed*: USP apparatus I (basket), at 100 rpm. *Medium*: (1) 0.1N HCl, (2) pH 4.5 buffer, (3) pH 6.8 buffer, (4) pH 7.4 buffer. *Volume*: 900 mL. *Temperature*: 37°C. *Sample times*: 5, 10, 15, 20, 30, 45, and 60 minutes and until at least 80% of the labeled content is dissolved.

Benzonatate Capsule/Oral. *Recommended studies*: Benzonatate capsules, 100 mg and 200 mg, may be considered for waiver of in vivo bioequivalence testing pursuant to 21 CFR 320.22(c) provided the in vitro dissolution profiles of your benzonatate capsules, 100 mg and 200 mg, and the reference listed drugs (RLDs) are comparable. *Analytes to measure (in appropriate biological fluid)*: Not applicable. *Bioequivalence based on (90% CI)*: Not applicable. *Waiver request of in vivo testing*: Not applicable.

Carbamazepine Extended-Release Capsules/Oral. *Recommended studies*: Three studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Female subjects should not be enrolled in bioequivalence studies of carbamazepine, if they are pregnant. Only females who are either surgically sterile or practicing a recognized safe method of contraception should be included in a study. You should clearly define in the study protocol what is considered a "safe method of contraception." Bioequivalence studies conducted for this product, may be referenced to support a request for a waiver of evidence of in vivo bioequivalence for generic products referencing Equetro. Please submit separate applications for each RLD. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see above comment. (3) *Type of study*: Fasting (capsule compared to RLD, sprinkled on a spoonful of applesauce). *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see above comment. *Analytes to measure (in appropriate biological fluid)*: Carbamazepine in plasma. *Bioequivalence based on (90% CI)*: Carbamazepine. *Waiver request of in vivo testing*: 100 mg and 200 mg based on (i) acceptable bioequivalence studies on the 300-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Cefdinir Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Cefdinir in plasma. *Bioequivalence based on (90% CI)*: Cefdinir. *Waiver request of in vivo testing*: Not applicable.

Celecoxib Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 400 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 400 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Celecoxib in plasma. *Bioequivalence based on (90% CI)*: Celecoxib. *Waiver*

request of in vivo testing: 100 mg and 200 mg based on (i) acceptable bioequivalence studies on the 400-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Cevimeline Hydrochloride Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 30 mg. *Subjects*: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 30 mg. *Subjects*: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Cevimeline in plasma. *Bioequivalence based on (90% CI)*: Cevimeline. *Waiver request of in vivo testing*: Not applicable.

Danazol Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 200 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Because of teratogenicity concerns, females in these studies should not be pregnant. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 200 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Because of teratogenicity concerns, females in these studies should not be pregnant. *Analytes to measure*: Danazol in plasma. *Bioequivalence based on (90% CI)*: Danazol. *Waiver request of in vivo testing*: 50 mg and 100 mg based on (i) acceptable bioequivalence studies on the 200-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.

Dantrolene Sodium Capsules/Oral. *Recommended studies*: One study. *Type of study*: Fasting. *Design*: single-dose, two-way crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Dantrolene in plasma. *Bioequivalence based on (90% CI)*: Dantrolene. *Waiver request of in vivo testing*: 25 mg and 50 mg based on (i) acceptable bioequivalence studies on the 100-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dicloxacillin Sodium Capsules/Oral. *Recommended studies*: One study. *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 500 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Dicloxacillin in plasma. *Bioequivalence based on (90% CI)*: Dicloxacillin. *Waiver request of in vivo testing*: 125 mg and 250 mg based on (i) acceptable bioequivalence study on the 500 mg, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.

Didanosine Delayed–Release Capsules Enteric–Coated Beadlets/Oral. *Recommended studies*: One study. *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 400 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Didanosine in plasma using an achiral method *Bioequivalence based on (90% CI)*: Didanosine. *Waiver request of in vivo testing*: 125 mg, 200 mg, and 250 mg, based on (i) acceptable bioequivalence studies on the 400-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Diltiazem Hydrochloride Extended-Release Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way, crossover in vivo. *Strength*: 360 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way, crossover in vivo. *Strength*: 360 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Diltiazem and the active metabolites desacetyldiltiazem and desmethyldiltiazem in plasma. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax. *Bioequivalence based on (90% CI)*: Diltiazem. *Waiver request of in vivo testing*: 120 mg, 180 mg, 240 mg, and 300 mg based on (i) acceptable bioequivalence studies on the 360-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. For modified-release products, dissolution profiles generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 capsules.

Diltiazem Hydrochloride Extended-Release Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 240 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 240 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comments above. *Analytes to measure (in appropriate biological fluid)*: Diltiazem and the active metabolites desacetyldiltiazem and desmethyldiltiazem in plasma. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax. *Bioequivalence based on (90% CI)*: Diltiazem. *Waiver request of in vivo testing*: 120 mg, and 180 mg based on acceptable (i) bioequivalence studies on the 240-mg strength, and (ii) proportional similarity of the formulations, and (iii) acceptable in vitro dissolution testing of all strengths. For modified-release products, dissolution profiles generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three

dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 capsules.

Diltiazem Hydrochloride Extended-Release Capsules/Oral. *Recommended studies*: Three studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 420 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 420 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comments above. (3) *Type of study*: Fasting, sprinkle-in-applesauce. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 420 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please administer the dose after sprinkling the entire contents of the capsule on a teaspoonful of applesauce in accordance with the approved labeling of the RLD. *Analytes to measure (in appropriate biological fluid)*: Diltiazem and the active metabolites desacetyldiltiazem and desmethyldiltiazem in plasma. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax. *Bioequivalence based on (90% CI)*: Diltiazem. *Waiver request of in vivo testing*: 120 mg, 180 mg, 240 mg, 300 mg, and 360 mg based on acceptable (i) bioequivalence studies on the 420-mg strength, and (ii) proportional similarity of the formulations, and (iii) acceptable in vitro dissolution testing of all strengths. For modified-release products, dissolution profiles generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 units.

Divalproex Sodium Delayed-Release Pellets Capsule/Oral. *Recommended studies*: Three studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 125 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Normal liver function test should be required prior to dosing with divalproex sodium in bioequivalence studies. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 125 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. (3) *Type of study*: Fasting sprinkle-in-applesauce. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 125 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure*: Valproic acid in plasma. It is not necessary to measure plasma concentrations of the metabolites. *Bioequivalence based on (90% CI)*: Valproic acid. *Waiver request of in vivo testing*: Not applicable.

Dofetilide Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single dose, two-way crossover in vivo. *Strength*: 0.5 mg. *Subjects*: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. *Additional comments*: A black box warning concerns the risk of drug-induced arrhythmia. The study should be conducted in a facility that can provide continuous cardiac monitoring in the presence of personnel trained in management of serious ventricular arrhythmias. Any subject that develops a prolonged QTc interval should be monitored until the QTc is within normal limits. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 0.5 mg. *Subjects*: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. *Additional comments*: Please see comments above. *Analytes to measure (in appropriate biological fluid)*: Dofetilide in plasma. *Bioequivalence based on (90% CI)*: Dofetilide. Waiver request of in vivo testing: 0.25 mg, 0.125 mg based on (i) acceptable bioequivalence studies on the 0.5-mg strength, (ii) proportionally similar to the 0.5-mg strength, and (iii) acceptable in vitro dissolution testing.

Doxycycline Delayed-Release Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluid)*: Doxycycline in plasma. *Bioequivalence based on (90% CI)*: Doxycycline. *Waiver request of in vivo testing*: Not applicable.

Duloxetine Hydrochloride Delayed-Release Pellets Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *trength*: 60 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. Because of the need to maintain the enteric coating, the subjects in a BE study should be advised not to crush or chew the enteric-coated pellets. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 60 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see above. *Analytes to measure (in appropriate biological fluid)*: Duloxetine in plasma. *Bioequivalence based on (90% CI)*: Duloxetine. *Waiver request of in vivo testing*: 20 mg, 30 mg based on (i) acceptable bioequivalence studies on the 60-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dutasteride Capsules/Oral. *Recommended studies*: Two studies. (1*) Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 0.5 mg. *Subjects*: Normal healthy males. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 0.5 mg. *Subjects*: Normal healthy males. *Additional comments*: *Note*: As an option, because of the relatively long half-life, the firm may wish to conduct these studies using a parallel design. As an additional option for either the crossover or parallel design, the firm may wish to truncate the AUC at 72 hours. *Analytes to measure (in appropriate biological fluid)*: Dutasteride in plasma. *Bioequivalence based on (90% CI)*: Dutasteride. Waiver request of in vivo testing: Not applicable.

Efavirenz Capsules/Oral. *Recommended studies*: One study. *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 200 mg. *Subjects*: Normal healthy males and females, general population *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Efavirenz in plasma. *Bioequivalence based on (90% CI)*: Efavirenz. *Waiver request of invivo testing*: 50 mg and 100 mg based on (i) acceptable bioequivalence study on the 200-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Emtricitabine Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 200 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 200 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comments above. *Analytes to measure*: Emtricitabine in plasma. *Bioequivalence based on (90% CI)*: Emtricitabine. *Waiver request of in vivo testing*: Not applicable.

Esomeprazole Magnesium Delayed-Release Capsules/Oral. *Recommended studies*: Three studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2). *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (3) *Type of study*: Sprinkle. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Fasting study, with treatments sprinkled over a spoonful of applesauce. *Analytes to measure*: Esomeprazole using an achiral assay. *Bioequivalence based on (90% CI)*: Esomeprazole. *Waiver request of in vivo testing*: 20 mg based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. For dissolution method development, please refer to USP, "Delayed-Release (Enteric-Coated) Articles-General Drug Release Standard." Esomeprazole is an acid labile drug substance; therefore, please measure esomeprazole from the beadlets of the EC capsule and not from the dissolution medium (0.1N HCl) during the acid stage; using 12 additional capsules of the test and reference products, proceed to the buffer stage.

Fenofibrate Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 150 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 150 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluid)*: Fenofibric acid, the active metabolite of fenofibrate in plasma. *Bioequivalence based on (90% CI)*: Fenofibric acid. *Waiver request of in vivo testing*: 50 mg and 100 mg based on (i) acceptable bioequivalence studies on the 150-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Fenofibrate Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 130 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 130 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Fenofibric acid in plasma. *Bioequivalence based on (90% CI)*: Fenofibric acid. *Waiver request of in-vivo testing*: 43 mg based on (i) acceptable bioequivalence studies on the 130-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Fexofenadine Hydrochloride Capsules/Oral. *Recommended studies*: One study. *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 60 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Fexofenadine in plasma. *Bioequivalence based on (90% CI)*: Fexofenadine. *Waiver request of in-vivo testing*: Not applicable.

Fluoxetine Hydrochloride; Olanzapine Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 50 mg/6 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 50 mg/6 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Fluoxetine and olanzapine in plasma. *Bioequivalence based on (90% CI)*: Fluoxetine and olanzapine. *Waiver request of in vivo testing*: 25 mg/3 mg, 25 mg/6 mg, 25 mg/12 mg, and 50 mg/12 mg based on (i) acceptable bioequivalence studies on the 50-mg strength/6-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Fluvastatin Sodium Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Because of teratogenicity concerns, female subjects enrolled in these studies should not be pregnant. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluid)*: Fluvastatin in plasma (achiral assay). *Bioequivalence based on (90% CI)*: Fluvastatin. *Waiver request of in vivo testing*: 20 mg based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Gabapentin Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 400 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 400 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Gabapentin in plasma. *Bioequivalence based on (90% CI)*: Gabapentin. *Waiver request of in vivo testing*: 100 mg and 300 mg based on (i) acceptable bioequivalence studies on the 400-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Galantamine Hydrobromide Extended-Release Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 8 mg. *Subjects*: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. *Additional comments*: The most frequent adverse events leading to drug discontinuation are nausea, vomiting, dizziness, and syncope. Please include appropriate safety precautions in your protocols. These include adequate monitoring of vital signs and adverse events, stopping criteria in the event of an unacceptable degree of hypotension or bradycardia, and appropriate evaluation and management of adverse events. Please assure that the investigator(s) will be vigilant in recognizing and managing any unacceptable clinical or laboratory findings. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 8 mg. *Subjects*: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. *Additional comments*: Please see comments above. *Analytes to measure (in appropriate biological fluid)*: Galantamine in plasma. *Bioequivalence based on (90% CI)*: Galantamine. *Waiver request of in vivo testing*: 16 mg, 24 mg based on (i) acceptable bioequivalence studies on the 8-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Ganciclovir Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 500 mg. *Subjects*: Because of safety concerns with the use healthy subjects, the study population should be patients with advanced HIV positive infection, who are at risk for developing cytomegalovirus disease. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 500 mg. *Subjects*: There are safety concerns with using healthy subjects. Therefore, the study population should be patients with advance HIV positive infection who are at risk for developing cytomegalovirus disease. *Additional comments*: *Analytes to measure*: Ganciclovir in plasma. *Bioequivalence based on (90% CI)*: Ganciclovir. *Waiver request of in vivo testing*: 250 mg based on (i) acceptable bioequivalence studies on the 500-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Hydrochlorothiazide Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 12.5 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 12.5 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Hydrochlorothiazide in plasma. *Bioequivalence based on (90% CI)*: Hydrochlorothiazide. *Waiver request of in vivo testing*: Not applicable.

Ibandronate Sodium Tablets/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, parallel design, or two-way crossover in vivo. *Strength*: 2.5 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please include as many postmenopausal women as possible in the studies. (2) *Type of study*: Fasting. *Design*: Single-dose, parallel design, or two-way crossover in vivo. *Strength*: 150 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please include as many postmenopausal women as possible in the studies. *Analytes to measure*: Ibandronate in plasma. *Bioequivalence based on (90% CI)*: Ibandronate. *Waiver request of in vivo testing*: Not applicable.

Indinavir Sulfate Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 400 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 400 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Indinavir in plasma. *Bioequivalence based on (90% CI)*: Indinavir. *Waiver request of in vivo testing*: 100 mg, 200 mg, and 333 mg based on (i) acceptable bioequivalence studies on the 400-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Isradipine Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 5 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 5 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Isradipine in plasma. *Bioequivalence based on (90% CI)*: Isradipine. *Waiver request of in vivo testing*: 2.5 mg based on (i) acceptable bioequivalence studies on the 5-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Itraconazole Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Itraconazole and its active metabolite, hydroxyitraconazole, in plasma.

Bioequivalence based on (90% CI): Itraconazole. *Waiver request of in vivo testing*: Not applicable.

Miglustat Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: single-dose, two-way crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. *Additional comments*: Pregnancy category X. Miglustat may cause fetal harm when administered to a pregnant woman. The drug is contraindicated in women who are or may become pregnant. (2) *Type of study*: Fed. *Design*: single-dose, two-way crossover in vivo. *Strength*: 100 mg *Subjects*: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. *Additional comments*: Please see comments above. *Analytes to measure (in appropriate biological fluid)*: Miglustat in plasma. *Bioequivalence based on (90% CI)*: Miglustat. *Waiver request of in vivo testing*: Not applicable.

Morphine Sulfate Extended-Release Capsules/Oral. *Recommended studies*: Three studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way, crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please use a narcotic antagonist such as naltrexone if the study involves healthy subjects. You should consult a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist. (2) *Type of study*: Fed. *Design*: Single-dose, two-way, crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please use a narcotic antagonist such as naltrexone, if the study involves healthy subjects. You should consult a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist. (3) *Type of study*: Sprinkle. *Design*: Single-dose, two-way, crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please use a narcotic antagonist such as naltrexone, if the study involves healthy subjects. You should consult a physician who is an expert in the administration of opioids for an appropriate dose of narcotic antagonist. *Analytes to measure*: morphine and morphine-6-glucuronide *Bioequivalence based on (90% CI)*: Morphine. *Waiver request of in vivo testing*: 20 mg, 30 mg, 50 mg, and 60 mg based on (i) acceptable bioequivalence studies on the 100-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Because of concerns of dose dumping from this drug product when taken with alcohol, please conduct additional dissolution testing using various concentrations of ethanol in the dissolution medium, as follows: *Testing conditions*: 900 mL, 0.1 N HCl, apparatus I (basket) at 100 rpm, with and without the alcohol (see below): Test 1: 12 units tested according to the proposed method (with 0.1 N HCl), with data collected every 15 minutes for a total of 2 hours. Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP, and data collection every 15 minutes for a total of 2 hours. Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range, and %CV on both strengths.

Mycophenolate Mofetil Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, randomized, two-treatment, two-period, two sequence, crossover in vivo. *Strength*: 250 mg. *Subjects*: Normal healthy males and females, general population. *Additional Comments*: (2) *Type of study*: Fed. *Design*: Single-dose, randomized, two-treatment, two-period, two sequence, crossover in vivo. *Strength*: 250 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Mycophenolate mofetil, and the active metabolite, mycophenolic acid (MPA) in plasma. *Bioequivalence based on (90% CI)*: Mycophenolate mofetil. If mycophenolate mofetil plasma concentrations can be reliably measured and its pharmacokinetics accurately determined, please analyze the data for the parent compound using the confidence interval approach. The data for the active metabolite can be used as supportive evidence. However, if you can demonstrate that it is not possible to measure mycophenolate mofetil in plasma accurately and reliably, please analyze the metabolite using the confidence interval approach. *Waiver request of in vivo testing*: Not applicable.

Olsalazine Sodium Capsule/Oral. *Recommended studies*: One study. *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 250 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please use the lowest single dose possible to obtain accurate pharmacokinetic parameters for both olsalazine and mesalamine. Please enroll enough subjects to achieve adequate statistical power to demonstrate bioequivalence to the RLD. A pilot study may be necessary to assist in the determination of the appropriate number of subjects to enroll in the pivotal study. The number of subjects should be sufficient to allow for dropouts. You may also refer to Appendix C of the Guidance for Industry, "Statistical Approaches to Establishing Bioequivalence" at http://www.fda.gov/cder/guidance/index.htm. *Analytes to measure (in appropriate biological fluid)*: Olsalazine and mesalamine in plasma. *Bioequivalence based on (90% CI)*: Olsalazine and mesalamine. *Waiver request of in vivo testing*: Not applicable. In addition, please perform dissolution testing over a range of pH values comparing the test and reference products. Varying pH conditions should be studied to approximate the pH conditions that olsalazine sodium capsules will be subjected to in the GI tract. Therefore, the following pH conditions should be used using 12 dosage units of the test and reference products: *Apparatus*: USP apparatus I (basket). *Speed*: 100 rpm. *Medium*: 0.1N HCl; pH 4.5 buffer; pH 6.8 buffer. *Volume*: 900 mL *Sampling times*: 5, 10, 15, 20, 30, 45, and 60 minutes and until at least 80% of the labeled content is dissolved.

Omeprazole Delayed–Release Capsule/Oral. *Recommended studies*: Four studies (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fasting, sprinkle. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please administer the dose after sprinkling the entire contents of the capsule on a teaspoonful of applesauce in accordance with the approved labeling of the RLD. (3) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (4) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 20 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Omeprazole in plasma. *Bioequivalence based on (90% CI)*: Omeprazole. *Waiver request of in vivo testing*: 10 mg based on (i) acceptable bioequivalence studies on the 20-mg strength, (ii) proportional similarity of the formulations on 10- and 20-mg strengths, and (iii) acceptable in vitro dissolution testing of 10 mg and 20 mg strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products.

Paricalcitol Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 4 μg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 4 μg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluid)*: Paricalcitol in plasma. *Bioequivalence based on (90% CI)*: Paricalcitol. *Waiver request of in vivo testing*: 2-μg, 1-μg tablets, based on (i) acceptable bioequivalence studies of the 4-μg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Phenytoin Sodium Extended-Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: Single dose of 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Washout period of at least 14 days. The single dose studies for fasting and fed can be conducted as single dose, two-treatment, four periods, replicated design. The strength(s) designated in the Orange Book as the RLD should be used in the studies. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: Singledose of 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comments above. *Analytes to measure*: Phenytoin in plasma. *Bioequivalence based on (90% CI)*: Phenytoin. *Waiver request of in vivo testing*: 200 mg based on (i) acceptable bioequivalence studies on the 300-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the USP method. In addition to the method above, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Phenytoin Sodium Extended-Capsule/Oral. *Recommended studies*: Four studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: Single dose of 300 mg (3 × 100 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Washout period of at least 14 days. The single dose studies for fasting and fed can be conducted as single dose, two-treatment, four periods, replicated design. The strength(s) designated in the Orange Book as the RLD should be used in the studies. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: Single dose of 300 mg (3 × 100 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comments above. (3) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: Single-dose of 300 mg (10 × 30 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comments above. (4) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: Single dose of 300 mg (10 × 30 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comments above. *Analytes to measure*: Phenytoin in plasma. *Bioequivalence based on (90% CI)*: Phenytoin. *Waiver request of in-vivo testing*: Not applicable. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the USP method. In addition to the method above, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Quinine Sulfate Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 324 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Subjects with a QTc interval of >480 msec by ECG should also be excluded. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 324 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comments above. *Analytes to measure (in appropriate biological fluid)*: Quinine in plasma. *Bioequivalence based on (90% CI)*: Quinine. *Waiver request of in vivo testing*: Not applicable.

Ramipril Capsule/Oral. Recommended studies: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 10 mg.

Subjects: Normal healthy males and females, general population. *Additional comments*: Female subjects enrolled in the BE studies should not be pregnant, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 10 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluid)*: Ramipril and the metabolite, ramiprilat in plasma. *Bioequivalence based on (90% CI)*: Ramipril. If ramipril can be reliably measured, a confidence interval approach for bioequivalence determination should be used for ramipril. If ramipril cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for ramiprilat. *Waiver request of in- vivo testing*: 1.25 mg, 2.5 mg, and 5 mg based on (i) acceptable bioequivalence studies on the 10-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Ribavirin Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 200 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 200 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Ribavirin in plasma. *Bioequivalence based on (90% CI)*: Ribavirin. *Waiver request of in-vivo testing*: Not applicable.

Rifampin Capsule/Oral. *Recommended studies*: One study. *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Rifampin in plasma. *Bioequivalence based on (90% CI)*: Rifampin. *Waiver request of in- vivo testing*: 150 mg based on (i) acceptable bioequivalence studies on the 300-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please submit separate applications for each strength. You may cross-refer the study submitted in the application for the higher strength to request waivers of in vivo testing for the lower strength. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the USP method.

Ritonavir Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Ritonavir in plasma. *Bioequivalence based on (90% CI)*: Ritonavir. *Waiver request of in- vivo testing*: Not applicable.

Saquinavir Mesylate Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 200 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 200 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Saquinavir in plasma. *Bioequivalence based on (90% CI)*: Saquinavir. *Waiver request of in-vivo testing*: Not applicable.

Sibutramine Hydrochloride Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 15 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Because of safety concerns, studies should not be conducted using doses higher than 15 mg. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 15 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure*: Sibutramine, and the major first-generation active (desmethyl) metabolites M1 and M2, using an achiral assay. *Bioequivalence based on (90% CI)*: Sibutramine. If sibutramine can be reliably measured, a confidence interval approach for bioequivalence determination should be used for sibutramine. If sibutramine cannot be reliably measured, a confidence interval approach for bioequivalence determination should be used for major first-generation active (desmethyl) metabolites M1 and M2. *Waiver request of in vivo testing*: 5 mg and 10 mg based on (i) acceptable bioequivalence studies on the 15-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Stavudine Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 40 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Stavudine in plasma. *Bioequivalence based on (90% CI)*: Stavudine. *Waiver request of in -vivo testing*: 15 mg, 20 mg, and 30 mg based on (i) acceptable bioequivalence studies on the 40-mg strength, (ii) acceptable dissolution testing of the 15-, 20-, 30-mg, and 40-mg strengths, and (iii) proportional similarity in the formulations of the 15-, 20-, 30-, and 40-mg strengths.

Tacrolimus Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 5 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 5 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comments above. *Analytes to measure (in appropriate biological fluid)*: Tacrolimus in whole blood. *Bioequivalence based on (90% CI)*: Tacrolimus. *Waiver request of in-vivo testing*: 0.5 mg and 1 mg, based on (i) acceptable bioequivalence studies on the 5-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Tamsulosin Hydrochloride Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 0.4 mg. *Subjects*: Normal, healthy, males and females, general

population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 0.4 mg. *Subjects*: Normal, healthy, males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Tamsulosin in plasma. *Bioequivalence based on (90% CI)*: Tamsulosin. *Waiver request of in vivo testing*: Not applicable.

Terazosin Hydrochloride Capsules/Oral. Recommended studies: One study. *Type of study:* Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 2 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Because of safety concerns, the studies should be conducted using the 2-mg strength. *Analytes to measure*: Terazosin in plasma. *Bioequivalence based on (90% CI)*: Terazosin. *Waiver request of in vivo testing*: 1 mg, 5 mg, and 10 mg based on (i) acceptable bioequivalence studies on the 2-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Tipranavir Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 250 mg (please administer a 500-mg dose; 2 × 250 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 250 mg (please administer a 500-mg dose; 2 × 250 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluid)*: Tipranavir in plasma. *Bioequivalence based on (90% CI)*: Tipranavir. *Waiver request of in vivo testing*: Not applicable.

Tizanidine Hydrochloride Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 6 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 6 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Tizanidine in plasma. *Bioequivalence based on (90% CI)*: Tizanidine. *Waiver request of invivo testing*: 2 mg and 4 mg based on (i) acceptable bioequivalence studies on the 6-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Tolterodine Tartrate Extended–Release Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 4 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 4 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Tolterodine and the 5-hydroxymethyl tolterodine (5-OHM) metabolite in plasma. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax. *Bioequivalence based on (90% CI)*: Tolterodine. *Waiver request of in vivo testing*: 2 mg, based on (i) acceptable bioequivalence studies on the 4-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. For modified-release products, dissolution profiles generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer, water) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, and 4 hours and every 2 hours thereafter, until at least 80% of the drug is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 capsules.

Topiramate Sprinkle Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 25 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 25 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comments above. *Analytes to measure (in appropriate biological fluid)*: Topiramate in plasma. *Bioequivalence based on (90% CI)*: Topiramate. *Waiver request of in vivo testing*: 15 mg based on (i) acceptable bioequivalence studies on the 25-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Triamterene Capsule/Oral. *Recommended studies*: One study. *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Triamterene in plasma. *Bioequivalence based on (90% CI)*: Triamterene. *Waiver request of in vivo testing*: 50 mg based on (i) acceptable bioequivalence study on the 100-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the USP method.

Venlafaxine Hydrochloride Extended-Release Capsule/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 150 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Because of safety concerns, bioequivalence studies under fasting conditions are not recommended. (2) *Type of study*: Fed, Sprinkle. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 150 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please administer the dose after sprinkling the entire contents of the capsule on a teaspoonful of applesauce in accordance with the approved labeling of the reference product under fed conditions. Please see comment above. *Analytes to measure*: Venlafaxine, and its metabolite *O*-desmethylvenlafaxine, in plasma. *Bioequivalence based on (90% CI)*: Venlafaxine. *Waiver request of in vivo testing*: 37.5 mg and 75 mg based on (i) acceptable

bioequivalence studies on the 150-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Verapamil Hydrochloride Extended-Release Capsules/Oral. *Recommended studies*: Three studies.(1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 360 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 360 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (3) *Type of study*: Fasting, sprinkled over applesauce. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 360 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Verapamil and its metabolite, norverapamil, in plasma. Please submit the metabolite data as supportive evidence of the comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax. *Bioequivalence based on (90% CI)*: Verapamil. *Waiver request of in vivo testing*: 120 mg, 180 mg, and 240 mg based on (i) acceptable bioequivalence studies on the 360-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. For modified-release products, dissolution profiles generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 phosphate buffer, water) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, 4, and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 capsules.

Verapamil Hydrochloride Extended-Release Capsules/Oral. *Recommended studies*: Three studies. (1) *Type of study*: Fasting, bedtime (PM) dosing. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Bedtime (PM) dosing. (2) *Type of study*: Fed, morning (AM) dosing. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Morning (AM) dosing. (3) *Type of study*: Fasting, sprinkled over applesauce, morning (AM) dosing. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 300 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Morning (AM) dosing. *Analytes to measure*: Verapamil and its metabolite, norverapamil in plasma utilizing a validated LC/MS/MS method. For norverapamil, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax. The following sampling times are recommended: pre-dose and 2, 3, 4, 6, 7, 8, 9, 10, 12, 14, 16, 20, 24, 30, 36, and 48 hours post dose. *Bioequivalence based on (90% CI)*: Verapamil. *Waiver request of in vivo testing*: 100 mg and 200 mg based on (i) acceptable bioequivalence studies on the 300-mg *strength*, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. For modified-release products, dissolution profiles generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 phosphate buffer, water) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. The following sampling times are recommended: 1, 2, 4, and every 2 hours thereafter, until at least 80% of the labeled content is dissolved. Comparative dissolution profiles should include individual tablet data as well as the mean, range, and standard deviation at each time point for 12 capsules.

Zidovudine Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Zidovudine in plasma. *Bioequivalence based on (90% CI)*: Zidovudine. *Waiver request of in vivo testing*: Not applicable. Please conduct dissolution testing on 12 dosage units each of the test and reference products using the USP method.

Ziprasidone Hydrochloride Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 20 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Given that the risk of QT prolongation is associated with higher doses and little, if any, such effect is expected with a 20-mg dose, a screening EKG to exclude subjects with prolonged QT, or other EKG abnormality is recommended, along with monitoring of vital signs and adverse events. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 20 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure*: Ziprasidone in plasma. *Bioequivalence based on (90% CI)*: Ziprasidone. *Waiver request of in vivo testing*: 40 mg, 60 mg, and 80 mg based on (i) acceptable bioequivalence studies on the 20-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Zonisamide Capsules/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. *Additional comments*: Since zonisamide has a long

half-life, you can consider performing a parallel design study, truncating the AUC at 72 hours. If you choose to do a crossover design study, the washout period should be adequate to provide for drug elimination. Please verify that zonisamide's clearance has low intrasubject variability. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 100 mg. *Subjects*: Normal healthy males and females, general population. Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. *Additional comments*: Please see *Additional comments* above. *Analytes to measure (in appropriate biological fluid)*: Zonisamide in serum *Bioequivalence based on (90% CI)*: Zonisamide. *Waiver request of invivo testing*: 25 mg and 50 mg, based on acceptable (i) bioequivalence studies on the 100-mg capsule, and (ii) proportional similarity of the formulations, and (iii) acceptable in vitro dissolution testing of all strengths.

Dissolution Testing of Uncompressed Solid Dosage Forms

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Acetaminophen/butalbital/caffeine/codeine phosphate	Capsule	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, 45, and 60	03/04/2006
Acetaminophen/caffeine/dihydrocodeine bitartrate	Capsule	I (Basket)	100	Water	900	10, 20, 30, 45, and 60	01/03/2007
Acitretin	Capsule	I (Basket)	100	3% SLS in water, pH 9.6	900	10, 20, 30, and 45	01/12/2004
Acrivastine/pseudoephedrine HCl	Capsule	II (Paddle)	50	0.01 N HCl	900	5, 10, 15, and 30	01/12/2004
Amlodipine besylate/benazepril HCl	Capsule	I (Basket)	100	0.01 N HCl	500	10, 20, 30, 45, and 60	06/20/2007
Amphetamine ER	Capsule	II (Paddle)	50	750 mL of dilute HCl, pH 1.1 for the first 2 hr, then add 200 mL of 200 mM phosphate buffer, and adjust to pH 6 (w/HCl or NaOH) for the remainder	750 mL of dilute HCl, 200 mL of phosphate buffer	1, 2, 3, 4, and 6 hr	08/17/2006
Amprenavir	Capsule	II (Paddle)	50	0.1 N HCl	900	10, 15, 30, and 45	02/19/2008
Anagrelide HCl	Capsule	I (Basket)	100	0.1 N HCl	900	5, 10, 15, 30, and 45	01/14/2004
Aprepitant	Capsule	II (Paddle)	100	2.2% sodium dodecyl sulfate in distilled water	900	10, 15, 20, 30, and 45	01/20/2006
Aspirin/dipyridamole	Capsule	I (Basket)	100	0.01 N HCl for first hour, 0.1 M phosphate buffer, pH 5.5, thereafter	0–1 hr: 900 mL. 900 mL thereafter	Acid stage: 10, 20, 30, 45, and 60 min. Buffer stage: 1, 2, 5, and 7 hr	10/09/2007
Atazanavir sulfate	Capsule	II (Paddle)	50	0.025 N HCl	1000	10, 20, 30, and 45	01/20/2006
Atomoxetine HCl	Capsule	II (Paddle)	50	0.1 N HCl	1000	10, 20, 30, and 45	12/20/2005
Auranofin	Capsule	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	01/15/2004
Balsalazide disodium	Capsule	II (Paddle) with sinker	50	pH 6.8 buffer	900	10, 20, 30, and 45	01/26/2006
Benzonatate	Capsule			Refer to USP			
Bexarotene	Capsule	II (Paddle)	50	Tier 1 medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5. Tier 2 medium: 0.5% HDTMA in 0.05 M phosphate buffer, pH 7.5 with 0.05 g/L pancreatin enzyme	900	15, 30, 45, and 60	08/17/2006

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Cefdinir	Capsule	II (Paddle)	50	Phosphate buffer, pH 6.8	900	5, 10, 15, 30, and 45	07/25/2007
Celecoxib	Capsule	II (Paddle)	100 mg and 200 mg: 50 rpm; 400 mg: 75 rpm	Tier 1 medium: 0.04 M tribasic sodium phosphate (pH 12) with 1% SLS. Tier 2 initial medium: 750 mL of simulated gastric fluid, USP (includes pepsin) At 20 min, 180 mL of 5% SLS solution and 70 mL of 1.2 N NaOH are added to initial medium. Tier 2 final medium: 1% SLS, pH 12	Tier 1: 1000 mL. Tier 2: 750 mL (initial) 1000 mL (final)	15, 30, 45, and 60	08/17/2006
Cevimeline HCL	Capsule	II (Paddle) with option to use a sinker	50	0.1 N HCl	900	5, 10, 15, and 30	01/26/2006
Cysteamine bitartrate	Capsule	I (Basket)	75	0.1 N HCl	900	10, 20, 30, and 45	01/24/2004
Danazol	Capsule			Refer to USP			06/18/2007
Dantrolene sodium	Capsule	I (Basket)	100	0.5% hyamine 10 times in water, adjust to pH 6.8 with 0.1 N KOH or 0.1 N HCl	900	10, 20, 30, 40, and 60	01/27/2004
Demeclocycline HCl	Capsule			Refer to USP			07/25/2007
Dicloxacillin sodium	Capsule			Refer to USP			06/18/2007
Diphenhydramine hydrochloride/ibuprofen	Capsule	I (Basket)	100	200 mM phosphate buffer, pH 7.2	900	10, 20, 30, and 45	01/14/2008
Dofetilide	Capsule	I (Basket)	100	0.001 M HCL	900	10, 15, 30, and 45	01/20/2006
Dronabinol	Capsule	II (Paddle)	100 and 150	10% labrasol in water; (In addition, the USP capsule rupture test should also be conducted)	500	5, 10, 15, 30, 45, 60, and until at least 80% of the labeled content is released	01/31/2007
Efavirenz	Capsule	II (Paddle). A sinker may be used with justification if necessary.	50	1% sodium lauryl sulfate in water	900	15, 30, 45, and 60	03/22/2006
Emtricitabine	Capsule	II (Paddle)	50	Tier 1: 0.1 N HCl. Tier 2: 0.1 N HCl containing pepsin 750,000 USP units/L. Tier 2 is used after failure of tier 1 testing	900	10, 20, 30, and 45	12/16/2005
Fenofibrate	Capsule	II (Paddle)	75	Phosphate buffer w/2% between 80 and 0.1% pancreatin, pH 6.8	900	15, 30, 45, 60, 90, and 120	02/19/2008
Fexofenadine HCl	Capsule	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, 45, and 60	01/29/2004

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Fluoxetine/olanzapine	Capsule	II (Paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	08/17/2006
Fluvastatin sodium	Capsule			Refer to USP			01/14/2008
Gabapentin	Capsule	II (Paddle)	50	0.06 N HCl	900	5, 10, 20, and 30	01/30/2004
Ganciclovir	Capsule	II (Paddle)	60	Water (deaerated)	900	10, 20, 30, 45, and 60	02/02/2004
Hydrochlorothiazide	Capsule	I (Basket)	100	0.1 N HCl	900	10, 20, 30, and 45	02/03/2004
Ibuprofen/diphenhydramine	Capsule	I (Basket)	100	Phosphate buffer (200 mM), pH 7.2	900	10, 20, 30, and 45	01/03/2007
Ibuprofen/pseudoephedrine HCl	Capsule	I (Basket)	150	Tier 1: 0.05 M phosphate buffer, pH 7.2. Tier 2: 0.05 M phosphate buffer, pH 7.2 with NMT 1750 USP protease units/L of 1 time USP pancreatin	900	10, 20, 30, and 45	03/04/2006
Imipramine pamoate	Capsule	I (Basket)	100	0.1 N HCl without pepsin and with 0.3% pepsin (addition of pepsin is recommended only when significant slow dissolution is observed)	900	30, 60, 90, 120, 150, and 180	01/14/2008
Indinavir sulfate	Capsule	II (Paddle)	50	0.1 M citrate buffer, pH 3.8	900	10, 15, 20, and 30	02/04/2004
Isradipine	Capsule	II (Paddle)	50	0.1% lauryl dimethylamine oxide (LDAO) in water	500	10, 20, 30, 45, and 60	02/25/2004
Itraconazole	Capsule	II (Paddle)	100	SGF without enzyme	900	10, 20, 30, 45, 60, and 90	02/04/2004
Ketoprofen	Capsule	II (Paddle)	50	0.05 M phosphate buffer pH 7.4	1000	10, 20, 30, and 45	07/25/2007
Lithium carbonate	Capsule			Refer to USP			07/25/2007
Metronidazole	Capsule	I (Basket)	100	0.1 N HCl	900	10, 20, 30, and 45	02/09/2004
Miglustat	Capsule	I (Basket)	100	0.1 N HCl	1000	10, 20, 30, and 45	01/03/2007
Mycophenolate mofetil	Capsule	II (Paddle)	40	0.1 N HCl	900	5, 10, 20, and 30	02/10/2004
Nicardipine HCl	Capsule	II (Paddle)	50	0.033 M citric acid buffer, pH 4.5	900	10, 20, 30, and 45	02/11/2004
Nimodipine	Capsule	II (Paddle)	50	0.5% SDS in water	900	10, 20, 30, and 45	04/09/2007
Nizatidine	Capsule			Refer to USP			01/14/2008
Olsalazine sodium	Capsule	I (Basket)	100	Phosphate buffer, pH 7.5	900	10, 20, 30, and 45	02/12/2004
Orlistat	Capsule	II (Paddle)	75	3% SLS in 0.5% sodium chloride, pH 6.0	900	10, 20, 30, 45, and 60	02/12/2004
Oseltamivir phosphate	Capsule	II (Paddle)	50	0.1 N HCl	900	5, 10, 20, and 30	01/03/2007
Paricalcitol	Capsule	I (Basket)	100	4 mg/mL (0.4%) lauryldimethylamine N-oxide (LDAO)	500	20, 30, 45, 60	06/18/2007

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Paromomycin sulfate	Capsule	I (Basket)	50	0.05 M phosphate buffer, pH 6.8	900	5, 10, 15, 20, 30, and 45	02/13/2004
Phentermine HCl	Capsule			Refer to USP			01/14/2008
Phenytoin sodium	Capsule			Refer to USP			06/18/2007
Pregabalin	Capsule	II (Paddle)	50	0.06 N HCl	900	10, 20, 30, and 45	03/22/2006
Quinine sulfate	Capsule			Refer to USP			01/14/2008
Ramipril	Capsule	II (Paddle)	50	0.1 N HCl	500	10, 20, 30, and 45	02/18/2004
Ranitidine HCl	Capsule	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	02/18/2004
Ribavirin	Capsule	I (Basket)	100	Water (deaerated)	900	10, 20, 30, and 45	02/18/2004
Rifampin	Capsule			Refer to USP			06/18/2007
Ritonavir	Capsule	II (Paddle)	50	0.1 N HCl with 25 mM polyoxyethylene 10 laurylether (POE10LE)	900	10, 20, 30, and 45	02/18/2004
Rivastigmine tartrate	Capsule	II (Paddle)	50	Water (deaerated)	500	10, 20, 30, and 45	01/03/2007
Saquinavir mesylate	Capsule			Refer to USP			09/13/2007
Sibutramine HCl	Capsule	II (Paddle)	50	0.05 M acetate buffer, pH 4.0	500	10, 20, 30, 45, and 60	02/25/2004
Stavudine	Capsule			Refer to USP			06/18/2007
Succimer	Capsule	II (Paddle)	50	0.01 N phosphoric acid	900	10, 20, 30, 45, 60, and 90	02/20/2004
Tacrolimus	Capsule	II (Paddle)	50	Hydroxypropyl cellulose solution (1 in 20,000). Adjust to pH 4.5 by phosphoric acid	900	30, 60, 90, and 120	02/20/2004
Tamsulosin HCl	Capsule	II (Paddle)	100	0–2 hr: 0.003% polysorbate 80, pH 1.2 2–8 hr: phosphate buffer, pH 7.2	500	1, 2, 3, 6, 8, and 10 hr	03/26/2007
Temazepam	Capsule			Refer to USP			01/14/2008
Temozolomide	Capsule	I (Basket)	100	Distilled water	500	10, 20, 30, and 45	01/03/2007
Terazosin HCl	Capsule	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, 45, 60, and 90	02/20/2004
Thalidomide	Capsule	II (Paddle)	100	1.5% (w/v) SLS (pH 3.0, adj w/HCl)	900	10, 20, 30, 60, and 90	03/04/2006
Tipranavir	Capsule	II (Paddle)	50	0.05 M phosphate buffer pH 6.8	900	15, 30, 45, and 60	12/03/2007
Tizanidine HCl	Capsule	II (Paddle)	50	0.01 N HCl	500	5, 10, 15, and 30	02/20/2004
Triamterene	Capsule			Refer to USP			06/18/2007
Trimipramine maleate	Capsule	I (Basket)	100	Water (deaerated)	1000	10, 20, 30, 45, 60, and 90	03/04/2006
Vancomycin hydrochloride	Capsule			Refer to USP			01/14/2008
Zaleplon	Capsule	II (Paddle)	75	Deionized water	900	5, 10, 20, and 30	01/03/2007

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Zidovudine	Capsule			Refer to USP			06/18/2007
Zinc acetate	Capsule	II (Paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	02/19/2004
Ziprasidone HCl	Capsule	II (Paddle)	75	Tier 1: 0.05 M Na phosphate buffer, pH 7.5 + 2% SDS (w/w). Tier 2: 0.05 M Na phosphate buffer, pH 7.5 (700 mL) + 1% pancreatin. After 15-min incubation, add 200 mL of phosphate buffer containg 9% SDS	900	10, 20, 30, 45, and 60	03/04/2006
Zonisamide	Capsule	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	01/03/2007
Didanosine	Capsule (delayed-release pellets)	I (Basket)	100	Acid stage: 0.1 N HCl. Buffer stage: 0.1 N HCl: 0.2 M tribasic sodium phosphate (3:1), pH 6.8	1000	Acid stage: 60, 90 and 120. Buffer stage: 10, 20, 30, 45, and 60	01/26/2004
Duloxetine HCl	Capsule (delayed-release pellets)	I (Basket)	100	Gastric challenge: 0.1 N HCl. Buffer medium: pH 6.8 phosphate buffer (USP)	1000	Acid stage: 120 min. Buffer stage: 15, 30, 45, 60, and 90 min	03/22/2006
Esomeprazole magnesium	Capsule (delayed-release pellets)	II (Paddle)	100	Acid stage: 0.1 N HCl. Buffer stage: sodium phosphate buffer, pH 6.8	Acid stage: 300. Buffer stage: 1000	Acid stage: 60, 90, and 120. Buffer stage: 10, 20, 30, 45, and 60	02/26/2004
Doxycycline	Capsule (delayed release)	II (Paddle)	75	Dilute HCl, pH 1.1 for 2 hr and then add 200 mL of 0.1 N NaOH in 200 mM phosphate buffer. Adjust pH to 6.0 using 2 N HCl and/or 2 N NaOH	Acid stage: 750. Buffer stage: 950.	0.5, 1, 2, 2.5, 3, and 4 hr	02/19/2008
Omeprazole	Capsule (delayed release)			Refer to USP			06/18/2007
Amphetamine aspartate/amphetamine sulfate/ dextroamphetamine saccharate/ dextroamphetamine sulfate	Capsule (extended release)	II (Paddle)	50	Dilute HCl, pH 1.1 for first 2 hr, then add 200 mL of 200 mM phosphate buffer and adjust to pH 6.0 for the remainder	0–2 hr: 750 mL. After 2 hr: 950 mL	0.5, 1, 2, 3, and 4 hr	07/25/2007
Carbamazepine	Capsule (extended release)	II (Paddle)	75	First 4 hr: Dilute acid, pH 1.1 with 1.8% *B*-cyclodextrin. After 4 hr: 50 mM phosphate buffer, pH 7.5 with 1.1% *B*-cyclodextrin.	First 4 hr: 600 mL. After 4 hr: 1000 mL	1, 2, 4, 8, and 10 hr	07/25/2007
Dexmethylphenidate HCl	Capsule (extended release)	I (Basket)	100	First 2 hr: 0.01 N HCl, Hours 2–10: phosphate buffer, pH 6.8	Acid stage: 500. Buffer stage: 500	0.5, 1, 2, 4, 6, and 10 hr	01/14/2008
Diltiazem HCl (AB2)	Capsule (extended release)			Refer to USP			02/19/2008

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Diltiazem HCl (AB3)	Capsule (extended release)			Refer to USP			02/19/2008
Diltiazem HCl (AB4)	Capsule (extended release)			Refer to USP			02/19/2008
Galantamine HBr	Capsule (extended release)	II (Paddle)	50	50 mM potassium dihydrogen phosphate buffer pH 6.5 comparative dissolution data should also be provided in 900 mL pH 0.1 HCl, pH 4.5 buffer, and water using apparatus II (Paddle) at 50 rpm.	900	1, 4, 10, and 12 hr	01/20/2006
Indomethacin	Capsule (extended release)			Refer to USP			07/25/2007
Methylphenidate HCl	Capsule (extended release)	I (Basket)	75	0–2 hr: 0.01 N HCl. 2–10 hr: phosphate buffer, pH 6.8.	0–2 hrs: 500. 2–10 hr: 500	0.5, 1, 3, 6, 8, and 10 hr	07/25/2007
Morphine sulfate	Capsule (extended release)	II (Paddle)	50	Phosphate buffer, pH 6.8	900	1, 3, 6, 12, 24 hr	01/14/2008
Morphine sulfate	Capsule (extended release)	I (Basket)	100	Acid stage: 0.1 N HCl. Buffer stage: phosphate buffer, pH 7.5	Acid stage: 600. Buffer stage: 500	1, 4, 6, 9, and 12 hr	01/14/2008
Propafenone HCl	Capsule (extended release)	II (Paddle)	50	0–2 hr: 0.08 N HCl. 2–15 hr: phosphate buffer, pH 6.8	900	1, 2, 4, 8, 10,12, and 15 hr	03/11/2008
Propranolol HCl	Capsule (extended release)			Refer to USP			07/25/2007
Tolterodine tartrate	Capsule (extended release)	I (Basket)	100	Phosphate buffer (pH 6.8)	900	1, 3, 7 hr	06/18/2007
Venlafaxine HCl	Capsule (extended release)	I (Basket)	100	Water	900	2, 4, 8, 12, and 20 hr	01/03/2007
Verapamil HCl (100, 200, 300 mg)	Capsule (extended release)	I (Basket)	75	Water, pH 3.0 (adjusted with 0.1 N or 2 N HCl)	1000	1, 4, 8, 11, and 24 hr	01/03/2007
Cyclosporine (100 mg) (AB1)	Capsule (liquid filled)	II (Paddle)	75	0.1 N HCl containing 4 mg of *N,N*-dimethydodecylamine-N-oxide per mL	1000	10, 20, 30, 45, 60, and 90	01/14/2008
Cyclosporine (25 mg) (AB1)	Capsule (liquid filled)	II (Paddle)	75	0.1 N HCl containing 4 mg of *N,N*-dimethydodecylamine-N-oxide per mL	500	10, 20, 30, 45, 60, and 90	01/14/2008
Fenofibrate (AB)	Capsule (Micronized)	II (Paddle)	75	0.05 M SLS in water	1000	10, 20, 30, 40, and 60	01/29/2004

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Dutasteride	Capsule (soft gelatin)	II (Paddle)	50	Tier 1: dissolution medium: 0.1 N HCl with 2% (w/v) sodium dodecyl sulfate (SDS) (900 mL). Tier 2: dissolution medium: 0.1 N HCl with pepsin (1.6 g/L, label activity 1:3000) (450 mL) for the first 25 min, followed by addition of 0.1 N HCl with SDS (4% w/v) (450 mL) for the remainder of the dissolution test.	900	15, 30, 45, and 60	01/26/2006
Ibuprofen potassium (Soft gelatin cap gel—liquid filled)	Capsule (soft gelatin/ liquid fill)	I (Basket)	150	Phosphate buffer, pH 7.2	900	5, 10, 20, and 30	02/04/2004
Lopinavir/ritonavir	Capsule (soft gelatin)	II (Paddle)	50	Tier 1: 0.05 M polyoxyethylene 10 lauryl ether with 10 mM sodium phosphate monobasic (pH 6.8). Tier 2: same as above with NMT 1750 USP units/L of pancreatin	900	10, 15, 30, and 45	06/18/2007
Divalproex sodium	Capsule (sprinkle)	II (Paddle)	50	0.05 M phosphate buffer, pH 7.5	500	2, 4, 6, 8, and 10 hr	03/04/2006
Topiramate	Capsule (sprinkle)	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, 45, and 60	02/19/2004
Verapamil HCl (120, 180, 240, 360 mg)	Capsule (sustained release)	I (Basket)	75	Water, pH 3.0 (adjusted with 0.1 N or 2 N HCl)	1000	1, 4, 8, 11, and 24 hr	01/03/2007
Procarbazine HCl	Capsules	II (Paddle)	50	Water	900	10, 20, 30, 45, and 60	01/14/2008
Fluoxetine	Capsules (delayed release)			Refer to USP			07/25/2007
Nelfinavir mesylate	Powder for suspension	II (Paddle)	50	0.1 N HCl	900	5, 10, 15, 20, 30, and 45	09/13/2007
Omeprazole sodium bicarbonate	Powder for suspension (immediate release)	II (Paddle)	50	0.25 mM sodium phosphate buffer, pH 7.4	900	5, 10, 15, and 30	06/20/2007

Approved Excipients in Uncompressed Solid Dosage Forms

Ingredient	Dosage Form	Qty	Unit
Acacia	Oral; capsule, sustained action	11.77	mg
Acacia	Oral; powder, for oral suspension	64.8	%
Acacia	Oral; powder	80	%
Acacia syrup	Oral; capsule, sustained action	69.64	mg
Acesulfame potassium	Oral; powder, for suspension	0.9	%
Acesulfame potassium	Oral; powder, for oral solution	117	mg
Acetophenone	Oral; capsule, soft gelatin	0.01	mg
Acetylated monoglycerides	Oral; capsule, sustained action	0.593	mg
Acetylated monoglycerides	Oral; capsule, extended release	2.37	mg
Acetyltributyl citrate	Oral; capsule, enteric-coated pellets	7.6	mg
Acetyltributyl citrate	Oral; capsule, sustained action	18.98	mg
Alcohol	Oral; capsule	0.058	mg
Alcohol	Oral; capsule, soft gelatin	15.36	mg
Alcohol, dehydrated	Oral; capsule, soft gelatin	159.6	mg
Alcohol, dehydrated	Oral; capsule	200	mg
Alcohol, diluted	Topical; powder, for solution	40	%
Alginic acid	Oral; capsule	80	mg
Alpha-tocopherol	Oral; capsule	0.5	mg
Alpha-tocopherol	Oral; capsule, soft gelatin	5	mg
Aluminum stearate	Oral; capsule, sustained action	0.4	mg
Amberlite	Oral; capsule	4.86	mg
Amberlite IR-120	Oral; capsule, sustained action	12	mg
Ammonia solution, strong	Oral; capsule, sustained action	0.05	mg
Ammonio methacrylate copolymer	Oral; capsule, sustained action	81.1	mg
Ammonio methacrylate copolymer type A	Oral; capsule, extended release	4.2	mg
Ammonio methacrylate copolymer type B	Oral; capsule, extended release	37.48	mg
Ammonium glycyrrhizate	Oral; granule	3.125	mg
Anidrisorb 85/70	Oral; capsule	35.09	mg
Anidrisorb 85/70	Oral; capsule, soft gelatin liquid-filled	93.4	mg
Anidrisorb 85/70	Oral; capsule, soft gelatin	123	mg
Antifoam	Oral; capsule, sustained action	0.16	mg
Ascorbic acid	Oral; capsule	7	mg
Ascorbyl palmitate	Oral; capsule	12	mg
Aspartame	Oral; powder, for oral suspension	1	%
Aspartame	Oral; powder, for reconstitution	1.25	%

Ingredient	Dosage Form	Qty	Unit
Aspartame	Oral; powder, for suspension	2	%
Aspartame	Oral; powder, for solution	4.7	%
Aspartame	Oral; granule, for suspension	35	mg
Aspartame	Oral; powder	45	%
Aspartame	Oral; powder, for oral solution	233	mg
Beeswax	Oral; capsule	2	mg
Beeswax	Oral; capsule, sustained action	15.7857	mg
Beeswax	Oral; capsule, soft gelatin	16.8	mg
Bentonite	Topical; powder	66.64	%
Benzyl alcohol	Oral; capsule, sustained action	1.231	mg
Benzyl alcohol	Oral; capsule	15	mg
Benzyl benzoate	Oral; capsule	0.6084	mL
Beta-naphthol	Oral; capsule	0.3	mg
Betose	Oral; capsule	0.0487	mg
Butylated hydroxyanisole	Oral; capsule	0.08	mg
Butylated hydroxyanisole	Oral; capsule, soft gelatin	1	mg
Butylated hydroxytoluene	Oral; capsule	0.2	mg
Butylated hydroxytoluene	Oral; capsule, soft gelatin	0.25	mg
Butylparaben	Oral; capsule	0.002	mg
Calcium carbonate	Oral; capsule, sustained action	4	mg
Calcium carbonate	Oral; capsule, hard gelatin	62.84	mg
Calcium carbonate	Oral; capsule	349.9	mg
Calcium citrate	Oral; powder	42.9	%
Calcium phosphate, dibasic	Oral; capsule, sustained action	287.6	mg
Calcium phosphate, dibasic	Oral; capsule	401	mg
Calcium phosphate, dibasic, dihydrate	Oral; capsule	400	mg
Calcium phosphate, tribasic	Oral; capsule, sustained action	32.727	mg
Calcium silicate	Oral; capsule, soft gelatin	1.03	mg
Calcium stearate	Oral; capsule, hard gelatin	1	mg
Calcium stearate	Oral; powder	3	%
Calcium stearate	Oral; capsule	21.1	mg
Calcium stearate	Oral; capsule, sustained action	91.9	mg
Calcium sulfate	Oral; capsule, sustained action	1.54	mg
Calcium sulfate	Oral; capsule	74.68	mg
Calcium sulfate dihydrate	Oral; capsule	370	mg
Calcium sulfate hemihydrate	Oral; capsule	10	mg
Calcium sulfate, anhydrous	Oral; capsule	50	mg
Canola oil	Oral; capsule, soft gelatin	165.55	mg
Caprylic/Capric triglyceride	Oral; powder, for suspension	67.8	%
Caprylic/Capric triglyceride	Oral; capsule	140.56	mg
Caprylic/Capric triglyceride	Oral; capsule, soft gelatin	250	mg
Caramel	Oral; granule	2.5	mg
Carbomer 934p	Oral; capsule	14.2	mg

Ingredient	Dosage Form	Qty	Unit
Carbon black	Oral; capsule, sustained action	0.2	mg
Carboxymethyl starch	Oral; capsule	15	mg
Carboxymethylcellulose calcium	Oral; capsule, hard gelatin	36	mg
Carboxymethylcellulose calcium	Oral; capsule	70	mg
Carboxymethylcellulose sodium	Oral; powder, for solution	0.2625	%
Carboxymethylcellulose sodium	Oral; capsule, sustained action	0.469	mg
Carboxymethylcellulose sodium	Oral; powder, for suspension	2	%
Carboxymethylcellulose sodium	Oral; capsule, enteric-coated pellets	4.2	mg
Carboxymethylcellulose sodium	Oral; granule	25.7	mg
Carboxymethylcellulose sodium	Oral; capsule	160	mg
Carnauba wax	Oral; capsule, sustained action	0.75	mg
Carrageenan	Oral; capsule	0.1534	mg
Carrageenan	Oral; powder, for suspension	1.5	%
Carrageenan	Oral; granule, for reconstitution	6	mg
Carrageenan	Oral; granule, for suspension	20.15	mg
Castor oil	Oral; capsule	0.03	mg
Castor oil	Oral; capsule, sustained action	1.756	mg
Castor oil	Oral; granule, for suspension	32	mg
Castor oil, hydrogenated	Oral; capsule	8	mg
Castor oil, hydrogenated	Oral; capsule, sustained action	410.82	mg
Cellacefate	Oral; capsule, sustained action	9.42	mg
Cellacefate	Oral; capsule, enteric-coated pellets	28.2	mg
Cellulose	Oral; capsule, hard gelatin	140	mg
Cellulose	Oral; capsule	405	mg
Cellulose acetate	Oral; capsule	18.08	mg
Cellulose microcrystalline, aqueous	Oral; capsule	47.85	mg
Cellulose microcrystalline, aqueous	Oral; capsule, hard gelatin	141	mg
Cellulose microcrystalline/Carboxymethylcellulose sodium	Oral; powder, for suspension	2.26	%
Cellulose microcrystalline/Carboxymethylcellulose sodium	Oral; powder, for oral suspension	2.5	%
Cellulose microcrystalline/Carboxymethylcellulose sodium	Oral; granule, for suspension	50	mg
Cellulose, microcrystalline	Oral; capsule, coated pellets	8.03	mg
Cellulose, microcrystalline	Oral; capsule, enteric-coated pellets	14	mg
Cellulose, microcrystalline	Oral; granule, for reconstitution	25	mg
Cellulose, microcrystalline	Oral; capsule, extended release	41.67	mg
Cellulose, microcrystalline	Oral; capsule (immed./comp. release), hard gelatin	44.33	mg
Cellulose, microcrystalline	Oral; powder, for suspension	58.65	%
Cellulose, microcrystalline	Oral; capsule, coated, soft gelatin	60	mg
Cellulose, microcrystalline	Oral; capsule, soft gelatin	105	mg
Cellulose, microcrystalline	Oral; capsule, hard gelatin	154.3	mg
Cellulose, microcrystalline	Oral; capsule, sustained action	186	mg
Cellulose, microcrystalline	Oral; capsule, sustained action, hard gelatin	282.6	mg
Cellulose, microcrystalline	Oral; capsule	363.75	mg
Cellulose, microcrystalline	Oral; granule, enteric coated	789.6	mg

Ingredient	Dosage Form	Qty	Unit
Cellulose, microcrystalline 101	Oral; capsule	39.1	mg
Cellulose, powder	Oral; capsule	170	mg
Cetyl alcohol	Oral; capsule, enteric-coated pellets	1	mg
Cetylpyridinium chloride	Oral; capsule, soft gelatin	0.0043	mg
Cetylpyridinium chloride	Oral; capsule, sustained action	0.02	mg
Cetylpyridinium chloride	Oral; capsule	1.5	mg
Chartreuse-colored spheres	Oral; capsule, sustained action	35.14	mg
Citric acid	Oral; for suspension	0.1	%
Citric acid	Oral; powder, for reconstitution	0.25	%
Citric acid	Oral; capsule, soft gelatin	1	mg
Citric acid	Oral; capsule, enteric-coated pellets	4.9	mg
Citric acid	Oral; granule, for oral suspension	4.9	mg
Citric acid	Oral; granule, for reconstitution	6	mg
Citric acid	Oral; granule	6.25	mg
Citric acid	Oral; powder, for oral suspension	8.1	%
Citric acid	Oral; granule, for suspension	9.1	mg
Citric acid	Oral; powder	9.5	%
Citric acid	Oral; capsule, extended release	18.8	mg
Citric acid	Oral; capsule, sustained action, hard gelatin	18.8	mg
Citric acid	Oral; capsule	30.75	mg
Citric acid	Oral; powder, for suspension	60	%
Citric acid, hydrous	Oral; granule, for suspension	14.1	mg
Coconut oil, fractioned	Oral; capsule, soft gelatin	99.77	mg
Coconut oil, fractioned	Oral; capsule	124.9497	mg
Compressible sugar	Oral; powder, for oral suspension	49.73	%
Compressible sugar	Oral; capsule, sustained action	75	mg
Compressible sugar	Oral; capsule	270	mg
Corn glycerides	Oral; capsule, soft gelatin	344	mg
Corn oil	Oral; capsule, soft gelatin	416	mg
Corn oil	Oral; capsule	918	mg
Corn oil PEG-6 esters	Oral; capsule, soft gelatin	300	mg
Cottonseed oil, hydrogenated	Oral; capsule	15	mg
Cottonseed oil, hydrogenated	Oral; capsule, sustained action	58	mg
Croscarmellose sodium	Oral; capsule, enteric-coated pellets	20	mg
Croscarmellose sodium	Oral; capsule, hard gelatin	20	mg
Croscarmellose sodium	Oral; capsule (immed./comp. release), hard gelatin	30	mg
Croscarmellose sodium	Oral; granule, for suspension	35.3	mg
Croscarmellose sodium	Oral; capsule	50	mg
Croscarmellose sodium	Oral; granule, for reconstitution	143.5	mg
Crospovidone	Oral; powder, for suspension	5	%
Crospovidone	Oral; capsule, sustained action	10.71	mg
Crospovidone	Oral; capsule, coated, soft gelatin	14	mg
Crospovidone	Oral; capsule	30	mg

Ingredient	Dosage Form	Qty	Unit
Crospovidone	Oral; capsule, hard gelatin	70	mg
Crospovidone	Oral; capsule, enteric-coated pellets	75	mg
Crospovidone	Oral; granule, for oral suspension	75	mg
D&C green no. 4	Oral; capsule	40	mg
D&C green no. 5	Oral; capsule, sustained action	0.0029	mg
D&C red no. 28	Oral; powder, for suspension	0.07	%
D&C red no. 28	Oral; capsule	0.2241	mg
D&C red no. 3 lake	Oral; capsule	0.005	mg
D&C red no. 30 lake	Oral; capsule, enteric-coated pellets	0.3	mg
D&C red no. 30 lake	Oral; powder	0.3	%
D&C red no. 30 lake	Oral; granule, for suspension	0.85	mg
D&C red no. 33	Oral; capsule, soft gelatin	0.0001	mg
D&C red no. 33	Oral; capsule, soft gelatin liquid-filled	0.0113	mg
D&C red no. 33	Oral; capsule, sustained action	0.134	mg
D&C red no. 33	Oral; capsule	0.39	mg
D&C red no. 40	Oral; capsule, sustained action	0.2	mg
D&C yellow no. 10	Oral; capsule, coated pellets	0.0145	mg
D&C yellow no. 10	Oral; capsule, coated, soft gelatin	0.047	mg
D&C yellow no. 10	Oral; capsule, enteric-coated pellets	0.0525	mg
D&C yellow no. 10	Oral; capsule (immed./comp. release), soft gelatin, perle	0.09	mg
D&C yellow no. 10	Oral; capsule, sustained action	0.491	mg
D&C yellow no. 10	Oral; powder	0.6	%
D&C yellow no. 10	Oral; capsule, soft gelatin	1.51	mg
D&C yellow no. 10	Oral; capsule	331	mg
D&C yellow no. 10–aluminum lake	Oral; capsule, sustained action	0.22	mg
D&C yellow no. 10–aluminum lake	Oral; capsule, enteric-coated pellets	0.3	mg
D&C yellow no. 10–aluminum lake	Oral; capsule	1.2	mg
D&C yellow no. 10–aluminum lake	Oral; powder	4.3	%
D&C yellow no. 6	Oral; capsule, sustained action	0.2	mg
D&C yellow no. 6 lake	Oral; capsule, enteric-coated pellets	0.5	mg
DC antifoam AF trituration 1% on sucrose	Oral; powder, for solution	0.2625	%
Dibutyl phthalate	Oral; capsule, extended release	11.18	mg
Dibutyl sebacate	Oral; capsule, enteric-coated pellets	0.893	mg
Dibutyl sebacate	Oral; capsule, sustained action	8.82	mg
Dibutyl sebacate	Oral; granule, enteric coated	43.2	mg
Diethyl phthalate	Oral; capsule, sustained action	3.6	mg
Diethyl phthalate	Oral; capsule, extended release	5.93	mg
Diethyl phthalate	Oral; capsule, enteric-coated pellets	12	mg
Dimethicone 350	Oral; capsule, sustained action	0.114	mg
Dimethicone 350	Oral; capsule	3.7	mg
Docusate sodium	Oral; capsule, sustained action	0.001	mg
Docusate sodium	Oral; capsule, hard gelatin	0.64	mg
Docusate sodium	Oral; capsule	8.2	mg

Ingredient	Dosage Form	Qty	Unit
Docusate sodium/Sodium benzoate	Oral; capsule	85	mg
Dye blue #1	Oral; capsule	0.027	mg
Dye casing 27–75	Oral; powder, for suspension	0.0014	%
Dye chromatone	Oral; capsule	29.6	mg
Dye DC red #27 lake	Oral; capsule	1.31	mg
Dye DC red #33 lake	Oral; capsule	0.0046	mg
Dye FDC yellow #10 lake	Oral; capsule, sustained action	0.28	mg
Dye FDC yellow #6 ht lake	Oral; capsule	0.8	mg
Dye yellow #62	Oral; capsule	5.1	mg
Edetate calcium disodium	Oral; powder, for solution	0.022	%
Edetate calcium disodium	Oral; capsule	0.272	mg
Edetate disodium	Topical; powder, for solution	0.01	%
Edetate disodium	Oral; powder, for suspension	0.06	%
Edetate disodium	Oral; capsule	1	mg
Edetate disodium	Oral; capsule, soft gelatin	1.004	mg
Edetate sodium	Oral; capsule, soft gelatin	1	mg
Ethyl acetate	Oral; capsule, sustained action	382.257	mg
Ethyl vanillin	Oral; capsule, coated, soft gelatin	0.124	mg
Ethyl vanillin	Oral; capsule	0.341	mg
Ethyl vanillin	Oral; capsule, soft gelatin	0.64	mg
Ethylcellulose	Oral; capsule	6	mg
Ethylcellulose	Oral; capsule, extended release	25.2	mg
Ethylcellulose	Oral; capsule, sustained action, hard gelatin	27.04	mg
Ethylcellulose	Oral; capsule, sustained action	39.2	mg
Ethylcellulose	Oral; granule, for suspension	85	mg
Ethylene glycol monoethyl ether	Oral; capsule	0.009	mg
Ethylparaben sodium	Oral; capsule, soft gelatin	1.004	mg
Eudragit E 100	Oral; capsule, sustained action	1.63	mg
Eudragit L 100	Oral; capsule, sustained action	22.08	mg
Eudragit L 100	Oral; capsule, enteric-coated pellets	93.36	mg
Eudragit L 30 D	Oral; capsule, sustained action	2.16	mg
Eudragit L 30 D	Oral; capsule, enteric-coated pellets	28	mg
Eudragit L 30D – 55	Oral; capsule, sustained action, hard gelatin	10.9	mg
Eudragit L 30D – 55	Oral; capsule, extended release	40.414	mg
Eudragit L 30D – 55	Oral; capsule, sustained action	48.1	mg
Eudragit L 30D – 55	Oral; capsule	75.18	mg
Eudragit L 30D – 55	Oral; capsule, enteric-coated pellets	80.36	mg
Eudragit NE 30 D	Oral; capsule, extended release	30.062	mg
Eudragit NE 30 D	Oral; capsule, enteric-coated pellets	93.36	mg
Eudragit NE 30 D	Oral; capsule, sustained action	187.3	mg
Eudragit RL 12.5	Oral; powder, for suspension	3.22	%
Eudragit RL 12.5	Oral; capsule, sustained action	25.59	mg
Eudragit RL 30 D	Oral; capsule, sustained action, hard gelatin	4.2	mg

Ingredient	Dosage Form	Qty	Unit
Eudragit RL 30 D	Oral; capsule, sustained action	4.706	mg
Eudragit RS 30 D	Oral; capsule, extended release	35.7	mg
Eudragit RS 30 D	Oral; capsule, sustained action	91.88	mg
Eudragit S 100	Oral; capsule, sustained action	28.38	mg
Fatty acid esters, saturated	Oral; capsule, enteric-coated pellets	0.2	mg
FD&C blue no. 1	Oral; capsule, coated pellets	0.0002	mg
FD&C blue no. 1	Oral; capsule, soft gelatin liquid-filled	0.017	mg
FD&C blue no. 1	Oral; powder, for suspension	0.02	%
FD&C blue no. 1	Oral; capsule, soft gelatin	0.04	mg
FD&C blue no. 1	Oral; capsule, sustained action	0.9	mg
FD&C blue no. 1	Oral; capsule, hard gelatin	3.708	mg
FD&C blue no. 1	Oral; capsule	26.3	mg
FD&C blue no. 1–aluminum lake	Oral; capsule	0.0412	mg
FD&C blue no. 1–aluminum lake	Oral; capsule, sustained action	0.095	mg
FD&C blue no. 1–aluminum lake	Oral; capsule, enteric-coated pellets	4	mg
FD&C blue no. 2	Oral; capsule, hard gelatin	0.0114	mg
FD&C blue no. 2	Oral; capsule, sustained action	0.03	mg
FD&C blue no. 2	Oral; capsule, delayed action	0.0769	mg
FD&C blue no. 2	Oral; capsule	0.218	mg
FD&C blue no. 2–aluminum lake	Oral; capsule	0.218	mg
FD&C blue no. 2–aluminum lake	Oral; capsule, enteric-coated pellets	3.5	mg
FD&C green no. 3	Oral; capsule, sustained action	0.067	mg
FD&C green no. 3	Oral; capsule, soft gelatin	0.17	mg
FD&C green no. 3	Oral; capsule, enteric-coated pellets	0.2192	mg
FD&C green no. 3	Oral; capsule	40	mg
FD&C red no. 2	Oral; capsule, soft gelatin	0.092	mg
FD&C red no. 2	Oral; capsule, sustained action	0.1	mg
FD&C red no. 2	Oral; capsule	0.101	mg
FD&C red no. 28	Oral; capsule	0.004	mg
FD&C red no. 3	Oral; powder, for oral suspension	0.008	%
FD&C red no. 3	Oral; powder, for suspension	0.1	%
FD&C red no. 3	Oral; capsule, soft gelatin	0.217	mg
FD&C red no. 3	Oral; granule	0.25	mg
FD&C red no. 3	Oral; capsule, sustained action	0.58	mg
FD&C red no. 3	Oral; capsule	59.16	mg
FD&C red no. 33	Oral; capsule	262	mg
FD&C red no. 3–aluminum lake	Oral; powder, for suspension	0.03	%
FD&C red no. 3–aluminum lake	Oral; capsule, sustained action	0.29	mg
FD&C red no. 3–aluminum lake	Oral; granule	50	mg
FD&C red no. 4	Oral; capsule	0.64	mg
FD&C red no. 40	Oral; powder, for oral suspension	0.003	%
FD&C red no. 40	Oral; capsule, coated, soft gelatin	0.0125	mg
FD&C red no. 40	Oral; powder, for reconstitution	0.0292	%

Ingredient	Dosage Form	Qty	Unit
FD&C red no. 40	Oral; powder, for suspension	0.0375	%
FD&C red no. 40	Oral; powder	0.05	%
FD&C red no. 40	Oral; capsule, soft gelatin	0.52	mg
FD&C red no. 40	Oral; powder, for solution	1.3325	%
FD&C red no. 40	Oral; capsule, sustained action	1.36	mg
FD&C red no. 40	Oral; capsule	73.2	mg
FD&C red no. 40–aluminum lake	Oral; powder, for oral suspension	0.008	%
FD&C red no. 40–aluminum lake	Oral; powder, for suspension	0.01	%
FD&C red no. 40–aluminum lake	Oral; capsule, sustained action	0.05	mg
FD&C red no. 40–aluminum lake	Oral; powder	0.1	%
FD&C yellow no. 10	Oral; capsule, sustained action	0.2	mg
FD&C yellow no. 10	Oral; capsule	0.34	mg
FD&C yellow no. 5	Oral; capsule, sustained action	0.065	mg
FD&C yellow no. 5	Oral; capsule, enteric-coated pellets	0.12	mg
FD&C yellow no. 5	Oral; capsule	652	mg
FD&C yellow no. 5–aluminum lake	Oral; capsule	0.09	mg
FD&C yellow no. 6	Oral; capsule, coated pellets	0.0017	mg
FD&C yellow no. 6	Oral; powder, for suspension	0.04	%
FD&C yellow no. 6	Oral; capsule, soft gelatin	0.8	mg
FD&C yellow no. 6	Oral; powder	2	%
FD&C yellow no. 6	Oral; capsule, sustained action	4.5	mg
FD&C yellow no. 6	Oral; capsule	327.6	mg
FD&C yellow no. 6–aluminum lake	Oral; powder, for suspension	0.032	%
FD&C yellow no. 6–aluminum lake	Oral; powder	0.15	%
FD&C yellow no. 6–aluminum lake	Oral; capsule, sustained action	0.24	mg
FD&C yellow no. 6–aluminum lake	Oral; capsule	0.385	mg
FD&C yellow no. 6–aluminum lake	Oral; capsule, enteric-coated pellets	1.25	mg
Ferric oxide	Oral; capsule	0.63	mg
Ferric oxide	Oral; capsule, enteric-coated pellets	2	mg
Ferric oxide, red	Oral; capsule, soft gelatin	2.28	mg
Ferric oxide, red	Oral; capsule	2.64	mg
Ferric oxide, yellow	Oral; granule, for reconstitution	0.25	mg
Ferric oxide, yellow	Oral; capsule	1.05	mg
Ferric oxide, yellow	Oral; capsule, soft gelatin	1.23	mg
Ferric oxide, yellow	Oral; capsule, enteric-coated pellets	1.8	mg
Ferric oxide, yellow	Oral; granule, for oral suspension	1.8	mg
Ferric oxide, yellow	Oral; capsule, sustained action	3.04	mg
Ferric oxide, brown	Oral; capsule	0.0983	mg
Ferric oxide, brown	Oral; capsule, soft gelatin	0.7	mg
Ferrosoferric oxide	Oral; capsule, soft gelatin	0.3	mg
Ferrosoferric oxide	Oral; capsule	0.82	mg
Ferrosoferric oxide	Oral; capsule, sustained action	1.492	mg
Flavor aromalok 182608	Oral; powder, for suspension	0.72	%

Ingredient	Dosage Form	Qty	Unit
Flavor banana 15223	Oral; powder, for oral suspension	23	%
Flavor banana 501013 ap0551	Oral; powder, for oral suspension	0.3906	%
Flavor black cherry 501027 ap0551	Oral; powder, for oral suspension	0.2344	%
Flavor cheri-beri PFC-8573	Oral; powder, for suspension	0.5	%
Flavor cherry 11929	Oral; powder, for oral suspension	14	%
Flavor cherry 594 S.D.	Oral; powder, for suspension	0.15	%
Flavor cherry 594 S.D.	Oral; granule, for reconstitution	7.5	mg
Flavor cherry-beri PFC-8573	Oral; granule	16.7	mg
Flavor cherry R-6556	Oral; powder, for suspension	0.05	%
Flavor cream EP-17688	Oral; powder, for suspension	0.08	%
Flavor creme de vanilla 28156	Oral; powder, for suspension	0.002	%
Flavor fruit gum 912	Oral; powder, for oral suspension	0.36	%
Flavor fruit gum 912	Oral; powder, for suspension	0.4	%
Flavor fruit gum 912	Oral; granule, for reconstitution	20	mg
Flavor grape 59.145/apo5.51	Oral; powder, for suspension	0.1	%
Flavor grape 59.266/apo5.51	Oral; powder, for suspension	0.1	%
Flavor grape micron ZD-3876	Oral; powder, for solution	0.3	%
Flavor kiwi S-718	Oral; powder	0.63	%
Flavor lemon spray V3938–1N1	Oral; powder, for oral solution	340	mg
Flavor mandarin 15228–71	Oral; granule, for suspension	70	mg
Flavor mask rbt-NV-7759	Oral; powder, for suspension	0.224	%
Flavor orange 249792	Oral; powder, for reconstitution	0.3	%
Flavor orange 57.458/apo5.51	Oral; powder, for oral suspension	6	%
Flavor orange 739 K (pb82)	Oral; powder, for reconstitution	0.625	%
Flavor orange 74016–71	Oral; granule, for suspension	70	mg
Flavor orange 9/79j839	Oral; powder, for reconstitution	0.225	%
Flavor perlarom strawberry	Oral; powder, for oral suspension	1.2	%
Flavor pharmaceutical 182608	Oral; powder, for suspension	0.72	%
Flavor prosweet 694	Oral; powder, for suspension	0.5	%
Flavor raspberry 954 K (bk77)	Oral; powder, for reconstitution	1.25	%
Flavor raspberry dy-04447	Oral; powder, for reconstitution	0.45	%
Flavor root beer 180339	Oral; powder, for suspension	0.042	%
Flavor strawberry 052311 ap0551	Oral; for suspension	0.5	%
Flavor strawberry 52.311ap	Oral; powder, for reconstitution	0.2	%
Flavor strawberry 52.311ap	Oral; powder, for suspension	0.5	%
Flavor strawberry 52312/ap	Oral; powder, for suspension	0.3	%
Flavor strawberry DY-04359	Oral; powder, for suspension	0.12	%
Flavor strawberry guarana 586.997/apo5.51	Oral; powder, for reconstitution	0.2	%
Flavor strawberry guarana 586.997/apo5.51	Oral; powder, for suspension	0.4	%
Flavor strawberry microseal	Oral; powder, for suspension	0.08	%
Flavor sweet-AM 918.005	Oral; granule, for suspension	30	mg
Flavor tutti frutti 51.880/apo5.51	Oral; powder, for suspension	2.04	%
Flavor tutti frutti permaseal 77919–31	Oral; powder, for solution	0.015	%

Ingredient	Dosage Form	Qty	Unit
Flavor tutti frutti WL-18481	Oral; powder, for suspension	0.6	%
Flavor vanilla 501441 ap2004	Oral; powder, for oral suspension	0.547	%
Flavor veralock bubble gum	Oral; powder, for suspension	0.167	%
Flavor wild cherry givaudan F-1813	Oral; powder, for solution	3.704	%
Flavor wild cherry givaudan F-1813	Oral; powder, for suspension	6.82	%
Flavor wild cherry NV-101–1489	Oral; powder, for suspension	0.05	%
Fluorescein	Oral; capsule	0.0068	mg
Fumaric acid	Oral; capsule, sustained action	150	mg
Gelatin	Oral; capsule (immed./comp. release), soft gelatin, perle	50	mg
Gelatin	Oral; capsule, hard gelatin	50.5	mg
Gelatin	Oral; capsule, enteric-coated pellets	60.7595	mg
Gelatin	Oral; capsule, coated pellets	65	mg
Gelatin	Oral; capsule, coated, soft gelatin	67.71	mg
Gelatin	Oral; capsule, extended release	96	mg
Gelatin	Oral; capsule, delayed action	97.012	mg
Gelatin	Oral; capsule, sustained action, hard gelatin	107	mg
Gelatin	Oral; capsule (immed./comp. release), soft gelatin	117.5	mg
Gelatin	Oral; capsule, soft gelatin liquid-filled	164	mg
Gelatin	Oral; capsule, sustained action	217.859	mg
Gelatin	Oral; capsule, soft gelatin	733	mg
Gelatin	Oral; capsule	756	mg
Gelucire 33/01	Oral; capsule, soft gelatin	114	mg
Glucose, liquid	Oral; pastille	826	mg
Glycerin	Oral; capsule (immed./comp. release), soft gelatin, perle	25	mg
Glycerin	Oral; capsule, coated, soft gelatin	31.2	mg
Glycerin	Oral; capsule (immed./comp. release), soft gelatin	75	mg
Glycerin	Oral; capsule, sustained action	132.31	mg
Glycerin	Oral; capsule	197.88	mg
Glycerin	Oral; capsule, soft gelatin	223.8	mg
Glyceryl behenate	Oral; capsule, enteric-coated pellets	1.7496	mg
Glyceryl behenate	Oral; capsule	5.7	mg
Glyceryl caprylate	Oral; capsule, soft gelatin	400	mg
Glyceryl caprylate/Caprate	Oral; capsule, soft gelatin	765	mg
Glyceryl distearate	Oral; capsule, sustained action	39.2	mg
Glyceryl stearate	Oral; capsule, enteric-coated pellets	0.95	mg
Glyceryl stearate	Oral; capsule, delayed action	1.896	mg
Glyceryl stearate	Oral; granule, for oral suspension	1.9	mg
Glyceryl stearate	Oral; capsule, sustained action	27	mg
Glycine	Oral; powder, for oral suspension	0.1	%
Glycine	Oral; powder, for suspension	1	%
Glycine	Oral; capsule, soft gelatin	3.6	mg
Glycine	Oral; powder, for solution	9.08	%
Glycine	Oral; capsule	25	mg

Ingredient	Dosage Form	Qty	Unit
Guar gum	Oral; for suspension	0.2	%
Guar gum	Oral; powder, for suspension	0.2	%
Guar gum	Oral; capsule	3.3	mg
Hydroxyethyl cellulose	Oral; capsule	2.98	mg
Hydroxymethyl cellulose	Oral; capsule, sustained action	1.6	mg
Hydroxymethyl cellulose	Oral; powder, for reconstitution	7.5	%
Hydroxypropyl cellulose	Oral; powder, for suspension	0.0004	%
Hydroxypropyl cellulose	Oral; capsule, coated pellets	3.96	mg
Hydroxypropyl cellulose	Oral; powder, for oral suspension	6.7	%
Hydroxypropyl cellulose	Oral; capsule, delayed action	8.88	mg
Hydroxypropyl cellulose	Oral; granule	10.4	mg
Hydroxypropyl cellulose	Oral; granule, for reconstitution	20	mg
Hydroxypropyl cellulose	Oral; granule, for suspension	31.4	mg
Hydroxypropyl cellulose	Oral; capsule	36	mg
Hydroxypropyl cellulose	Oral; granule, for oral suspension	39	mg
Hydroxypropyl cellulose	Oral; capsule, enteric-coated pellets	41.4	mg
Hydroxypropyl cellulose	Oral; capsule, sustained action	41.5	mg
Hydroxypropyl cellulose	Oral; capsule, hard gelatin	71.3	mg
Hydroxypropyl cellulose, low substituted	Oral; capsule, hard gelatin	6	mg
Hydroxypropyl cellulose, low substituted	Oral; capsule, enteric-coated pellets	20	mg
Hydroxypropyl methylcellulose 2208	Oral; capsule, sustained action, hard gelatin	2.771	mg
Hydroxypropyl methylcellulose 2208	Oral; capsule	80.25	mg
Hydroxypropyl methylcellulose 2208	Oral; capsule, sustained action	336	mg
Hydroxypropyl methylcellulose 2906	Oral; capsule	3.5	mg
Hydroxypropyl methylcellulose 2906	Oral; granule, enteric coated	33.2	mg
Hydroxypropyl methylcellulose 2910	Oral; powder, for reconstitution	1.593	%
Hydroxypropyl methylcellulose 2910	Oral; capsule, hard gelatin	2	mg
Hydroxypropyl methylcellulose 2910	Oral; powder, for suspension	3	%
Hydroxypropyl methylcellulose 2910	Oral; capsule, sustained action, hard gelatin	4.772	mg
Hydroxypropyl methylcellulose 2910	Oral; capsule, extended release	10.6	mg
Hydroxypropyl methylcellulose 2910	Oral; capsule, sustained action	10.88	mg
Hydroxypropyl methylcellulose 2910	Oral; capsule, enteric-coated pellets	13.82	mg
Hydroxypropyl methylcellulose 2910	Oral; capsule, delayed action	33.42	mg
Hydroxypropyl methylcellulose 2910	Oral; capsule	40.5519	mg
Hydroxypropyl methylcellulose 4000	Oral; capsule, sustained action	100.4	mg
Hydroxypropyl methylcellulose acetate succinate	Oral; capsule	44.6	mg
Hydroxypropyl methylcellulose acetate succinate	Oral; capsule, delayed action	66.78	mg
Hydroxypropyl methylcellulose E5	Oral; capsule	9	mg
Hydroxypropyl methylcellulose phthalate	Oral; capsule, coated pellets	13.26	mg
Hydroxypropyl methylcellulose phthalate	Oral; capsule	16.8	mg
Hydroxypropyl methylcellulose phthalate	Oral; capsule, sustained action	19.63	mg
Hydroxypropyl methylcellulose phthalate	Oral; capsule, enteric-coated pellets	76.4	mg
Hydroxypropyl methylcellulose phthalate	Oral; granule, for suspension	302.4	mg

Ingredient	Dosage Form	Qty	Unit
Ink black GG-606	Oral; capsule	37	mg
Ink edible black	Oral; capsule	0.05	mg
Ink edible white	Oral; capsule	0.0005	mg
Ink red and aqua imprinting GG-827	Oral; capsule	95	mg
Ink red and caramel imprinting GG-825	Oral; capsule	62	mg
Ink red imprinting GG-826	Oral; capsule	78	mg
Ink white 21-K	Oral; capsule, sustained action	0.5	mg
Ink white A-8154	Oral; capsule	0.8	mg
Isopropyl alcohol	Oral; capsule	46.4	mg
Isopropyl alcohol	Oral; capsule, sustained action	392.8	mg
Kaolin	Oral; capsule, enteric-coated pellets	14.61	mg
Karion 83 (D-sorbitol content 19–25%)	Oral; capsule	55.79	mg
Lac resin	Oral; capsule, sustained action	31.2	mg
Lactic acid	Oral; capsule, soft gelatin liquid-filled	44	mg
Lactitol monohydrate	Oral; capsule	133	mg
Lactose	Oral; capsule, hard gelatin	100	mg
Lactose	Oral; capsule, coated pellets	102.44	mg
Lactose	Oral; capsule, soft gelatin	115.75	mg
Lactose	Oral; capsule, sustained action	120	mg
Lactose	Oral; capsule, enteric-coated pellets	135.2	mg
Lactose	Oral; capsule	530	mg
Lactose monohydrate	Oral; powder, for inhalation	1.25	%
Lactose monohydrate	Oral; capsule, sustained action, hard gelatin	18.8	mg
Lactose monohydrate	Oral; capsule, extended release	23.3	mg
Lactose monohydrate	Oral; capsule, sustained action	67	mg
Lactose monohydrate	Oral; capsule, hard gelatin	161.8	mg
Lactose monohydrate	Oral; capsule, coated, soft gelatin	178.90	mg
Lactose monohydrate	Oral; capsule	427.26	mg
Lactose, anhydrous	Oral; powder, for inhalation	0.1161	%
Lactose, anhydrous	Oral; granule, for reconstitution	15.688	mg
Lactose, anhydrous	Oral; capsule, coated, soft gelatin	71.906	mg
Lactose, anhydrous	Oral; capsule, enteric-coated pellets	117	mg
Lactose, anhydrous	Oral; capsule, sustained action	300.8	mg
Lactose, anhydrous	Oral; capsule	402.5	mg
Lactose, anhydrous	Oral; granule	433	mg
Lactose, hydrous	Oral; capsule, hard gelatin	141	mg
Lactose, hydrous	Oral; capsule, sustained action	147.6	mg
Lactose, hydrous	Oral; capsule	430.42	mg
Lauroyl polyoxylglycerides	Oral; capsule, hard gelatin	218	mg
Lauryl sulfate	Oral; capsule	0.15	mg
Lecithin	Oral; capsule, coated, soft gelatin	1	mg
Lecithin	Oral; powder, for suspension	3.34	%
Lecithin	Oral; capsule	15	mg

Ingredient	Dosage Form	Qty	Unit
Lecithin, soybean	Oral; capsule	5	mg
Lecithin, soybean	Oral; capsule, soft gelatin	20	mg
Lemon oil	Oral; capsule	5	mg
Lemon oil	Oral; capsule, soft gelatin	8.5	mg
Light mineral oil	Oral; capsule	0.8	mg
Lubritab	Oral; capsule	1.5	mg
Magnasweet 135	Oral; powder	20	%
Magnasweet 135	Oral; granule, for suspension	60	mg
Magnasweet 185	Oral; powder, for solution	53	%
Magnesium acetate	Oral; capsule	1.475	mg
Magnesium aluminum silicate	Oral; granule	8.3	mg
Magnesium aluminum silicate hydrate	Oral; granule, for suspension	11	mg
Magnesium aluminum silicate hydrate	Oral; granule	12.5	mg
Magnesium aluminum silicate hydrate	Oral; capsule	19.8	mg
Magnesium carbonate	Oral; capsule	19.44	mg
Magnesium carbonate	Oral; capsule, enteric-coated pellets	22.4	mg
Magnesium carbonate	Oral; capsule, sustained action	22.4	mg
Magnesium hydroxide	Oral; powder, for oral suspension	25	%
Magnesium oxide	Oral; capsule	10	mg
Magnesium silicate	Oral; capsule	40	mg
Magnesium stearate	Oral; powder, for inhalation	0.0028	%
Magnesium stearate	Oral; capsule, coated pellets	0.15	mg
Magnesium stearate	Oral; powder, for suspension	0.65	%
Magnesium stearate	Oral; granule	1.25	mg
Magnesium stearate	Oral; granule, for oral suspension	2.6	mg
Magnesium stearate	Oral; capsule, delayed action	2.604	mg
Magnesium stearate	Oral; capsule, coated, soft gelatin	3	mg
Magnesium stearate	Oral; capsule, soft gelatin	9	mg
Magnesium stearate	Oral; capsule, extended release	9.157	mg
Magnesium stearate	Oral; capsule (immed./comp. release), hard gelatin	10	mg
Magnesium stearate	Oral; capsule, hard gelatin	11.4	mg
Magnesium stearate	Oral; capsule, enteric-coated pellets	34.87	mg
Magnesium stearate	Oral; capsule, sustained action	100	mg
Magnesium stearate	Oral; capsule	256.4	mg
Magnesium sulfate, anhydrous	Oral; capsule	29.8	mg
Maleic acid	Oral; capsule	2	mg
Maltodextrin	Oral; powder, for suspension	19	%
Maltodextrin	Oral; powder	26.68	%
Maltodextrin	Oral; granule, for suspension	238.1	mg
Mannitol	Oral; powder, for suspension	20	%
Mannitol	Oral; powder, for reconstitution	29.362	%
Mannitol	Oral; capsule, sustained action	56.1	mg
Mannitol	Oral; capsule, hard gelatin	92	mg

Ingredient	Dosage Form	Qty	Unit
Mannitol	Oral; capsule, enteric-coated pellets	170.7	mg
Mannitol	Oral; capsule	297.2	mg
Mannitol	Oral; granule	484.2	mg
Mannitol	Oral; granule, for suspension	500	mg
Menthol	Oral; capsule	0.87	mg
Methacrylic acid copolymer	Oral; capsule, extended release	18.04	mg
Methacrylic acid copolymer	Oral; capsule, delayed action	37.916	mg
Methacrylic acid copolymer	Oral; capsule, sustained action	44.6	mg
Methacrylic acid copolymer	Oral; capsule, enteric-coated pellets	95.876	mg
Methacrylic acid copolymer	Oral; granule, enteric coated	430.8	mg
Methacrylic acid copolymer type A	Oral; capsule, extended release	37.48	mg
Methacrylic acid copolymer type B	Oral; capsule, extended release	5.39	mg
Methacrylic acid copolymer type C	Oral; capsule, delayed action	15.82	mg
Methacrylic acid copolymer type C	Oral; capsule, enteric-coated pellets	25.6	mg
Methacrylic acid copolymer type C	Oral; granule, for oral suspension	38	mg
Methyl acrylate – methyl methacrylate	Oral; capsule, extended release	37.5	mg
Methyl alcohol	Oral; capsule, sustained action	0.03	mL
Methyl salicylate	Oral; capsule	16	mg
Methylated spirits	Oral; capsule	0.101	mg
Methylcellulose	Oral; powder, for suspension	1.19	%
Methylcellulose	Oral; capsule, extended release	2.67	mg
Methylcellulose	Oral; capsule, sustained action	3.2	mg
Methylcellulose	Oral; capsule	13.5	mg
Methylene chloride	Oral; capsule	69.658	mg
Methylparaben	Oral; powder, for suspension	0.1	%
Methylparaben	Oral; capsule, coated, soft gelatin	0.156	mg
Methylparaben	Oral; powder, for solution	0.1575	%
Methylparaben	Oral; capsule, soft gelatin	0.48	mg
Methylparaben	Oral; capsule, sustained action	0.864	mg
Methylparaben	Oral; capsule	1	mg
Methylparaben	Oral; granule	50	mg
Methylparaben sodium	Oral; powder, for suspension	0.1	%
Microcrystalline wax	Oral; capsule, sustained action	6	mg
Mineral oil	Oral; capsule	5	mg
Mineral oil	Oral; capsule, sustained action	50	mg
Monosodium citrate	Oral; powder, for reconstitution	0.12	%
Monosodium citrate	Oral; powder, for suspension	2.2	%
N-Decyl-methyl sulfoxide	Topical; powder, for solution	0.125	%
Neutral oil	Oral; capsule, sustained action	240	mg
Nonpareil seeds	Oral; capsule, coated pellets	122.191	mg
Nonpareil seeds	Oral; capsule	299.9	mg
Nonpareil seeds	Oral; capsule, sustained action	823.5	mg
Nonpareil seeds blue	Oral; capsule	65	mg

Ingredient	Dosage Form	Qty	Unit
Nonpareil seeds orange	Oral; capsule, sustained action	35	mg
Nonpareil seeds white	Oral; capsule	43	mg
Oleic acid	Oral; capsule, soft gelatin	598.6	mg
Opacode S-1–1681 red	Oral; capsule	1	mg
Opacode S-1–7085 white	Oral; capsule, sustained action	0.028	mg
Opacode S-1–7085 white	Oral; capsule	0.0332	mg
Opacode S-1–8090 black	Oral; capsule	0.05	mg
Opacode S-1–8114 black	Oral; capsule	0.0275	mg
Opacode S-1–8114 black	Oral; capsule, sustained action	0.033	mg
Opacode S-1–8115 black	Oral; capsule, sustained action	0.0232	mg
Opacode S-1–8115 black	Oral; capsule	0.0275	mg
Opacode S-1–9460hv brown	Oral; capsule	0.15	mg
Opacode S-19–7014 white	Oral; capsule, sustained action	0.5	mg
Opadry 03F12920 yellow	Oral; capsule	5.4	mg
Opadry II Y-19–19054 clear	Oral; capsule, sustained action	45.14	mg
Opadry II Y-19–7483 clear	Oral; capsule, sustained action	5.74	mg
Opadry II Y-22–7719 white	Oral; capsule	4.44	mg
Opadry YS-1–17274 A beige	Oral; capsule, delayed action	1.49	mg
Opadry YS-1–17274 A beige	Oral; capsule, sustained action	9.1	mg
Opadry YS-1–19025-A clear	Oral; capsule, sustained action	2.76	mg
Opadry YS-1–7003 white	Oral; capsule	7	mg
Opadry YS-1–7003 white	Oral; capsule, extended release	10.7	mg
Opadry YS-1–7006 clear	Oral; capsule, extended release	4.29	mg
Opadry YS-1–7006 clear	Oral; capsule, sustained action	12.156	mg
Opadry YS-1–7552 gray	Oral; capsule	7.3	mg
Opalux AS 4151 blue	Oral; capsule	2.76	mg
Opalux AS 8050-L black	Oral; capsule	2	mg
Opaque white 001	Oral; capsule	78	mg
Opaque white 002	Oral; capsule	62	mg
Opaque white 535	Oral; capsule	45	mg
Opaque white 536	Oral; capsule	65	mg
Opaque white 538	Oral; capsule	38	mg
Opaspray K-1–1414 pink	Oral; capsule, sustained action	1.112	mg
Opaspray K-1–5024 red	Oral; capsule, sustained action	0.75	mg
Orange juice	Oral; powder	1.25	%
Palm oil—soybean oil, hydrogenated	Oral; capsule	4	mg
Parabens	Oral; capsule (immed./comp. release), soft gelatin, perle	0.16	mg
Paraffin	Oral; capsule, sustained action	50	mg
PD base-1000	Oral; capsule, sustained action	225	mg
Peanut oil	Oral; capsule, coated, soft gelatin	149	mg
Peanut oil	Oral; capsule	313.8	mg
Pectin	Oral; powder	25.5	%
Peg-8 caprylic/Capric glycerides	Oral; capsule, soft gelatin	70	mg

Ingredient	Dosage Form	Qty	Unit
Peppermint oil	Oral; capsule	1.01	mg
Peppermint oil	Oral; capsule, soft gelatin	1.02	mg
Petrolatum	Oral; capsule, sustained action	0.07	mg
Pharmaceutical glaze	Oral; capsule, coated pellets	0.429	mg
Pharmaceutical glaze	Oral; capsule	34.48	mg
Pharmaceutical glaze	Oral; capsule, sustained action	75.01	mg
Polacrilin potassium	Oral; capsule	23	mg
Poloxamer 188	Oral; powder, for oral suspension	0.34	%
Poloxamer 331	Oral; powder, for suspension	0.5286	%
Poloxamer 331	Oral; powder, for solution	2.5926	%
Poloxamer 407	Oral; powder, for oral suspension	12.6	%
Polyethylene	Oral; capsule	2	mg
Polyethylene glycol 20000	Oral; capsule, hard gelatin	13.5	mg
Polyethylene glycol 20000	Oral; capsule	18	mg
Polyethylene glycol 3350	Oral; capsule	27.2	mg
Polyethylene glycol 3350	Oral; capsule, soft gelatin	76.92	mg
Polyethylene glycol 400	Oral; capsule, extended release	1.7	mg
Polyethylene glycol 400	Oral; capsule, sustained action, hard gelatin	1.7	mg
Polyethylene glycol 400	Oral; capsule, coated, soft gelatin	103.55	mg
Polyethylene glycol 400	Oral; capsule	500	mg
Polyethylene glycol 400	Oral; capsule, soft gelatin	960.78	mg
Polyethylene glycol 4000	Oral; capsule, soft gelatin	15	mg
Polyethylene glycol 4000	Oral; capsule	449.6	mg
Polyethylene glycol 600	Oral; capsule, soft gelatin	324	mg
Polyethylene glycol 600	Oral; capsule	448.4	mg
Polyethylene glycol 600	Oral; capsule, soft gelatin liquid-filled	580.6	mg
Polyethylene glycol 6000	Oral; capsule	10	mg
Polyethylene glycol 6000	Oral; capsule, extended release	12	mg
Polyethylene glycol 6000	Oral; capsule, sustained action	17.46	mg
Polyethylene glycol 6000	Oral; capsule, hard gelatin	450	mg
Polyethylene glycol 8000	Oral; capsule, sustained action	1.39	mg
Polyethylene glycol 8000	Oral; capsule	10	mg
Polyethylene glycol 8000	Oral; capsule, hard gelatin	27.8	mg
Polygalacturonic acid	Oral; powder, for solution	14.5	%
Polyglyceryl-10 oleate	Oral; capsule, soft gelatin	199.9	mg
Polyglyceryl-3 oleate	Oral; capsule, soft gelatin	330.7	mg
Polyoxyl 35 castor oil	Oral; capsule	120	mg
Polyoxyl 35 castor oil	Oral; capsule, soft gelatin	599.4	mg
Polyoxyl 40 hydrogenated castor oil	Oral; capsule	200	mg
Polyoxyl 40 hydrogenated castor oil	Oral; capsule, soft gelatin	405	mg
Polyoxyl 40 stearate	Oral; capsule, hard gelatin	0.6	mg
Polyoxyl 40 stearate	Oral; capsule	2.4	mg
Polysorbate 20	Oral; powder, for suspension	0.026	%

Ingredient	Dosage Form	Qty	Unit
Polysorbate 20	Oral; capsule	56.25	mg
Polysorbate 80	Oral; powder, for suspension	0.2	%
Polysorbate 80	Oral; capsule, soft gelatin	0.41	mg
Polysorbate 80	Oral; capsule, extended release	0.528	mg
Polysorbate 80	Oral; capsule, delayed action	1.064	mg
Polysorbate 80	Oral; granule, for oral suspension	1.1	mg
Polysorbate 80	Oral; capsule, enteric-coated pellets	2	mg
Polysorbate 80	Oral; capsule, sustained action	2.6	mg
Polysorbate 80	Oral; powder	3	%
Polysorbate 80	Oral; granule	20	mg
Polysorbate 80	Oral; capsule	418.37	mg
Polyvinyl acetal	Oral; capsule, sustained action	5	mg
Potassium carbonate	Oral; capsule	27.69	mg
Potassium chloride	Oral; capsule	62	mg
Potassium hydroxide	Oral; capsule, soft gelatin	25.6	mg
Potassium hydroxide	Oral; capsule, soft gelatin liquid-filled	25.6	mg
Potassium phosphate, dibasic	Oral; powder, for suspension	5	%
Potassium phosphate, dibasic	Oral; capsule	30	mg
Potassium phosphate, monobasic	Oral; capsule, enteric-coated pellets	17	mg
Potassium sorbate	Oral; granule, for suspension	20	mg
Povidone K25	Oral; capsule	1.5	mg
Povidone K25	Oral; capsule, extended release	12.6	mg
Povidone K25	Oral; capsule, sustained action, hard gelatin	12.6	mg
Povidone K25	Oral; capsule, sustained action	17.79	mg
Povidone K29–32	Oral; capsule, extended release	6.19	mg
Povidone K29–32	Oral; granule	6.7	mg
Povidone K29–32	Oral; capsule, sustained action	10.05	mg
Povidone K29–32	Oral; capsule, enteric-coated pellets	14.2	mg
Povidone K29–32	Oral; capsule	15	mg
Povidone K30	Oral; powder, for suspension	0.26	%
Povidone K30	Oral; capsule, extended release	5.625	mg
Povidone K30	Oral; capsule, sustained action	6.875	mg
Povidone K30	Oral; capsule, hard gelatin	8	mg
Povidone K30	Oral; capsule, soft gelatin liquid-filled	17.7	mg
Povidone K30	Oral; capsule	20	mg
Povidone K30	Oral; capsule, soft gelatin	30	mg
Povidone K90	Oral; capsule, hard gelatin	5.95	mg
Povidone K90	Oral; capsule	16	mg
Povidone K90	Oral; capsule, extended release	18.8	mg
Povidone K90	Oral; capsule, sustained action, hard gelatin	18.8	mg
Povidone K90	Oral; granule, for suspension	32	mg
Propyl gallate	Oral; capsule, soft gelatin	2	mg
Propylene glycol	Oral; capsule, sustained action	0.7954	mg

Ingredient	Dosage Form	Qty	Unit
Propylene glycol	Oral; capsule, enteric-coated pellets	1.7	mg
Propylene glycol	Oral; powder	5.5	%
Propylene glycol	Oral; capsule, soft gelatin liquid-filled	17.7	mg
Propylene glycol	Oral; capsule	52	mg
Propylene glycol	Oral; capsule, soft gelatin	148.31	mg
Propylene glycol alginate	Oral; powder	50.248	%
Propylparaben	Oral; powder, for solution	0.0158	%
Propylparaben	Oral; capsule, coated, soft gelatin	0.041	mg
Propylparaben	Oral; powder, for suspension	0.08	%
Propylparaben	Oral; capsule, soft gelatin	0.12	mg
Propylparaben	Oral; capsule	0.21	mg
Propylparaben	Oral; capsule, sustained action	0.216	mg
Propylparaben sodium	Oral; powder, for suspension	0.1	%
Propylparaben sodium	Oral; capsule, soft gelatin	0.35	mg
Quatrimycin hydrochloride	Topical; powder, for solution	0.28	%
Saccharin	Oral; granule, for suspension	16	mg
Saccharin sodium	Oral; powder, for oral suspension	0.0666	%
Saccharin sodium	Oral; powder, for reconstitution	0.312	%
Saccharin sodium	Oral; capsule, soft gelatin	0.51	mg
Saccharin sodium	Oral; powder, for suspension	1.3354	%
Saccharin sodium	Oral; capsule	2.02	mg
Saccharin sodium	Oral; powder, for solution	53.32	%
Saccharin sodium, anhydrous	Oral; powder, for suspension	1.875	%
Sea spen	Oral; powder, for suspension	1.5	%
Sesame oil	Oral; capsule	162.5	mg
Shellac	Oral; capsule	24.83	mg
Shellac	Oral; capsule, enteric-coated pellets	29	mg
Shellac	Oral; capsule, sustained action	60	mg
Shellac P.V.P. solution no. 4	Oral; capsule, sustained action	87	mg
Silica, diatomaceous	Oral; capsule	3.4	mg
Silicon	Oral; capsule	15	mg
Silicon dioxide	Oral; powder, for oral suspension	0.4	%
Silicon dioxide	Oral; capsule, hard gelatin	2	mg
Silicon dioxide	Oral; powder, for reconstitution	4	%
Silicon dioxide	Oral; powder, for suspension	4.5	%
Silicon dioxide	Oral; capsule, sustained action	5.26	mg
Silicon dioxide	Oral; capsule, enteric-coated pellets	9.635	mg
Silicon dioxide	Oral; granule, for suspension	10	mg
Silicon dioxide	Oral; capsule	22	mg
Silicon dioxide, colloidal	Oral; for suspension	0.3	%
Silicon dioxide, colloidal	Oral; capsule, coated, soft gelatin	0.5	mg
Silicon dioxide, colloidal	Oral; capsule, enteric-coated pellets	0.6	mg
Silicon dioxide, colloidal	Oral; capsule, extended release	1.7	mg

Ingredient	Dosage Form	Qty	Unit
Silicon dioxide, colloidal	Oral; capsule, sustained action, hard gelatin	1.7	mg
Silicon dioxide, colloidal	Oral; capsule, soft gelatin	1.73	mg
Silicon dioxide, colloidal	Oral; powder, for reconstitution	2.5	%
Silicon dioxide, colloidal	Oral; granule, enteric coated	3.2	mg
Silicon dioxide, colloidal	Oral; powder, for suspension	5.5	%
Silicon dioxide, colloidal	Oral; capsule, hard gelatin	5.8	mg
Silicon dioxide, colloidal	Oral; capsule, sustained action	7.02	mg
Silicon dioxide, colloidal	Oral; powder	10	%
Silicon dioxide, colloidal	Oral; powder, for oral suspension	11	%
Silicon dioxide, colloidal	Oral; capsule	11.66	mg
Silicon dioxide, colloidal	Oral; granule, for reconstitution	16.25	mg
Silicon dioxide, colloidal	Oral; granule, for suspension	25	mg
Silicon dioxide, colloidal	Oral; granule	100	mg
Silicone	Oral; powder, for suspension	0.1	%
Silicone	Oral; capsule, sustained action	0.14	mg
Silicone	Oral; capsule, hard gelatin	0.42	mg
Silicone	Oral; capsule	10	mg
Silicone emulsion	Oral; capsule, sustained action	0.078	mg
Silicone emulsion	Oral; powder, for suspension	1.24	%
Simethicone	Oral; capsule, extended release	0.0446	mg
Simethicone	Oral; capsule, sustained action	0.062	mg
Simethicone	Oral; capsule, enteric-coated pellets	0.61	mg
Simethicone	Oral; powder, for suspension	0.666	%
Simethicone	Oral; granule	3.3	mg
Simethicone	Oral; capsule	5.7	mg
Simethicone	Oral; granule, effervescent	36	mg
Simethicone emulsion	Oral; powder, for suspension	0.5	%
Simethicone emulsion	Oral; capsule	14.4	mg
Simethicone emulsion	Oral; capsule, sustained action	15.63	mg
Sodium acetate	Oral; powder, for solution	9.93	%
Sodium alginate	Oral; capsule	80	mg
Sodium aminobenzoate	Oral; capsule	0.0017	mg
Sodium benzoate	Oral; powder, for reconstitution	0.1	%
Sodium benzoate	Oral; capsule, hard gelatin	0.11	mg
Sodium benzoate	Oral; for suspension	0.2	%
Sodium benzoate	Oral; capsule	0.3	mg
Sodium benzoate	Oral; powder, for oral suspension	3.6	%
Sodium benzoate	Oral; powder, for suspension	8	%
Sodium benzoate	Oral; powder, for solution	9.332	%
Sodium benzoate	Oral; granule, for reconstitution	10	mg
Sodium benzoate	Oral; granule, for suspension	10	mg
Sodium bicarbonate	Oral; capsule, hard gelatin	2	mg
Sodium bicarbonate	Oral; powder, for solution	8.72	%

Ingredient	Dosage Form	Qty	Unit
Sodium bicarbonate	Oral; capsule	26.5	mg
Sodium bisulfite	Topical; powder, for solution	0.1	%
Sodium bisulfite	Oral; capsule	0.36	mg
Sodium carbonate	Oral; capsule, sustained action	6	mg
Sodium carbonate hydrate	Oral; powder, for oral suspension	0.6	%
Sodium cellulose	Oral; capsule	150	mg
Sodium chloride	Oral; powder, for oral suspension	0.1	%
Sodium chloride	Oral; powder, for suspension	0.25	%
Sodium chloride	Oral; granule, for suspension	13.5	mg
Sodium citrate	Oral; powder, for reconstitution	0.04	%
Sodium citrate	Oral; granule, for reconstitution	0.7	mg
Sodium citrate	Oral; powder, for suspension	3.5	%
Sodium citrate	Oral; powder, for oral suspension	4.5	%
Sodium citrate	Oral; granule, for suspension	15	mg
Sodium citrate	Oral; granule	210.625	mg
Sodium citrate, anhydrous	Oral; for suspension	0.18	%
Sodium citrate, anhydrous	Oral; powder, for reconstitution	0.75	%
Sodium citrate, anhydrous	Oral; powder, for solution	4.8	%
Sodium citrate, anhydrous	Oral; powder, for suspension	6.67	%
Sodium citrate, anhydrous	Oral; granule	1250	mg
Sodium hydroxide	Oral; capsule	0.74	mg
Sodium laureth sulfate	Oral; capsule	3.5	mg
Sodium lauryl sulfate	Oral; powder, for suspension	0.066	%
Sodium lauryl sulfate	Oral; capsule, delayed action	0.118	mg
Sodium lauryl sulfate	Oral; capsule, enteric-coated pellets	0.6	mg
Sodium lauryl sulfate	Oral; capsule, sustained action	1.6	mg
Sodium lauryl sulfate	Oral; capsule, extended release	1.7	mg
Sodium lauryl sulfate	Oral; capsule, sustained action, hard gelatin	1.7	mg
Sodium lauryl sulfate	Oral; capsule, hard gelatin	6	mg
Sodium lauryl sulfate	Oral; capsule	15	mg
Sodium lauryl sulfate	Oral; capsule, soft gelatin	24	mg
Sodium metabisulfite	Topical; powder, for solution	0.1	%
Sodium metabisulfite	Oral; capsule	0.36	mg
Sodium phosphate	Oral; capsule	36	mg
Sodium phosphate, dibasic, anhydrous	Oral; capsule	300	mg
Sodium phosphate, dibasic, dihydrate	Oral; capsule, enteric-coated pellets	0.9	mg
Sodium phosphate, dibasic, heptahydrate	Oral; capsule, sustained action	92	mg
Sodium phosphate, dibasic, heptahydrate	Oral; capsule	500	mg
Sodium phosphate, monobasic, monohydrate	Oral; capsule	109.5	mg
Sodium phosphate, tribasic, anhydrous	Oral; powder, for oral suspension	35.3	%
Sodium phosphate, tribasic, hydrate	Oral; powder, for suspension	8.8	%
Sodium propionate	Oral; powder, for suspension	0.25	%
Sodium propionate	Oral; capsule	0.362	mg

Ingredient	Dosage Form	Qty	Unit
Sodium starch glycolate	Oral; capsule, soft gelatin	7.75	mg
Sodium starch glycolate	Oral; capsule, coated pellets	16.714	mg
Sodium starch glycolate	Oral; capsule, enteric-coated pellets	16.8	mg
Sodium starch glycolate	Oral; capsule, sustained action	18.6	mg
Sodium starch glycolate	Oral; capsule, hard gelatin	20	mg
Sodium starch glycolate	Oral; capsule	180	mg
Sodium stearyl fumarate	Oral; capsule	7.263	mg
Sodium thiosulfate	Oral; capsule	20	mg
Sorbitan monooleate	Oral; capsule, soft gelatin	153.9	mg
Sorbitan trioleate	Oral; capsule	0.0244	mL
Sorbitol	Oral; granule, for suspension	28	mg
Sorbitol	Oral; powder, for suspension	34.284	%
Sorbitol	Oral; capsule, soft gelatin	66.82	mg
Sorbitol	Oral; capsule	185.18	mg
Sorbitol solution	Oral; capsule	3.112	mg
Sorbitol solution	Oral; capsule, coated, soft gelatin	3.114	mg
Sorbitol solution	Oral; capsule, soft gelatin	28.9	mg
Sorbitol–glycerin blend	Oral; capsule	61.232	mg
Soybean oil	Oral; capsule, soft gelatin	227	mg
Soybean oil	Oral; capsule	263	mg
Soybean oil, hydrogenated	Oral; capsule	1	mg
Soybean oil, hydrogenated	Oral; capsule, soft gelatin	15.3	mg
Soybean oil, refined	Oral; capsule	101	mg
Starch	Oral; capsule, soft gelatin	15.5	mg
Starch	Oral; capsule, hard gelatin	33.5	mg
Starch	Oral; capsule, enteric-coated pellets	36.4	mg
Starch	Oral; capsule, sustained action	65.2	mg
Starch	Oral; capsule	605	mg
Starch 1500 pregelatinized	Oral; capsule	294	mg
Starch 1500, pregelatinized	Oral; capsule	365.1	mg
Starch 1551	Oral; capsule	30	mg
Starch 21	Oral; capsule	150	mg
Starch 7150	Oral; capsule	0.44	mg
Starch 825	Oral; capsule	217	mg
Starch 826	Oral; capsule	237	mg
Starch, corn	Oral; capsule, sustained action	27	mg
Starch, corn	Oral; capsule, hard gelatin	289.2	mg
Starch, corn	Oral; capsule	1135	mg
Starch, corn 21	Oral; capsule	125	mg
Starch, modified	Oral; powder, for suspension	0.2	%
Starch, modified	Oral; capsule	23	mg
Starch, pregelatinized	Oral; capsule, coated, soft gelatin	15	mg
Starch, pregelatinized	Oral; capsule, hard gelatin	128.75	mg

Ingredient	Dosage Form	Qty	Unit
Starch, pregelatinized	Oral; capsule, sustained action	141.75	mg
Starch, pregelatinized	Oral; capsule	600	mg
Starch, pregelatinized corn	Oral; capsule, coated, soft gelatin	27.75	mg
Starch, pregelatinized corn	Oral; capsule	195.9	mg
Starch, pregelatinized tapioca	Oral; capsule	100	mg
Starch, wheat	Oral; capsule, sustained action	0.75	mg
Stearic acid	Oral; capsule, coated, soft gelatin	3	mg
Stearic acid	Oral; capsule, sustained action	9.32	mg
Stearic acid	Oral; capsule, hard gelatin	15	mg
Stearic acid	Oral; powder, for suspension	24.06	%
Stearic acid	Oral; capsule	52	mg
Stear-O-wet M	Oral; capsule, hard gelatin	0.25	mg
Stear-O-wet M	Oral; capsule, coated, soft gelatin	1.5	mg
Stear-O-wet M	Oral; capsule, sustained action	6	mg
Stear-O-wet M	Oral; capsule	14	mg
Stearoyl polyoxylglycerides	Oral; capsule	260	mg
Stearyl alcohol	Oral; capsule, sustained action	72	mg
Succinic acid	Oral; powder, for reconstitution	0.15	%
Sucralose	Oral; powder, for oral suspension	8	%
Sucrose	Oral; powder	25.61	%
Sucrose	Oral; powder, for solution	48.4	%
Sucrose	Oral; powder, for oral suspension	90.274	%
Sucrose	Oral; powder, for suspension	93.237	%
Sucrose	Oral; capsule, enteric-coated pellets	140.758	mg
Sucrose	Oral; capsule, delayed action	175.14	mg
Sucrose	Oral; capsule, extended release	396.14	mg
Sucrose	Oral; capsule	413.655	mg
Sucrose	Oral; capsule, sustained action	481.7	mg
Sucrose	Oral; granule, for suspension	1052.9	mg
Sucrose palmitate	Oral; powder, for suspension	1	%
Sucrose polyesters	Topical; powder, for solution	0.125	%
Sucrose stearate	Oral; capsule, extended release	31.835	mg
Sucrose stearate	Oral; capsule, sustained action	44.569	mg
Sugar confectioners	Oral; powder, for suspension	3.32	%
Sugar confectioners	Oral; capsule, sustained action	17.6	mg
Sugar confectioners	Oral; capsule	527.425	mg
Sugar fruit fine	Oral; powder, for suspension	27.52	%
Sugar/Starch insert granules	Oral; capsule, sustained action	254.49	mg
Surelease E-719010 clear	Oral; capsule, sustained action	37.44	mg
Surelease E-7–7050	Oral; capsule, enteric-coated pellets	28.331	mg
Talc	Oral; capsule, soft gelatin	0.1	mg
Talc	Oral; capsule, coated pellets	0.257	mg
Talc	Oral; capsule, sustained action, hard gelatin	16.7	mg

Ingredient	Dosage Form	Qty	Unit
Talc	Oral; capsule, enteric-coated pellets	17	mg
Talc	Oral; granule, for oral suspension	34	mg
Talc	Oral; capsule, extended release	39	mg
Talc	Oral; capsule, delayed action	70.46	mg
Talc	Topical; powder	98	%
Talc	Oral; capsule, hard gelatin	108	mg
Talc	Oral; capsule, sustained action	122.06	mg
Talc	Oral; granule, enteric coated	215.2	mg
Talc	Oral; capsule	220.4	mg
Talc triturate	Oral; capsule	1.92	mg
Tartaric acid	Oral; capsule	9	mg
Tartaric acid	Oral; capsule, sustained action	215.1	mg
Timing solution clear N-7	Oral; capsule, sustained action	26.2	mg
Titanium dioxide	Oral; capsule, extended release	0.7305	mg
Titanium dioxide	Oral; capsule, delayed action	0.7625	mg
Titanium dioxide	Oral; capsule, coated, soft gelatin	0.78	mg
Titanium dioxide	Oral; capsule, hard gelatin	0.8512	mg
Titanium dioxide	Oral; capsule, enteric-coated pellets	4.4	mg
Titanium dioxide	Oral; capsule, sustained action	4.4	mg
Titanium dioxide	Oral; capsule, soft gelatin	6	mg
Titanium dioxide	Oral; powder, for suspension	9	%
Titanium dioxide	Oral; granule, for suspension	35.7	mg
Titanium dioxide	Oral; powder, for oral suspension	40	%
Titanium dioxide	Oral; capsule	1387	mg
Tocophersolan	Oral; capsule, soft gelatin	282	mg
Tocophersolan	Oral; capsule	300	mg
Tragacanth	Oral; powder, for suspension	24	%
Triacetin	Oral; capsule	1.08	mg
Triacetin	Oral; capsule, coated pellets	1.205	mg
Triacetin	Oral; capsule, sustained action	2.76	mg
Triacetin	Oral; capsule, enteric-coated pellets	5.1	mg
Triethyl citrate	Oral; capsule, sustained action, hard gelatin	3.3	mg
Triethyl citrate	Oral; granule, for oral suspension	3.8	mg
Triethyl citrate	Oral; capsule, delayed action	3.848	mg
Triethyl citrate	Oral; capsule, sustained action	7.5	mg
Triethyl citrate	Oral; capsule	8.9	mg
Triethyl citrate	Oral; capsule, enteric-coated pellets	9.16	mg
Triethyl citrate	Oral; capsule, extended release	15.03	mg
Triglyceride, synthetic	Oral; capsule, soft gelatin	160	mg
Triglycerides, medium chain	Oral; capsule	159.9764	mg
Tristearin	Oral; capsule	225	mg
Tromethamine	Oral; capsule, soft gelatin	15	mg
Vanillin	Oral; powder, for suspension	0.666	%

Ingredient	Dosage Form	Qty	Unit
Vegetable oil	Oral; capsule	2	mg
Vegetable oil, hydrogenated	Oral; capsule	82	mg
Vegetable oil, hydrogenated	Oral; capsule, soft gelatin	82.8	mg
Vegetable shortening	Oral; capsule	10.56	mg
Vitamin E	Oral; capsule	1	mg
Vitamin E	Oral; capsule, soft gelatin	1	mg
Vitamin E acetate	Oral; capsule	2	mg
Wax, white	Oral; capsule	3	mg
Wax, white	Oral; capsule, sustained action	7.183	mg
Wax, white	Oral; capsule, soft gelatin	18.36	mg
Wax, yellow	Oral; capsule	2.72	mg
Xanthan gum	Oral; for suspension	0.075	%
Xanthan gum	Oral; powder, for reconstitution	2.5	%
Xanthan gum	Oral; powder, for solution	4.1	%
Xanthan gum	Oral; powder, for oral suspension	6.7	%
Xanthan gum	Oral; powder, for suspension	8	%
Xanthan gum	Oral; powder	9	%
Xanthan gum	Oral; granule, for suspension	15	mg
Xanthan gum	Oral; capsule, enteric-coated pellets	75	mg
Xanthan gum	Oral; granule, for oral suspension	75	mg
Zinc stearate	Oral; capsule	2.04	mg

Part II

Manufacturing Formulations

Uncompressed Solids Formulations

Acebutolol Hydrochloride Capsules

The capsules are provided in two dosage strengths, which contain 200 or 400 mg of acebutolol as the hydrochloride salt. The inactive ingredients present are D&C red No. 22, FD&C blue No. 1, FD&C yellow No. 6, gelatin, povidone, starch, stearic acid, and titanium dioxide. The 200-mg dosage strength also contains D&C red No. 28; the 400-mg dosage strength also contains FD&C red No. 40.

Aceclofenac Instant Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
50.00	1	Aceclofenac	50.00
165.83	2	Orange Flavor	165.83
3292.30	3	Sorbitol	3292.30
169.23	4	Lutrol F 68	169.23
169.23	5	Cremophor RH 40	169.23
QS	6	Deionized water	~2 kg

Manufacturing Directions

1. Granulate items 1 to 3 with a solution of items 4 to 6. Pass through a 0.8-mm screen, dry, and sieve again.
2. Fill 3.9 g in sachets corresponding to 50 mg aceclofenac.

Acetaminophen and Diphenhydramine Hydrochloride Hot Therapy Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
650.00	1	Acetaminophen (micronized)	650.00
250.00	2	Diphenhydramine hydrochloride	250.00
0.90	3	FD&C yellow dye No. 10 lake	0.90
0.0005	4	FD&C red dye No. 40	0.0005
18081.10	5	Castor sugar	18081.10
200.00	6	Aspartame	200.00
250.00	7	Maize starch (dried)	250.00
180.00	8	Citric acid	180.00
38.00	9	Sodium citrate	38.00
200.00	10	Sodium chloride	200.00
240.00	11	Honey flavor (dry)	240.00
100.00	12	Lemon flavor (dry)	100.00
QS	13	Purified water	QS

Manufacturing Directions

1. Mix items 1 and 2 well, then pass through 0.8-mm sieves.
2. Mix items 3, 5, and 13 to make a clear solution.
3. Add mixture of items 1 and 2 to second step mixture and mix well.
4. Add this mixture to item 4 and mix. Take care to avoid lump formation.
5. Dry in an oven and maintain a constant temperature.
6. Sieve and add items 6 to 12. Mix well. Make sure all the solids added are in fine powder form.
7. Fill 20 g of powder into sachets and seal.

Acetaminophen Capsules (500 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500.00	1	Acetaminophen powder	500.00
30.00	2	Sodium starch glycolate	30.00
1.00	3	Aerosil® 200	1.00
2.00	4	Magnesium stearate	2.00
17.00	5	Starch dried	15.00

Manufacturing Directions

1. Charge all items after passing through No. 60 screen mesh and mix for 1 hour.
2. Fill 550 mg in size 0 capsule.

Acetaminophen, Doxylamine, and Caffeine Effervescent

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
500.00	1	Acetaminophen powder	500.00
5.00	2	Doxylamine succinate	5.00
33.00	3	Caffeine (knoll)	33.00
391.00	4	Tartaric acid	391.00
417.00	5	Sodium hydrogen carbonate	417.00
6.00	6	Kollidon® 30	6.00
–	7	Isopropanol (or ethanol)	QS
30.00	8	Sodium citrate	30.00
707.00	9	Sugar	707.00

Manufacturing Directions

1. Granulate a mixture of items 1 to 5 with a solution of items 6 and 7. Dry at 60°C under vacuum conditions. Sieve and mix with items 8 and 9.
2. Fill 2.1 g in sachets at a maximum 30% of relative atmospheric humidity. If the solvent isopropanol is replaced by water, the granulation should be done in a fluidized bed.

Acetaminophen Instant Granules

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
166.66	1	Acetaminophen fine powder	166.66
426.64	2	Sucrose fine powder	426.64
300.00	3	Kollidon® CL-M	300.00
23.33	4	Aspartame	23.33
16.66	5	Orange flavor	16.66
16.66	6	Strawberry flavor	16.66
40.00	7	Kollidon 30	40.00
250.00	8	Ethanol 96%	250.00

Manufacturing Directions

1. Granulate items 1 to 6 with solution made from items 7 and 8 and pass through a 0.8-mm sieve.
2. Fill 1.5 or 3.0 g in sachets (for 250- or 500-mg strength, respectively). The free-flowing granules are well dispersible in cold water. Suspend 1.5 or 3.0 g of the granules (=250 or 500 mg acetaminophen, respectively) in a glass of water.

Acetaminophen Instant Granules

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
192.30	1	Acetaminophen fine powder	192.30
500.00	2	Sorbitol instant (Merck)	500.00
192.30	3	Kollidon CL-M	192.30
27.00	4	Aspartame	27.00
19.23	5	Orange flavor	19.23
19.23	6	Strawberry flavor	19.23
11.53	7	Sodium citrate	11.53
11.53	8	Citric acid	11.53
30.76	9	Kollidon® 90 F	30.76
192.30	10	Ethanol 96%	192.30

Manufacturing Directions

1. Granulate items 1 to 8 with a solution made from items 9 and 10 and pass through a 0.8-mm sieve.
2. Fill 1.3 or 2.6 g in sachets (for 250- or 500-mg strength, respectively).
3. The free-flowing granules are well dispersible in cold water. Suspend 1.2 or 2.6 g of the granules (=250 or 500 mg acetaminophen, respectively) in a glass of water.

Acetaminophen Instant Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
500.00	1	Acetaminophen fine powder	500.00
1300.00	2	Sorbitol instant (Merck)	1300.00
500.00	3	Lutrol F 127	500.00
30.00	4	Citric acid powder	30.00
30.00	5	Sodium citrate	30.00
80.00	6	Kollidon 90 F	80.00
500.00	7	Ethanol 96%	500.00

Manufacturing Directions

1. Granulate a mixture of items 1 to 5 in a solution of item 6 in item 7. Fill 2.44 g in sachets (=500 mg acetaminophen).
2. The free-flowing granules are well dispersible in cold water.
3. The taste of the suspension is only slightly bitter (2.44 g in a glass of water).

Acetaminophen, Pseudoephedrine Hydrochloride, Chlorpheniramine Hot Therapy Sachet

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
650.00	1	Acetaminophen micronized	650.00
60.00	2	Pseudoephedrine hydrochloride	60.00
4.00	3	Chlorpheniramine maleate	4.00
1.20	4	Dispersed orange	1.20
18081.10	5	Castor sugar	18081.10
200.00	6	Aspartame	200.00
250.00	7	Cornstarch dried	250.00
180.00	8	Citric acid	180.00
38.00	9	Sodium citrate	38.00
200.00	10	Sodium chloride	200.00
400.00	11	Blood orange dry flavor	400.00
QS	12	Purified water	QS

Manufacturing Directions

1. Items 1 and 2 are mixed well, followed by passing through sieves and adding to items 3 and 12 premixed and made into a clear solution.
2. Take care to avoid lump formation.
3. Dry in an oven.
4. Sieve and add items 6 to 11. Mix well.
5. Make sure all the solids added are in fine powder form. Fill 20 g powder into sachets and seal.

Acetaminophen, Pseudoephedrine Hydrochloride Hot Therapy Sachet

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
650.00	1	Acetaminophen micronized	650.00
260.00	2	Pseudoephedrine hydrochloride	260.00
0.90	3	FD&C yellow No. 10 lake	0.90
18081.10	4	Castor sugar	18081.10
200.00	5	Aspartame	200.00
250.00	6	Cornstarch dried	250.00
180.00	7	Citric acid	180.00
38.00	8	Sodium citrate	38.00
200.00	9	Sodium chloride	200.00
240.00	10	Apple dry flavor	240.00
100.00	11	Cinnamon dry flavor	100.00
QS	12	Purified water	QS

Manufacturing Directions

1. Items 1 and 2 are mixed well, followed by passing through sieves and added to items 3 and 12 premixed and made into a clear solution.
2. Take care to avoid lump formation.
3. Dry in an oven.
4. Sieve and add items 6 to 11. Mix well.
5. Make sure all the solids added are in fine powder form. Fill 20 g powder into sachets and seal.

Acetaminophen Swallow Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
325.00	1	Acetaminophen fine powder	325.00
409.50	2	Sodium carbonate fine powder	409.50
13.91	3	Cornstarch	13.91
32.50	4	Starch pregelatinized	32.50
1.30	5	Polyvinylpyrrolidone K25	1.30
0.39	6	Potassium sorbate	0.39
9.75	7	Talc	9.75
3.25	8	Stearic acid	3.25
23.86	9	Ac-Di-Sol®	23.86
QS	10	Water purified	QS

Manufacturing Directions

1. Sift items 1 to 6 through a 16-mesh sieve into a suitable mixer and granulate with a suitable quantity of item 10 to form a medium/heavy granule.
2. Dry the granules in a suitable oven at 45°C until the water content is <1%.
3. Pass the dried granule through a 12-mesh sieve to produce a white granule (yield 20.250 kg).
4. Fill 819.46 mg in a suitable capsule size.

Acetazolamide Sustained-Release Capsules

Each sustained-release capsule, for oral administration, contains 500 mg of acetazolamide and the following inactive ingredients: ethyl vanillin, FD&C blue No. 1, FD&C yellow No. 6, gelatin, glycerin, microcrystalline cellulose, methylparaben, propylene glycol, propylparaben, silicon dioxide, and sodium lauryl sulfate.

Acetylcysteine Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
66.66	1	Acetylcysteine BP (200 mg/sachet)	66.66
914.16	2	Sugar (18–60 mesh)	914.16
3.33	3	Saccharin sodium	3.33
0.66	4	Silicon dioxide (colloidal)	0.66
0.16	5	FD&C yellow dye No. 6	0.16
QS	6	Mandarin flavor (e.g., Naarden)	~13.00 mL

Manufacturing Directions

1. Load the acetylcysteine and half the amount of sugar and saccharin sodium into a suitable blender and premix for 30 minutes.
2. Sift the premix through a 0.8-mm screen.
3. Load again into the blender.
4. Add the remaining amount of sugar and colloidal silicon dioxide and blend until uniform (typically this is achieved on the PK processor® by heating the envelope to 40°C and mixing until the product cools to 30–35°C).
5. Dissolve the dye in 13 mL of distilled water.
6. Continue mixing the blended powders and slowly add the solution from step above.
7. When addition of the solution is complete, continue massing until the granulation is evenly wetted and colored. If necessary, complete massing by adding additional quantities of distilled water (approximately 1 mL increments).
8. Verify that massing is adequate and note the total quantity of added water. Record the total quantity of water added. Do not overmass.
9. Spread the wet granules on trays and dry at 50°C until loss on drying (LOD) is NMT 1% (3 hours at 60°C at 5 mm Hg).
10. Allow the granules to cool, then sift on an oscillating granulator fitted with 1.18-mm aperture screen.
11. Load the granules from step above into a suitable blender, add the flavor, and blend until uniform (15 minutes), passing it through a 1.18-mm screen if necessary.
12. Fill into suitable approved sachets at a theoretical fill weight of 3 g per sachet.

Acitretin Capsules

Acitretin, a retinoid, is available in 10- and 25-mg gelatin capsules for oral administration. Each capsule contains acitretin, microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink, and maltodextrin (a mixture of polysaccharides). Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, and edetate calcium disodium.

Acrivastine and Pseudoephedrine Hydrochloride Capsules

Acrivastine and pseudoephedrine hydrochloride is a fixed combination product formulated for oral administration. Acrivastine is an antihistamine and pseudoephedrine is a decongestant. Each capsule contains 8 mg of acrivastine and 60 mg of pseudoephedrine hydrochloride and the following inactive ingredients: lactose, magnesium stearate, and sodium starch glycolate. The green and white capsule shell consists of gelatin, D&C yellow No. 10, FD&C green No. 3, and titanium dioxide. The yellow band around the capsule consists of gelatin and D&C yellow No. 10. The capsules may contain one or more parabens and are printed with edible black and white inks.

Acrivastine and Pseudoephedrine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
8.00	1	Acrivastine	8.00
60.00	2	Pseudoephedrine	60.00
440.00	3	Lactose	440.00
5.00	4	Magnesium stearate	5.00

Manufacturing Directions

1. Blend items 1 to 3 after sifting through an 80-mesh screen.
2. Pass item 4 through a 100-mesh screen and add to step 1. Blend for 2 minutes.
3. Fill 513 mg in size 0 capsules.

Acyclovir Capsules

Each capsule contains 200 mg of acyclovir and the inactive ingredients cornstarch, lactose, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&C blue No. 2, and titanium dioxide. It may contain one or more parabens and is printed with edible black ink.

Acyclovir Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
200.00	1	Acyclovir, USE acyclovir micronized	212.00
3.00	2	Sodium lauryl sulfate	3.00
20.00	3	Cornstarch	20.00
52.00	4	Lactose monohydrate	52.00
2.00	5	Magnesium stearate	2.00
–	6	Ethanol	60 mL

Manufacturing Directions

1. Charge items 1 to 4 in a suitable mixer and mix for 5 minutes with slow chopper speed.
2. Add item 6 slowly with mixing at slow speed. Mix and chop for 2 to 3 minutes.
3. Check for satisfactory massing. Use additional item 6 if necessary.
4. Spread granules to $^1/_4$-inch thick layer on paper trays and dry at 50°C for 4 hours to a moisture of not more than (NMT) 1%. Dry further if required after testing.
5. Pass the dried granules through a granulator equipped with a 0-mm sieve.
6. Pass item 5 through 250-mm sieve and add to step 5. Mix for 3 minutes.
7. Use size 1 capsules to fill 289 mg.

Adenosine Monophosphate Topical Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
30.00	1	DBcAMP[a]	30.00
920.00	2	Polyethylene glycol 6000	920.00
30.00	3	Talc	30.00
20.00	4	Colloidal silica Aerosil 200	20.00

[a]Sodium N^6, 2'-O-dibutyryladenosine-3',5'-cyclic phosphate.

Manufacturing Directions

1. Pass all items through a 100-mesh sieve and blend.
2. Pack in a bottle. Topical powder for treatment of dermatosis.

Aluminum Acetate Powder

Each powder packet, when dissolved in water and ready for use, provides the active ingredient aluminum acetate, resulting from the reaction of calcium acetate (938 mg) and aluminum sulfate (1191 mg). The resulting astringent solution is buffered to an acid pH.

Aluminum Hydroxide and Magnesium Carbonate Dry Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
200.00	1	Aluminum hydroxide dry gel (Giulini)	200.00
200.00	2	Basic magnesium carbonate	200.00
240.00	3	Kollidon CL-M	240.00
211.50	4	Sorbitol, crystalline	211.50
41.30	5	Orange flavor	41.30
82.60	6	Kollidon 30	82.60
3.30	7	Coconut flavor	3.30
4.13	8	Banana flavor	4.13
4.13	9	Saccharin sodium	4.13
8.26	10	Water	8.26

Manufacturing Directions

Granulate mixture of items 1 to 5 with solution of items 6 to 10, pass through a sieve, and dry. Shake 58 g of the granules with 100 mL of water.

Aminosalicylic Acid Granules

Delayed-release granule preparation of aminosalicylic acid (p-aminosalicylic acid: 4-aminosalicylic acid) for use with other antituberculosis drugs for the treatment of all forms of active tuberculosis due to susceptible strains of tubercle bacilli. The granules are designed for gradual release to avoid high peak levels that are not useful (and perhaps toxic) with bacteriostatic drugs. Aminosalicylic acid is rapidly degraded in acid media; the protective acid-resistant outer coating is rapidly dissolved in neutral media such that a mildly acidic food, such as orange, apple, or tomato juice or yogurt or applesauce should be consumed. PASER granules are the free base of aminosalicylic acid and do *not* contain sodium or sugar. With heat p-aminosalicylic acid is decarboxylated to produce CO_2 and m-aminophenol. If the airtight packets are swollen, storage has been improper. Supply warning: DO NOT USE if packets are swollen or the granules have lost their tan color and are dark brown or purple. The granules are supplied as off-white, tan-colored granules with an average diameter of 1.5 mm and an average content of 60% aminosalicylic acid by weight. The acid-resistant outer coating will be completely removed after a few minutes at a neutral pH. The inert ingredients are colloidal silicon dioxide, dibutyl sebacate, hydroxypropyl methylcellulose, methacrylic acid copolymer, microcrystalline cellulose, and talc.

Amlodipine Besylate and Benazepril Hydrochloride Capsules

The capsules are formulated for oral administration with a combination of amlodipine besylate equivalent to 2.5 or 5 mg of amlodipine and 10 or 20 mg of benazepril hydrochloride. The inactive ingredients of the capsules are calcium phosphate, cellulose compounds, colloidal silicon dioxide, crospovidone, gelatin, hydrogenated castor oil, iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch glycolate, starch, talc, and titanium dioxide.

Amlodipine Besylate and Benazepril Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Benazepril hydrochloride	20.00
32.92	2	Lactose monohydrate	32.92
5.00	3	Pregelatinized starch	5.00
1.00	4	Colloidal silica	1.00
2.00	5	Crospovidone	2.00
10.00	6	Microcrystalline cellulose	10.00
4.00	7	Hydrogenated castor oil	4.00
–	8	Water purified	QS
4.88	9	Hydroxypropyl methylcellulose 2910, 3 cps	4.88
0.12	10	Polysorbate 80	0.12
–	11	Water purified	QS
QS	12	Talc	QS
5.00	13	Amlodipine, USE amlodipine besylate	6.94
124.05	14	Microcrystalline cellulose, Avicel PH102	124.05
63.00	15	Dibasic calcium phosphate	63.00
4.00	16	Sodium starch glycolate	4.00
2.00	17	Magnesium stearate	2.00

Manufacturing Directions

1. Mill items 1 to 3 and blend together.
2. Add water (item 8) to granulate the blend.
3. Screen the wet granules and dry them in oven.
4. Mill the dried granules and then mill together with items 5 to 7.
5. Screen item 4 and mix in step 4.
6. Compress into a core.
7. Dissolve item 10 in item 11 and add item 9 to it.
8. Coat the core prepared in step 6 using item 12 to dust the cores.
9. Mix items 13 to 16, then blend and screen. Blend again in a separate vessel.
10. Screen item 17 separately and add to step 9.
11. Fill in size 1 hard gelatin capsules the coated cores with 200 mg of the powder in step 10.

Amlodipine Besylate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
5.00	1	Amlodipine, USE amlodipine besylate	7.00
93.00	2	Microcrystalline cellulose, Avicel PH102	93.00
65.00	3	Dibasic calcium phosphate	65.00
8.00	4	Sodium starch glycolate	8.00
0.50	5	Colloidal silicon dioxide Aerosil 200	0.50
1.50	6	Magnesium stearate	1.50
1	7	Empty hard gelatin shell, size 3	1000.00

Manufacturing Directions

1. Sift amlodipine besylate, Avicel PH102, dibasic calcium phosphate, and Primojel® through a 0.5-mm sieve and mix well in a mixer.
2. Lubricate the powder mixture in step 1 with magnesium stearate and Aerosil 200 that has been previously sieved. Mix for 2 minutes to get a homogeneous powder.
3. Fill the capsule in the capsule-filling machine to a weight adjusted to provide 5 mg amlodipine per capsule.

Amlodipine Free Base Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
5.00	1	Amlodipine base	5.00
20.00	2	Predried potato starch	20.00
72.60	3	Microcrystalline cellulose	72.60
0.50	4	Magnesium stearate	0.50

Manufacturing Directions

1. The amlodipine base was sieved through a 500-micron screen.
2. The other excipients have been sieved through an 850-micron screen.
3. All excipients except magnesium stearate have been mixed in a free fall mixer for 15 minutes at approximately 25 rpm.
4. Magnesium stearate was added and the powder blend was mixed for another 5 minutes at approximately 25 rpm and fill gelatin capsules.

Amlodipine Maleate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
6.42	1	Amlodipine maleate	6.42
72.60	2	Microcrystalline cellulose	72.60
20.00	3	Predried potato starch	20.00
0.50	4	Magnesium stearate	0.50

Manufacturing Directions

1. The amlodipine maleate was sieved through a 500-micron screen. The other excipients have been sieved through an 850-micron screen.
2. All excipients except magnesium stearate have been mixed in a free fall mixer for 15 minutes at approximately 25 rpm. The pH value was checked in 20% aqueous slurry (pH around 5.9).
3. Magnesium stearate was added and the powder blend was mixed for another 5 minutes at approximately 25 rpm.
4. Gelatin capsules filled at approximately 100 mg weight.

Amoxicillin and Bromhexine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Amoxicillin, USE amoxicillin trihydrate	290.00
8.00	2	Bromhexine, USE bromhexine hydrochloride	8.80
34.00	3	Starch dried	34.00
3.00	4	Magnesium stearate	3.00
3.50	5	Aerosil 200	3.50
40.00	6	Talc	40.00
1.00	7	Hard gelatin capsule, size 1	1000.00

Manufacturing Directions

1. Charge items 1 and 3 to 6 in a suitable blender and mix for 10 minutes.
2. In a separate mixer, add small portion of step 1 and add by geometric dilution item 2 and mix well.
3. Sift through No. 60 mesh screen.
4. Fill 398 mg in each capsule.

Amoxicillin and Clavulanic Acid Powder for Suspension, 125 mg and 31.25 mg per 5 mL (Amoxil)*

Each capsule, with a royal blue opaque cap and pink opaque body, contains 250 or 500 mg of amoxicillin as the trihydrate. The cap and body of the 250-mg capsule are imprinted with the product name and 250; the cap and body of the 500-mg capsule are imprinted with AMOXIL and 500. The inactive ingredients are D&C red No. 28, FD&C blue No. 1, FD&C red No. 40, gelatin, magnesium stearate, and titanium dioxide.

Amoxicillin and Clavulanic Acid Powder for Suspension

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
19.00	1	Amoxicillin trihydrate	19.00
10.60	2	Potassium clavulanate (eq. clavulanic acid) 1:1 in sylloid	10.60
15.00	3	Aerosil 200	15.00
48.80	4	Mannitol	48.80
0.50	5	Citric acid monohydrate	0.50
1.90	6	Sodium citrate	1.90
1.20	7	Xanthan gum	1.20
2.00	8	Powdered flavor	2.00
0.45	9	Sweetener	0.45

Manufacturing Directions

1. Charge items 1 to 9 after passing through a No. 60 screen mesh at a temperature of 25°C and RH of NMT 30% in a suitable blender-mixer.
2. Fill 5 g in a 30-mL bottle. Reconstitution with water gives 125 mg of item 1 and 31.25 mg of item 2 per 5 mL.

Amoxicillin and Clavulanate Potassium for Suspension*

The inactive ingredients are powder for oral suspension (i.e., colloidal silicon dioxide, flavorings, succinic acid, xanthan gum, and aspartame) hydroxypropyl methylcellulose, mannitol, silica gel, silicon dioxide, and sodium saccharin.

Amoxicillin and Clavulanate Potassium for Suspension*

Bill of Materials			
Scale (mg/bottle) (7 g/60 mL)	Item	Material Name	Qty/1000 Bottle (g)
1500.00	1	Amoxicillin trihydrate (equivalent to 1250 g of amoxicillin)	1500.00
393.60	2	Potassium clavulanate	393.60
150.00	3	Xanthan gum	150.00
1800.00	4	Hydroxypropyl methylcellulose dried	1800.00
150.00	5	Saccharin sodium	150.00
300.00	6	Silicon dioxide colloidal	300.00
10.00	7	Succinic acid	10.00
1500.00	8	Silica gel	1500.00
183.60	9	Peach dry flavor	183.60
236.40	10	Strawberry dry flavor	236.40
731.14	11	Lemon dry flavor	731.14

Note: 156 mg/5 mL syrup 60 mL (125 mg amoxicillin and 31.25 mg clavulanic acid.) 6.95 g/60 mL: Each 5 mL of reconstituted syrup contains 156.25 mg of amoxicillin and clavulanic acid.

Manufacturing Directions

Note: Throughout the process of manufacturing and filling, maintain a relative humidity (RH) of NMT 40%.

I. Preparation of powder mix
   A. Mill 50% of amoxicillin trihydrate, saccharin sodium (dried to NMT 2% moisture by the Karl Fischer method), succinic acid through a 250-mm sieve or using a Fitz mill or equivalent with blades forward. Transfer to a blending mixer and mix for 15 minutes.
   B. Mill remaining amoxicillin trihydrate through a No. 100 mesh using a Fitz mill or equivalent and mix with above screened powders. Mix for 15 minutes.
   C. Mill xanthan gum, hydroxypropyl methylcellulose (dried to NMT 2% moisture dried at 105°C for 2 hours), colloidal silica, and silica gel through a No. 250-mm sieve or using a Fitz mill or equivalent with knives forward. Add to above mixture in step band mix for 15 minutes at medium speed.
   D. Screen all dry flavors through a 250-mm mesh screen and add to above mixture from step C.

II. Finishing
   A. Fill dry powder approximately 7 g in dry 60-mL glass bottles at a fill weight based on the assay of the active constituent.

Amoxicillin Powder for Suspension (125 and 250 mg)

Bill of Materials			
Scale (mg/5 mL)[a]	Item	Material Name	Qty/5 l (g)
125.00	1	Amoxicillin, USE amoxicillin trihydrate with 8% excess	143.50
1.04	2	Simethicone A	1.04
111.11	3	Castor sugar	111.11
444.44	4	Castor sugar	444.44
2479.86	5	Castor sugar	2479.86
23.33	6	Sodium citrate	23.33
1.67	7	Xanthan gum	1.67
13.33	8	Blood orange dry flavor	13.33
0.74	9	Vanilla dry flavor	0.74
4.44	10	Orange banana dry flavor	4.44
14.44	11	Aerosil 200	14.44

[a]After reconstitution.

Manufacturing Directions

1. Charge item 3 and item 2 in a mixer and mix for 2 minutes.
2. Add item 4 and items 6 to 11 and mix for 5 minutes.
3. Pass through a Fitz mill; impact forward at high speed using sieve 24228.
4. In a separate mixer, charge item 5 and item 1 and mix well, passing through a sifter.
5. Add to step 3 and mix for 20 minutes.
6. Fill 65 g for 100-mL and 39 g for 60-mL pack size.

Amoxicillin Trihydrate Capsules (250 and 500 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500.00	1	Amoxicillin, USE amoxicillin trihydrate	576.00
1.20	2	Aerosil 200	1.20
7.72	3	Magnesium stearate	7.72
8.91	4	Sodium lauryl sulfate	8.91

Manufacturing Directions

1. All operations are to be completed at RH 40% to 45% and temperature 20°C to 25°C.
2. Pass item 1 through a 1-mm sieve in a mixing vessel.
3. Pass items 2 to 4 after passing through a 250-mm sieve; add one-third portion of item 1 from step 2 and mix for 10 minutes; add another one-third item 1 and mix; and finally, add balance and mix.
4. Fill 594 mg in size 0 capsules.

Ampicillin Dry Syrup (5% = 500 mg/10 mL)

Formulation

Ampicillin trihydrate, 5.0 g; sodium citrate, 5.0 g; citric acid, crystalline, 2.1 g; sodium gluconate, 5.0 g; sorbitol crystalline [10], 40.0 g; Kollidon CL-M [1], 6.0 g; orange flavor, 1.5 g; lemon flavor, 0.5 g; saccharin sodium, 0.4 g.

Manufacturing

Mix all components and fill in a bottle.

Preparation of the Suspension for Administration

To 66 g of the powder, add water to fill to a total volume of 100 mL shaking well.

Ampicillin Powder for Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/5 l (g)
125.00	1	Ampicillin, USE ampicillin trihydrate 8% excess	144.25
1.00	2	Simethicone A	1.00
138.90	3	Castor sugar	138.90
27.44	4	Sodium citrate	27.44
7.00	5	Xanthan gum	7.00
15.00	6	Blood orange dry flavor	15.00
0.78	7	Vanilla dry flavor	0.78
7.55	8	Strawberry dry flavor	7.55
10.00	9	Aerosil 200	10.00
138.90	10	Castor sugar	138.90
2747.90	11	Castor sugar	2747.90

Manufacturing Directions

1. All operations should be completed in a RH of 45% to 55% and a temperature of 23°C to 25°C.
2. Charge items 2 and 3 in a suitable blender and mix for 5 minutes.
3. Charge items 1 and 4 to 10 in a separate mixer and mix for 5 minutes.
4. Add step 2 into step 3 and mix for 10 minutes.
5. Add item 11 and mix for 10 minutes.
6. Fill 65 g for a 100-mL pack and 39 g for a 60-mL pack. For 250-mg strength, adjust active ingredient and adjust with item 11.

Ampicillin Trihydrate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500.00	1	Ampicillin, USE ampicillin trihydrate compacted	582.13
1.17	2	Aerosil 200	1.17
11.69	3	Magnesium stearate	11.69

Manufacturing Directions

1. Pass item 1 through a 1-mm sieve into a double-cone blender, except approximately 5% of the quantity.
2. In a separate container, pass and collect items 2 and 3 through a 250-mm sieve.
3. Add the balance of item 1 retained in step 1 into step 2 and blend for 10 minutes; pass through a 900-mm sieve if necessary.
4. Add to step 2 and blend for 10 minutes.
5. Fill 223.125 mg in size 0 capsules.

Ampicillin Trihydrate Capsules for Suspension

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Ampicillin, USE ampicillin trihydrate	250.00
2.50	2	Magnesium stearate	2.50
–	3	Gelatin capsule, size 2	1000.00

Manufacturing Directions

1. Dry blend ampicillin trihydrate and magnesium stearate in Baker Perkins mixer; bag off into polyethylene-lined drums.
2. Fill on Zanasi AZ20 capsule-filling machine. The average fill weight is 295±9 mg; the average total weight is 360 mg. For a 500-mg capsule (size 0 capsules), the average fill weight is 593±15 mg; the average total weight is 690 mg.

Ampicillin Trihydrate Powder for Suspension

Bill of Materials			
Scale (mg/bottle) (15 mL)	Item	Material Name	Qty/1000 Bottles (g)
1500.00	1	Ampicillin, USE ampicillin trihydrate (assuming potency 871; adjust amount accordingly)	1722.22
3072.10	2	Sucrose (adjust amount based on item 1 potency)	3072.10
372.53	3	Sodium citrate Dihydrate	372.53
31.93	4	Saccharin sodium	31.93
2.12	5	Acid citric anhydrous	2.12
45.23	6	Sodium carboxymethyl cellulose	45.23
22.61	7	Magnesium aluminum silicate Veegum® F	22.61
7.98	8	Dye	7.98
26.60	9	Flavor	26.60
18.00	10	Sodium benzoate	18.00
QS	11	Water purified	400.00

Note: Simethicone 0.15% can be added to reduce foaming during reconstitution. Adjust fill volume for the final size of reconstitution container, such as 60 mL or different strength desired, e.g., 250 mg/5 mL upon reconstitution.

Manufacturing Directions

Caution: Handle with extreme care. Protect face and hands from amoxicillin because some individuals may be sensitive and reactions may occur.

1. Mixing
   a. Pass sugar through a 2.38-mm aperture screen using an oscillating granulator.
   b. Pass the following ingredients through a 595-mm aperture screen in a Fitz mill (high speed, impact forward): Sodium citrate, acid citric, saccharin sodium, carboxymethylcellulose, amoxicillin, and magnesium aluminum silicate.
   c. Charge ingredients from steps A and B into a suitable mixer and mix for 10 minutes until uniform.
   d. Dissolve yellow dye in approximately 60 g of purified water.
   e. Mass mixture from step C with dye solution from step D. If necessary, pass wet mass through a 4.76-mm aperture screen. *Caution*: Do not overwet or overmass. Product must remain as wet granules.
   f. Spread evenly on stainless steel trays. If necessary, pass wet mass through a 4.76-mm aperture screen.
   g. Oven dry granules at 45°C until LOD is NMT 0.6% (vacuum 60°C, 2 hours).
2. Finishing
   a. Fill product into suitable containers. Theoretical fill weight is 5.32 g (+3% fill excess) per 15-mL container, requiring approximately 12 mL of water for reconstitution.

Antibacterial and Bacterial Culture Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
125–500 mg	1	Penicillin, cephalosporin, or macrolide	125—500
10–100 million	2	*Lactobacillus acidophilus*[a]	10–100 B

[a]Substitute with *Lactobacillus* spores, 300–600 million; *Streptococcus thermophilus*, 10 million; *Lactobacillus lactis*, 10–500 million; *Streptococcus lactis*, 10 million; *Saccharomyces cerevisiae*, 10 million; lactobacilli, GG 10^{10} units. This formulation includes the anti-infective agent, which can be penicillin, a cephalosporin, or a macrolide in doses ranging from 125 to 500 mg per capsule. Also included in the same capsule is a granulation of the bacteria, which is known to be eradicated during the therapy with these antibiotics. The bacterial are coated to protect them from the effect of coadministered antibiotic and last in the intestine for over 3 months replenishing the lost flora and reduce many side effects related to use of antibiotics.

Manufacturing Directions

1. Granules of one of the active ingredients (e.g., microorganisms) are first prepared by the following process.
   Ingredients Parts by weight
   Microorganism: 42.86%
   Microcrystalline cellulose: 53.93%
   Magnesium stearate: 1.07%
   Colloidal silicone dioxide: 0.71%
   Cross carmellose sodium: 1.43%
   The granules formed are compressed into a tablet-by-tablet compression machine heaving a laying facility at a temperature less than 25°C and RH NMT 50%.
   'Tablets are transferred to a coating pan for coating using the following formulation.
   Ingredients Parts by weight
   Hydroxypropyl methylcellulose phthalate: 4.37%
   Titanium dioxide: 0.96%
   Purified talc: 0.19%
   Polyethylene glycol: 0.99%
   Isopropyl alcohol: 34.95%
   Dichloromethane: 58.54%
2. The remaining active ingredient (antibacterial agent) is mixed with excipients and filled into gelatin capsules. Before sealing of capsules the coated tablet containing active ingredients is introduced into capsules. The relative proportion of antiinfective agent and excipients for filling in capsule:
   Ingredients Parts by weight
   Anti-infective agent: 91.94%
   Pregelatinized starch: 6.24%
   Magnesium stearate: 1.44%
   Sodium lauryl sulfate: 0.38%

Antifungal Foot Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Dichlorobenzyl alcohol (myacide SF)	5.00
5.00	2	Allantoin	5.00
200.00	3	Cornstarch	200.00
790.00	4	Talc	790.00

Manufacturing Directions

1. Mix all ingredients using the geometric dilution technique.
2. Fill.

Antioxidant Eye Nutrition Supplement Capsules

This is an antioxidant supplement formulated to provide nutritional support for the eye. It contains essential antioxidant vitamins, minerals, and 6 mg of lutein. Each capsule contains ascorbic acid, 60 mg; DL-alpha-tocopheryl acetate, 30 IU; zinc oxide, 15 mg (elemental); cupric oxide, 2 mg (elemental). The inactive ingredients are lactose monohydrate, crospovidone, magnesium stearate, and silicone dioxide.

Aspartame Granules in Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
30.00	1	Aspartame	30.00
2.00	2	Silicon dioxide colloidal	2.00
968.00	3	Cerelose powder No. 60[a]	1052.00

[a] Std. qty. of cerelose powder allows for loss on drying.

Manufacturing Directions

1. Protect from moisture; 40% RH at 25°C.
2. Oven dry cerelose powder at 50°C overnight until LOD is no more than 3% (3 hours, vacuum at 60°C). Pass dried cerelose powder through 595-µm aperture screen in oscillating granulator.
3. Charge the following ingredients into suitable blender: aspartame, half the amount dried of cerelose powder (milled), and silicon dioxide colloidal. Add balance of dried cerelose powder (total amount of dried powder is 968 g/kg) and blend for 15 minutes.
4. Pass blended powders through an 840-mm aperture screen using an oscillating granulator and discharge into polyethylene-lined drums. Fill weight of 1 g/sachet.

Aspartame Powder in Sachets

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
47.50	1	Aspartame	47.50
2.50	2	Silicon dioxide (colloidal)	2.50
950.00	3	Mannitol granules	950.00

Manufacturing Directions

1. Protect from humidity. Maintain a RH of 40% and a temperature of 25°C.
2. Pass mannitol granules and colloidal silicon dioxide through an 840-µm screen in oscillating granulator.
3. Charge the following ingredients into suitable blender: aspartame, half of the amount of mannitol granules, and colloidal silicon dioxide.
4. Add balance of mannitol granules and blend for 15 minutes.
5. Pass blended powders through an 840-µm screen using an oscillating granulator and discharge into polyethylene-lined drums.
6. Fill weight is 0.8 g/sachet.

Aspirin and Chlorpheniramine Powder

The active ingredients are aspirin (650 mg) and chlorpheniramine maleate (4 mg) per powder. The inactive ingredients are fumaric acid, glycine, lactose, potassium chloride, silica, and sodium lauryl sulfate.

Aspirin-Coated Crystals

Formulation: aqueous-based polymeric coating solution: hydroxypropylmethylcellulose (HPMC E5) 6%, propylene glycol 1%, FD&C red No. 3 0.01%, and distilled Water QS to 100.

Manufacturing Directions

1. A standard coating pan and an air suspension 6-inch column are used to coat aspirin crystals of 100 to 200 mesh using top-spray, bottom-spray, and tangential-spray fluid bed coating processes.
2. Aspirin crystal load is placed in the product container.
3. The crystals are fluidized in an expansion chamber.
4. The spray nozzle is located low in the expansion chamber so that liquid is applied when the crystals are moving at a higher velocity.
5. This serves to minimize surface wetting and to inhibit agglomeration.
6. A filter is used to separate entrained crystals from the exiting process air stream.
7. The pump is calibrated with coating solution prior to start-up of the coating process.
8. The turbine is activated and the process air is heated to 55°C.
9. The spray and shake cycle is started and ran continually until the coating solution is completely depleted.
10. The coated aspirin crystal bed is dried for 10 minutes and the product is cooled to 35°C.

11. The product is removed, weighed, and passed through a 20-mesh screen to remove any agglomerates.
12. Aspirin-coated crystals can be used to make tablets or capsules. Tablets are prepared containing five components: 50% by weight aspirin crystals (100–200 mesh) coated previously with 3% to 6% polyvinylpyrrolidone; 25% calcium carbonate buffer, 5% to 15% hydroxypropymethylcellulose (K100LV) as the gel forming hydrophilic matrix material; 14.5% to 19.5% microcrystalline cellulose (Avicel PH 101) as the excipient/binder; and 0.5% stearic acid as the hydrophobic lubricant.
13. 650-mg samples are either compressed in $^1/_2$ inch punches or filled in size 0 capsules.

Aspirin and Phenylpropanolamine Powder

The active ingredients are aspirin (650 mg), phenylpropanolamine hydrochloride (25 mg) per powder, and pseudoephedrine hydrochloride (60 mg) per powder sachet. The inactive ingredients are fumaric acid, glycine, lactose, potassium chloride, silica, and sodium lauryl sulfate.

Aspirin Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
320.00	1	Aspirin	320.00
480.00	2	Gelatin	480.00
QS	3	Water purified	QS
QS	4	Corn oil	QS
QS	5	Petroleum ether	QS
QS	6	Isopropyl alcohol	QS
QS	7	Glutaraldehyde 1%	QS

Manufacturing Directions

1. Item 2 is added to 0.8 L of item 3 and the mixture is allowed to stand at 25°C for 1 hour while the gelatin hydrates and swells.
2. This preparation is then heated to 60°C while it is stirred at 300 rpm for 30 minutes; 0.5 L of distilled water, previously heated to 60°C, is then added, and the solution is stirred at 500 rpm for an additional 5 minutes.
3. Item 1, as finely powdered aspirin, is then added to the solution while stirring is continued to give a uniform suspension.
4. After 1 minute, the warm suspension is poured without delay into 5 L of a rapidly stirred (500 rpm) solution of 20% corn oil in petroleum ether, which has been previously brought to 25°C, and the resulting emulsion is rapidly (i.e., over a period of no more than 5 minutes) cooled to 5°C while the stirring is continued.
5. L of cold (5°C) isopropyl alcohol is then added to dehydrate the gelatin microspheres while the preparation is stirred for another 10 minutes.
6. The microspheres are then collected by filtration and washed 3 times with cold (5°C) isopropyl alcohol.
7. They are then immersed in 0.8 L of a 1% solution of glutaraldehyde in cold (5°C) isopropyl alcohol for 8 hours and then washed 3 times with isopropyl alcohol, collected by filtration, and vacuum dried for 24 hours.
8. The microspheres, which average 300 to 400 μm in diameter, are filled into gelatin capsules for administration as a safer, long-acting analgesic product (800 mg of the microsphere mix, which contains 320 mg of aspirin, is filled into each size 0 capsule). The capsules, when released into the stomach following ingestion, provide for sustained release of the drug for from 1 to 4 hours and also ensure that the drug reaches the gastrointestinal mucosa while in the solution state, instead of the more deleterious solid state that is characteristic of conventional dosage forms of this drug. Physical integrity of the matrix is maintained for 1 to 4 hours after the release of its drug content, after which time the matrix dissolves.

Aspirin, Salicylamide, and Caffeine Powder

Each powder contains aspirin (650 mg), salicylamide (195 mg), and caffeine (33.3 mg). The inactive ingredients are dioctyl sodium sulfosuccinate, fumaric acid, lactose, and potassium chloride. For arthritis strength powder, the active ingredients in each powder are aspirin (742 mg), salicylamide (222 mg), and caffeine (38 mg). The inactive ingredients are dioctyl sodium sulfosuccinate, fumaric acid, lactose, and potassium chloride.

Azithromycin Suspension

Manufacturing Directions

1. Sucrose (1433.216 g), azithromycin dihydrate (530.784 g), mannitol (1200 g), pregelatinized starch (200 g), and magnesium oxide (280 g) were placed in a blender and blended for 15 minutes.
2. The blend was passed through a sieve and blended for another 15 minutes. To the blend were added aspartame (100 g), artificial cherry flavor (8 g), artificial cream flavor (8 g), and artificial strawberry flavor (8 g) and the mixture was blended for 10 minutes.
3. To the blend was added magnesium stearate (30 g) and the mixture was further blended for 5 minutes. The contents of the blender were removed from the blender and packaged for constitution with water.

Azithromycin Capsules

Each capsule contains azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard gelatin capsules (containing FD&C red No. 40). They also contain the following inactive ingredients: anhydrous lactose, cornstarch, magnesium stearate, and sodium lauryl sulfate.

Azithromycin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Azithromycin, USE azithromycin dihydrate[a]	263.00
196.00	2	Anhydrous lactose	196.00
50.00	3	Starch (cornstarch dried)	50.00
9.00	4	Magnesium stearate	9.00
2.00	5	Sodium lauryl sulfate	2.00
–	6	Empty hard gelatin capsules, size 0	1000.00

Note: Weight of one capsule = 520 mg + shell.

[a]Considering the potency of the active ingredient is 1000 μg/mg (anhydrous basis) with water content 5%, the required quantity of azithromycin dihydrate depends on the provided potency.

Manufacturing Directions

Note: Processing should be done under a controlled room temperature and humidity area. The limits are room temperature: 20°C to 25°C, RH: 40% to 45%.

1. Mix items 1 and 2 in a polyethylene bag. Pass through a 500-mm stainless steel sieve. Collect in a stainless steel drum lined with a polyethylene bag.
2. Mix items 3 to 5 in a polyethylene bag. Pass through a 250-mm stainless steel sieve. Collect in a polyethylene bag.
3. Take a polyethylene bag. Check if there is any leakage. Add the powder mix from steps 1 and 2. Mix manually for 1 minute.
4. Unload the powder in a stainless steel drum.
5. Check the temperature and RH of the room before beginning encapsulation. The limits are RH: 40% to 45%, temperature: 20°C to 25°C.
6. Load the empty capsule shells, size 0, in the hopper.
7. Switch the power to "ON." Check the locking of the capsules without powder. The locking length is 21.1 to 21.7 mm.
8. Load the powder in the hopper by scoop. Switch the power to "ON." Adjust the fill net weight to 520 mg per capsule. Nominal weight of one capsule: 520 mg + weight of one empty shell (95 mg). Target weight: 520 mg±2% + weight of one empty shell (95 mg).

Azithromycin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Azithromycin base, USE azithromycin monohydrate	263.72
149.88	2	Lactose anhydrous	149.88
9.40	3	Magnesium stearate/Sodium lauryl sulfate (90/10)	9.40

Note: Based on bulk potency of 94.8%, adjust with item 2.

Manufacturing Directions

1. Sift items 1 and 2 through an 80-mesh screen and blend.
2. Add item 3 and mix for 3 minutes.
3. Fill 470 mg in size 0 capsules.

Azithromycin Capsules and Oral Suspension

Capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard gelatin capsules (containing FD&C red No. 40). They also contain the following inactive ingredients: anhydrous lactose, cornstarch, magnesium stearate, and sodium lauryl sulfate. It is also supplied as a powder for oral suspension in bottles containing azithromycin dihydrate powder equivalent to 300, 600, 900, or 1200 mg azithromycin per bottle and the following inactive ingredients: sucrose; sodium phosphate tribasic anhydrous; hydroxypropyl cellulose; xanthan gum; FD&C red No. 40; and spray-dried artificial cherry, creme de vanilla, and banana flavors. After constitution, each 5 mL of suspension contains 100 or 200 mg of azithromycin.

Azithromycin for Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/Bottles (g)
200.00	1	Azithromycin, USE azithromycin dihydrate[a]	1.263
3861.50	2	Castor sugar	23.169
18.00	3	Tribasic sodium phosphate	0.108
15.00	4	Sodium benzoate	0.090
2.50	5	Hydroxypropyl cellulose (Klucel EF)	0.015
2.50	6	Xanthan gum	0.015
15.00	7	Cherry dry flavor	0.090
33.33	8	Vanilla dry flavor	0.200
25.00	9	Banana dry flavor	0.150

[a]Considering the potency of the active ingredient is 1000 μg/mg (anhydrous basis) with water content 5%, the required quantity of azithromycin dihydrate depends on the provided potency.

Manufacturing Directions

Note: Processing should be done under controlled room temperature and humidity conditions. The limits are room temperature: 20°C to 25°C, RH: 40% to 45%.

1. Dry item 3 at 90°C for 2 hours.
2. Sift item 2 through a Fitz mill, impact forward, medium speed using sieve No. 24228.
3. Collect in a stainless steel drum.
4. Sift 12 g of item 2 (From step 2) and item 1 through 630-μm s.s. sieve in sifter. Load into a drum blender. Mix for 3 minutes.
5. Mix 5 g of item 2 (from step 2), item 3 from step 1, and items 4 to 9 in a polyethylene bag. Sift through 630-mm s.s. sieve in sifter. Collect in a polyethylene bag.
6. Load the powder mix from step 4 into step 3 in a drum blender. Mix for 3 minutes.
7. Load 6.17 g of item 2 (from step 2) into step 5 in a drum blender. Mix for 3 minutes.
8. The fill weight for a 30-mL pack is 25.10 g.

Azithromycin for Oral Suspension

Bill of Materials			
Scale (mg/bottle)	Item	Material Name	Qty/1000 Bottles (g)
838.57	1	Azithromycin dihydrate	838.57
15487.74	2	Sucrose	15487.74
70.01	3	Sodium phosphate tribasic anhydrous	70.01
26.62	4	Hydroxypropyl cellulose (Klucel EF)	26.62
26.62	5	Xanthan gum (Keltrol)	26.62
0.67	6	FD&C red No. 40	0.67
59.94	7	Cherry flavor spray-dried artificial No. 11929	59.94
133.28	8	Vanilla flavor artificial No. 11489	133.28
99.96	9	Banana flavor spray-dried artificial No. 15223	99.96

Note: Based on bulk potency of 95.4%, adjust with item 2.

Manufacturing Directions

1. Sift all ingredients through an 80-mesh screen and mix well.
2. Fill 16.743 g per bottle.
3. To reconstitute, add 0.52 mL/g of dry suspension.

Azithromycin Sachets for Oral Suspension

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
1.000	1	Azithromycin base, USE azithromycin dihydrate	1.048
9.707	2	Sucrose	9.707
0.088	3	Sodium phosphate tribasic anhydrous	0.088
0.055	4	Colloidal silicon dioxide	0.055
0.038	5	Cherry flavor spray-dried artificial	0.038
0.064	6	Banana flavor spray-dried artificial	0.064

Note: Based on bulk potency of 95.4% of azithromycin, adjust for potency using item 2.

Manufacturing Directions

1. Sift items 1 to 4 through an 80-mesh screen into a blender. Blend.
2. Sift items 5 and 6 and add to step 1. Blend.
3. Fill 11 g in one sachet, approximately 3.25 in × 4 in, polyethylene-lined. To reconstitute, add contents to 60 mL water and stir well.

Balsalazide Disodium Capsules

Each capsule contains 750 mg of balsalazide disodium. The inactive ingredients are colloidal silicon dioxide and magnesium stearate. The sodium content of each capsule is approximately 86 mg.

Benazepril Hydrochloride and Amlodipine Besylate Capsules

These capsules are a combination of amlodipine besylate and benazepril hydrochloride. The capsules are formulated for oral administration with a combination of amlodipine besylate equivalent to 2.5 or 5 mg of amlodipine and 10 or 20 mg of benazepril hydrochloride. The inactive ingredients of the capsules are calcium phosphate, cellulose compounds, colloidal silicon dioxide, crospovidone, gelatin, hydrogenated castor oil, iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch (potato) glycolate, starch (corn), talc, and titanium dioxide.

Benazepril Hydrochloride and Amlodipine Besylate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Benazepril hydrochloride	20.00
32.90	2	Lactose monohydrate	32.90
5.00	3	Pregelatinized starch	5.00
1.00	4	Colloidal silicon dioxide	1.00
2.00	5	Crospovidone	2.00
10.00	6	Microcrystalline cellulose	10.00
4.00	7	Hydrogenated castor oil	4.00
QS	8	Water purified	QS
4.88	9	Hydroxypropyl methylcellulose 2910, 3 cps	4.88
0.19	10	Polysorbate 80	0.19
QS	11	Purified water	QS
QS	12	Talc	QS
5.00	13	Amlodipine, USE amlodipine besylate	6.94
124.05	14	Microcrystalline cellulose	124.05
63.00	15	Calcium phosphate dibasic	63.00
4.00	16	Sodium starch glycolate	4.00
2.00	17	Magnesium stearate	2.00

Manufacturing Directions

1. Benazepril hydrochloride cores are prepared using the following:
   a. Items 1 to 3 are milled and blended together and water is added to granulate the blend.
   b. The wet granules are screened and oven dried. The dried granules are then milled together with items 5 to 7.
   c. Item 4 is screened and then mixed with the other ingredients. The resulting mixture is then compressed into a core.
2. The resulting cores are coated with a coating solution prepared as follows: Item 10 is dissolved in the water and item 9 is added thereto.
   a. The previously made cores are then coated with this solution and the wet coated tablets are dried.
   b. The dried tablets are then dusted with item 12.
3. Amlodipine besylate for incorporation into the formulation is prepared as follows:
   a. Items 13 to 16 are mixed together and the blended mixture is screened and reblended.
   b. Item 17 is separately screened and then blended with the reblended mixture containing the amlodipine.
4. No. 1 hard gelatin capsules are used to encapsulate benazepril hydrochloride containing coated core along with 200 mg of the amlodipine besylate containing powder per capsule.

Bisacodyl Colonic Delivery Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
210.00	1	Sugar sphere	210.00
5.00	2	Hydroxypropyl methylcellulose	5.00
3.00	3	Bisacodyl micronized	3.00
1.00	4	Hydroxypropyl methylcellulose	1.00
18.00	5	Eudragit® L100–55	18.00
5.00	6	Eudragit S	5.00
4.00	7	Dibutyl phthalate	4.00
8.00	8	Talc	8.00
1.00	9	Red ferric oxide	1.00
2.00	10	Talc	2.00

Manufacturing Directions

1. Bisacodyl is micronized in a fluid energy mill using a grinding pressure of 50 psi to produce a powder with 90% of the particles below 10 μm.
2. It is dispersed in water at a level of 2.7% by weight, with 0.9% by weight of hydroxypropyl methylcellulose (HPMC) as a binding polymer sprayed onto sugar spheres (6.53–6.63 mm diameter) in a perforated pan coater maintaining an outlet airbed temperature of approximately 40°C.
3. Barrier coat: HMPC is dissolved in water to produce 4% by weight solution, which is coated on the substrates described above in a perforated pan coater maintaining an outlet air/bed temperature of approximately 40°C.
4. Inner enteric coat: Eudragit L100–55 and dibutyl phthalate are dissolved in a solution of isopropanol, acetone, and water (37:9:1) at levels of 8.0% and 1.6% (total weight percent) respectively. Talc is then suspended in the solution at a level of 3.3% by weight. The resulting mixture is coated onto the barrier-coated substrates in step 4 in a perforated pan coater maintaining an outlet air/bed temperature of approximately 30°C.
5. Outermost enteric coat: Eudragit S and dibutyl phthalate are dissolved in a solution of isopropanol, acetone, and water (37:9:1) at levels of 8.0% and 1.6% (total weight percent) respectively. Red ferric oxide and talc are then suspended in the solution at levels of 1.2% and 2.1% by weight respectively. The resulting mixture is coated onto the barrier-coated substrates above in a perforated pan coater maintaining an outlet air/bed temperature of approximately 30°C.
6. Appropriate theoretical quantity is filled in hard capsules.

Brompheniramine and Pseudoephedrine Capsules

These capsules are light green and clear, and contain white beads. The extended-release capsule contains brompheniramine maleate (12 mg) and pseudoephedrine hydrochloride (120 mg) in a specially prepared base to provide prolonged action. Alternate strength is 6 mg and 60 mg respectively. The capsules also contain the following inactive ingredients: calcium stearate, D&C yellow No. 10, FD&C blue No. 1, FD&C yellow No. 6, gelatin, pharmaceutical glaze, starch, sucrose, and talc.

Budesonide Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
1.00	1	Budesonide micronized	1.00
321.00	2	Sugar spheres	321.00
6.60	3	Aquacoat ECD30	6.60
0.50	4	Acetyltributyl citrate	0.50
0.10	5	Polysorbate 80	0.10
17.50	6	Eudragit L100–55	17.50
1.80	7	Triethylcitrate	1.80
8.80	8	Talc	8.80
0.01	9	Antifoam MMS	0.01

Manufacturing Directions

1. Budesonide (32.2 g) is suspended in the Aquacoat ECD30 dispersion (0.70 kg) with the aid of the polysorbate 80 (0.42 g) together with acetyltributyl citrate (15.8 g).
2. The mixture is sprayed onto sugar spheres (10.2 kg) in a fluid bed apparatus.
3. The enteric coating, consisting of the Eudragit L100–55 dispersion [Eudragit L100–55 (0.558 kg), triethylcitrate (55.8 g), talc (0.279 kg), antifoam MMS (0.44 g), and polysorbate 80 (2.79 g)] is then sprayed on the spheres.
4. The pellets are dried in the fluid bed apparatus, sieved, and filled in hard gelatin capsules.

Budesonide Inhalation Powder

The inhalation-driven, multidose dry powder inhaler contains only micronized budesonide. Each actuation of container provides 200 μg budesonide per metered dose, which delivers approximately 160 μg budesonide from the mouthpiece (based on in vitro testing at 60 L/min for 2 sec).

Butalbital and Acetaminophen Capsules

Each capsule contains butalbital (50 mg) and acetaminophen (325 mg). In addition, each capsule may also contain the following inactive ingredients: benzyl alcohol, butylparaben, D&C red No. 28, D&C red No. 33, edetate calcium disodium, FD&C blue No. 1, FD&C red No. 40, gelatin, methylparaben, propylparaben, silicon dioxide, sodium lauryl sulfate, sodium propionate, and titanium dioxide.

The fluid bed sprayer/dryer is operated with the following parameters.

Flow rate: 1.5 mL/min
Inlet air temperature: 25°C
Outlet air temperature: 25°C
Air flap: 35
Atomizer: 2 bar

1. A size 0 capsule after the enteric coating will typically have the following composition.
   Preemulsion solution: 0.589 g
   Undercoat polymer: 0.027 g
   Enteric coat polymer: 0.032 g, 0.648 g

Calcitonin (Salmon) Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500 IU	1	Salmon calcitonin	500000 IU
0.048	2	Dimyristoyl phosphatidic acid	0.048
3.44	3	Aprotinina	3.44
3.78	4	Hydroxypropyl cellulose-LF	3.78
3.78	5	Polyoxy-40 stearate	3.78
140.97	6	Polyethylene glycol 400	140.97
15.55	7	Propylene glycol	15.55
8.83	8	Citrate buffer	8.83
31.49	9	Cholesterol	31.49
17.40	10	Tween 80	17.40
63.69	11	Egg yolk lecithin	63.69
19.79	12	D-Alpha-tocopherol	19.79
28.15	13	Glyceryl monooleate	28.15
251.45	14	Isostearic acid	251.45

Note: Human Growth Hormone: 2.6 IU = 1 mg.
[a]Aprotinin: 7500 KIU = 1 mg.

Manufacturing Directions

1. Polyoxy-40 stearate is dispersed in the solvent mixture of polyethylene glycol 400 and propylene glycol.
2. Sodium cholate is also separately dispersed in the mixture.
3. A water solution containing recombinant human growth hormone, phospholipid, and aprotinin is then added to the solvent mixture from step 1 and the pH is adjusted to 2.5 with the help of buffer.
4. The lipid solution is made separately in another vessel.
5. To the oil solution, the polyol solution is added drop-wise while mixing continuously. While mixing, it is suggested that the vessel be ice jacketed to prevent the denaturation of the protein in the formulation.
6. Clear transparent liquid, which is called the preemulsion solution, is obtained after approximately 5 minutes of mixing at low speed. An in situ emulsion can be made by mixing any ratio of the preemulsion solution with the simulated intestinal fluid.
7. The preemulsion solution is filled in a size 0 hard gelatin capsule, and the capsule is sealed with a band of gelatin solution. The banding helps to coat the capsule uniformly.
8. The capsule is then coated with a 10% hydroxypropyl methylcellulose solution as an undercoat. The amount of coat required is sufficient just enough to cover the capsule uniformly with a thin layer of the polymer coat. Usually, a 3.5% to 4.5% weight gain of the capsules is a good indication of the amount required as an undercoat.
9. Once the capsule is coated with an undercoat, enteric coating is applied. For enteric coating purposes, different polymers, such as hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, are used.
10. Anionic copolymers, which are based on methacrylic acid and methyl methacrylate and are commercially available as Eudragit, are also suitable polymers for enteric coating purposes. The polymer is dissolved in organic solvents such as ethyl alcohol, methyl alcohol, acetone, or isopropyl alcohol. A combination of two solvents can also be used. The amount of enteric coating solution required is 5% to 6% of the weight gain of the capsules from the original weight of the capsules before applying enteric coat. A typical enteric coating solution is made as follows: methacrylic acid and methyl, 10% w/w; methacrylate copolymer (polymer); diethyl butyl phthalate (plasticizer), 2% w/w; acetone, 22% w/w; isopropanol, 66% w/w.
11. Mix acetone and isopropanol. Add the polymer slowly with constant mixing. Once the polymer is dissolved, add the plasticizer slowly and let it dissolve.
12. For size 0 capsules, the above-mentioned enteric coating solution can be sprayed using fluidizing.

Calcitriol Capsules

It is available as capsules containing 0.25 or 0.50 μg calcitriol, BHA, and BHT as antioxidants. The capsules contain a fractionated triglycerides of palm seed oil. Gelatin capsule shell contains glycerin, methyl, and propyl parabens, and sorbitol, with the following dye system: 0.25 μg of FE&C red No. 3, FD&C yellow No. 6, and titanium dioxide.

Calcium Carbonate Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
600.00	1	Calcium carbonate	600.00
900.00	2	Gelatin	900.00
QS	3	Water purified	1.5 l
QS	4	Corn oil	QS
QS	5	Petroleum ether	QS
QS	6	Isopropyl alcohol	QS
QS	7	Glutaraldehyde 1%	QS

Manufacturing Directions

1. Item 2 is added to 1.5 L of item 3 and the mixture is allowed to stand at 25°C for 1 hour while the gelatin hydrates and swells.
2. To this mixture is added item 1 and the preparation is heated to 60°C while it is stirred at 300 rpm for 30 minutes to effect dissolution of the gelatin and to ensure even suspension of the calcium carbonate. Additional distilled water, previously heated to 60°C, is then added to bring the total volume to 100°C while the stirring is continued.
3. This preparation is slowly poured into 12 L of a mixture consisting of 20% by volume of corn oil in petroleum ether, which has previously been heated to 60°C while the petroleum ether solution is stirred at 500 rpm. This preparation is then cooled to 5°C with continued stirring and the stirring is continued at 500 rpm for 1 hour after the lower temperature is reached.
4. While stirring of the preparation at 5°C is continued, 6 L of isopropanol is then added.
5. The solid microspheres are then collected by filtration and washed 3 times with isopropyl alcohol.
6. The capsules are then immersed in 1.5 L of a 1% solution of glutaraldehyde in isopropyl alcohol for 8 hours at 5°C.
7. The capsules are then washed again 3 times with isopropyl alcohol, filtered, and vacuum dried for 24 hours.
8. The microspheres, which average between 200 and 300 μm in diameter, are filled into gelatin capsules for administration as a long-acting antacid product (1.5 g of the microsphere mix, which contains 600 mg calcium carbonate, are filled into each size 0 capsule).
9. The microcapsules, when released into the stomach following ingestion, delay the reaction of the calcium carbonate with the acid of the stomach for a useful period of time (between 3 and 6 hours), which provides for sustained antacid protection for the patient.
10. Physical integrity of the matrix is maintained from 1 to 4 hours after the release of its drug contents, after which the matrix dissolves through hydrolytic cleavage of its bonds and proteolytic digestion.

Camptothecin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	CPT-11	100.00
470.00	2	Polyethylene glycol 13000	470.00
50.00	3	Triacetin	50.00
5.00	4	Polysorbate 80	5.00
QS	5	Capsule shell HPMC	1000.00

Manufacturing Directions

1. Items 2 to 4 are melted and item 1 is added and admixed thoroughly; the mixture is allowed to cool and solidify.
2. Mill the step 1 mixture into a suitable size and fill in an HPMC shell capsules.

Carbamazepine Extended-Release Capsules

The capsule is a multicomponent capsule formulation consisting of three different types of beads: immediate-release beads, extended-release beads, and enteric-release beads. The three bead types are combined in a specific ratio to provide twice daily dosing of carbamazepine. The inactive ingredients are citric acid, colloidal silicon dioxide, lactose monohydrate, microcrystalline cellulose, polyethylene glycol, povidone, sodium lauryl sulfate, talc, triethyl citrate, and other ingredients. The 200-mg capsule shells contain gelatin, FD&C red No. 3, FD&C yellow No. 6, yellow iron oxide, FD&C blue No. 2, and titanium dioxide, and are imprinted with white ink. The 300-mg capsule shells contain gelatin, FD&C blue No. 2, FD&C yellow No. 6, red iron oxide, yellow iron oxide, and titanium dioxide, and are imprinted with white ink.

Manufacturing Directions

This product is made from three types of pellets, one with instant-release profile and two with sustained-release profile; generally, an equal component of each pellet is used but other variations may be used as well.

	Percent	Kilograms
Pellet A: Immediate-Release Component		
Microcrystalline cellulose, N.F. (MCC) (Avicel PH-101/102, Emcocel)	40.0	40.0
Hydroxypropyl methylcellulose (HPMC) (Methocel E5/E50/K5/K50)	2.5	0.025
Croscarmellose, type A, N.F. (Ac-Di-Sol)	2.0	0.020
Sodium lauryl sulfate (SLS)	0.1	0.001
Carbamazepine	55.4	0.554
Total	100.0	1.000
Pellet B: Sustained-Release Component		
Microcrystalline cellulose	30.0	0.300
Hydroxypropyl methylcellulose	5.0	0.050
Sodium monoglycerate	8.0	0.080
Tartaric acid	5.0	0.050
Sodium lauryl sulfate	0.2	0.002
Carbamazepine	51.8	0.518
Total	100.0	1.000
Coating		
Ethacrylic/Methacrylic acid esters (Eudragit RS100)	45.0	0.450
Ethacrylic/Methacrylic acid esters (Eudragit RL100)	45.0	0.450
Propylene glycol	9.0	0.090
Talc	1.0	0.010
Total	100.0	1.000
Pellet C: Delayed-Release Component		
Microcrystalline cellulose	25.0	0.250
Hydroxypropyl methylcellulose phthalate	10.0	0.100
Tartaric acid	10.0	0.100
Sodium monoglycerate	7.5	0.075
Dioctyl sodium sulfosuccinate	0.5	0.005
Carbamazepine	47.0	0.470
Total	100.0	1.000
Coating		
Cellulose acetate phthalate (CAP)	60.0	0.600
Ethylcellulose	25.0	0.250
PEG400	15.0	0.150
Total	100.0	1.000

Cefaclor Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Cefaclor	250.00
15.00	2	Starch	15.00
5.00	3	Silicon fluid 350 CS	5.00
4.00	4	Magnesium stearate	4.00

Note: For 500-mg strength, fill proportionally higher quantity.

Manufacturing Directions

1. Mix cefaclor with silicon fluid and magnesium stearate.
2. Slug and granulate if necessary for flow.
3. Mix with starch powder.
4. Fill in appropriate size 2 capsules. Finish capsules with polishing methods.

Cefdinir Capsules and Oral Suspension*

Capsules contain 300 mg cefdinir and the following inactive ingredients: carboxymethylcellulose calcium, polyoxyl 40 stearate, magnesium stearate, and silicon dioxide. The capsule shells contain FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, titanium dioxide, gelatin, and sodium lauryl sulfate. Powder for oral suspension, after reconstitution, contains 125 mg/5 mL cefdinir and the following inactive ingredients: sucrose, citric acid, sodium citrate, sodium benzoate, xanthan gum, guar gum, artificial strawberry and cream flavors, silicon dioxide, and magnesium stearate.

Cefixime for Oral Suspension*

Powder for oral suspension, when reconstituted, provides 100 mg/5 mL. The powder for oral suspension is strawberry flavored and contains sodium benzoate, sucrose, and xanthan gum.

Cefpodoxime Proxetil for Oral Suspension*

Each 5 mL of oral suspension contains cefpodoxime proxetil equivalent to 50 or 100 mg of cefpodoxime activity after constitution and the following inactive ingredients: artificial flavorings, butylated hydroxy anisole (BHA), carboxymethylcellulose sodium, microcrystalline cellulose, carrageenan, citric acid, colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, lactose, maltodextrin, natural flavorings, propylene glycol alginate, sodium citrate, sodium benzoate, starch, sucrose, and vegetable oil.

Cefprozil for Oral Suspension*

Cefprozil for oral suspension contains cefprozil equivalent to 125 or 250 mg of anhydrous cefprozil per 5 mL of constituted suspension. In addition, the oral suspension contains the following inactive ingredients: aspartame, cellulose, citric acid, colloidal silicone dioxide, FD&C red No. 3, flavors (natural and artificial), glycine, polysorbate 80, simethicone, sodium benzoate, sodium carboxymethylcellulose, sodium chloride, and sucrose.

Ceftibuten Capsules and Oral Suspension*

Capsules contain ceftibuten dihydrate equivalent to 400 mg of ceftibuten. Inactive ingredients contained in the capsules formulation include magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The capsule shell and band contain gelatin, sodium lauryl sulfate, titanium dioxide, and polysorbate 80. The capsule shell may also contain benzyl alcohol, sodium propionate, edetate calcium disodium, butylparaben, propylparaben, and methylparaben. Oral suspension after reconstitution contains ceftibuten dihydrate equivalent to 90 mg of ceftibuten per 5 mL. Oral suspension is cherry flavored and contains the following inactive ingredients: cherry flavoring, polysorbate 80, silicon dioxide, simethicone, sodium benzoate, sucrose (approximately 1 g/5 mL), titanium dioxide, and xanthan gum.

Ceftibuten for Oral Suspension

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
72.00	1	Ceftibuten trihydrate	72.00
0.40	2	Polysorbate 80	0.40
0.80	3	Simethicone	0.80
16.00	4	Xanthan gum	16.00
10.00	5	Silicone dioxide	10.00
18.00	6	Titanium dioxide	18.00
8.00	7	Sodium benzoate	8.00
3.66	8	Cherry flavor, natural and artificial (microencapsulated)	3.66
QS	9	Sucrose QS to 1 kg	QS

Manufacturing Directions

Note: This formulation, upon reconstitution, gives a final concentration of 19 mg/mL. For 36 mg/mL, use 144.00 g of item 1 and 4 g of item 7. Adjust quantity of item 1 based on moisture content. The quantity given here is for anhydrous form; adjust with item 9.

1. Pass all items through an 80-mesh screen and blend.
2. Fill into 60-mL bottles at either 5, 7.5, or 15 g, or 120-mL bottles at 25 or 30 g aliquots.

Cefuroxime for Oral Suspension*

The oral suspension, when reconstituted with water, provides the equivalent of 125 or 250 mg of cefuroxime (as cefuroxime axetil) per 5 mL of suspension. It contains the following inactive ingredients: povidone K30, stearic acid, sucrose, and tutti-frutti flavoring.

Celecoxib Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
200.00	1	Celecoxib	200.00
204.00	2	Lactose	204.00
12.00	3	Sodium lauryl sulfate	12.00
7.00	4	Polyvinyl pyrrolidine potassium 30	7.00
–	5	Isopropyl alcohol	45.00 L
6.00	6	Polyvinyl pyrrolidine potassium 30	6.00
6.00	7	Magnesium stearate	6.00
15.00	8	Talc	15.00
50.00	9	Croscarmellose sodium	50.00

Manufacturing Directions

1. Charge items 1 to 3 in suitable vessel after passing through a No. 60 mesh and mix for 15 minutes.
2. In a separate container, mix and prepare a solution of items 4 and 5.
3. Add step 2 into step 1 and mix, pass the granules through a 2.5-mm sieve, dry the granules at 40°C in an open room or a fluid-bed dryer to moisture of NMT 1%.
4. Pass the dried granules through a No. 30 sieve and recycle through 1.5-mm sieve to size all granules through No. 30 mesh.
5. Pass items 7 to 9 through No. 40 mesh and add to step 4; mix for 5 to 10 minutes.
6. Tap density is NMT 0.80 g/cc; fines are NMT 10%.
7. Fill 600 mg in size 0 capsules.

Celecoxib Tablets Celebrex*

Celebrex oral capsules contain 100 and 200 mg of celecoxib. The inactive ingredients in Celebrex capsules include croscarmellose sodium, edible inks, gelatin, lactose monohydrate, magnesium stearate, povidone, sodium lauryl sulfate, and titanium dioxide.

Cellulose Triacetate Liquefiable Topical Powder

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
120.00	1	Cellulose triacetate	120.00
880.00	2	Dow Corning® 345	880.00

Manufacturing Directions

1. A liquefiable powder was prepared by evaporative spray drying. Dow Corning 345, a slightly volatile cyclic silicone liquid, was used as the porogen.
2. Cellulose triacetate (40 g) was dissolved in 3000 g of methylene chloride by moderate stirring for 4 hours. To that solution was added 270 g of the porogen dissolved in 1000 g of methylene chloride.
3. The resulting homogeneous solution was sprayed at 1000 psi from a 0.0135-in nozzle, downward into a tower 100 cm in diameter and 300 cm tall, through which 1250 L/min of solvent-free air was passing from top to bottom.
4. The evaporatively formed powder was collected on a fabric filter spanning the bottom of the tower and the solvent-laden air was passed through carbon beds to collect and recover solvent.
5. The product was transferred to a steel tray and exposed as a 1-cm deep layer in a ventilated hood for 25 minutes to remove residual solvent.
6. An analysis showed 12% cellulose triacetate, 88% DC 345, and less than 4 ppm of residual methylene chloride.
7. The white powder readily could be dusted onto the feet and made to liquefy and vanish by gentle rubbing.

Cephalexin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500.00	1	Cephalexin, USE cephalexin monohydrate (0–2% excess)	526.31
2.50	2	Magnesium stearate	2.50
QS	3	Cornstarch	600.00

Manufacturing Directions

1. Charge magnesium stearate, cornstarch, and one-tenth part of cephalexin into a suitable mixer. Mix well.
2. Pass blend from step 1 and balance of cephalexin through an 840-mm aperture screen by hand or with a mechanical shaker.
3. Charge into a suitable mixer and mix well. Discharge into polyethylene-lined drums.

Note: For slugging, first use 624 mg of magnesium stearate; balance after milling slugs through a 1.2-mm aperture screen in an oscillating granulator.

4. Machine fill using either size 00 or size 0 capsules; the theoretical weight of 10 capsules is 6 g. Sort and final clean with sodium chloride.

Cephalexin Powder for Oral Suspension

Bill of Materials			
Scale (mg/5 mL)[a]	Item	Material Name	Qty/5 l (g)
125.00	1	Cephalexin, USE cephalexin monohydrate, 1.5% excess	131.50
0.50	2	FD&C No. 6	0.50
10.00	3	Orange flavor	10.00
5.00	4	Vanilla dry flavor	5.00
5.00	5	Raspberry dry flavor	5.00
277.54	6	Castor sugar	277.54
2844.80	7	Castor sugar	2844.80

[a]Upon reconstitution as recommended. For 250-mg strength, adjust with items 6 and 7.

Manufacturing Directions

1. Charge items 2 to 6 in a suitable mixer and mix for 5 minutes.
2. Add item 1 in portions and mix well.
3. Pass through a Fitz mill, impact forward at high speed using sieve 24338.
4. Collect milled powder in step 3 in a suitable mixer and mix for 10 minutes.
5. Pass item 7 through 900-mm sieve, add 15% of quantity to step 4, and mix for 10 minutes.
6. Load in a double-cone blender. Add the balance of item 7 from step 5 and mix for 20 minutes.
7. Fill appropriate quantity in bottles.

Cephradine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500.00	1	Cephradine, USE cephradine compacted (1000 μg/mg with 5% moisture)[a]	526.00
7.00	2	Magnesium stearate	7.00
8.40	3	Talc	8.40
18.60	4	Lactose monohydrate[b]	18.60

[a]Adjust according to potency; taken as 105.2% of label.
[b]Adjust according to quantity of item 1.

Manufacturing Directions

1. Process limits are relative humidity: 40% to 45%, temperature: 20°C to 25°C.
2. Pass item 1 through 630-μm sieve; crush larger particles in a Frewitt mill using a 1-mm sieve.
3. Load approximately half of item 1 from steps 1 and 2 into a mixer.
4. Sift items 2 to 4 through a 250-mm sieve in a suitable blender; blend for 5 minutes at slow speed.
5. Charge balance of item 1 to step 4 and blend for 5 minutes at slow speed.
6. Fill 560 mg per capsule.

Cephradine Powder for Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/5 L (g)
125.00	1	Cephradine, USE cephradine monohydrate with 10.8% excess[a]	131.50
8.00	2	Sodium citrate	8.00
4.00	3	Citric acid anhydrous	4.00
10.00	4	Guar gum	10.00
5.00	5	Methylcellulose, 15 cps	5.00
2.00	6	Yellow FD&C No. 6	2.00
20.00	7	Blood orange flavor	20.00
10.00	8	Orange banana flavor	10.00
3095.28	9	Castor sugar	3095.28

[a]For 250 mg/5 mL, adjust active ingredient and adjust with item 9.

Manufacturing Directions

1. Pass item 9 through a 500-mm sieve for use in later steps.
2. Charge items 1 to 6 in a mixing vessel and add approximately 10% of item 9 from step 1; mix for 5 minutes.
3. Pass the powder mixture in step 2 through a Fitz mill.
4. Charge 10% of item 9 from step 1 in a separate mixing vessel and add items 7 and 8; blend for 5 minutes.
5. Add to step 3 and blend for 5 minutes.
6. Pass step 5 through a 500-mm sieve.
7. Add item 9 (about 15%) and mix for 5 minutes; transfer to a double-cone blender.
8. Add 40% of item 9 and mix for 10 minutes.
9. Add the balance of item 9 and mix for another 15 minutes.
10. Fill weight for 100 mL = 66 g; fill weight for 60 mL = 39.60 g.

Cevimeline Capsules

Each capsule contains 30 mg of active ingredient. The inactive ingredients are lactose monohydrate, hydroxypropyl cellulose, and magnesium stearate.

Cevimeline Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
30.00	1	Cevimeline	30.00
60.00	2	Hydroxypropyl cellulose	50.00
15.00	3	Sodium carboxymethyl cellulose cross-linked	15.00
189.00	4	Lactose	189.00
6.00	5	Magnesium stearate	6.00

Manufacturing Directions

1. Sift items 1 to 3 through an 80-mesh screen and blend.
2. Pass item 5 through a 100-mesh screen and add to step 1 and blend for 3 minutes.
3. Fill 300 mg in size 0 capsules.

Chlordiazepoxide Hydrochloride Capsules*

It is available as capsules containing 5, 10, or 25 mg chlordiazepoxide HCl. Each capsule also contains cornstarch, lactose, and talc. Gelatin capsule shells may contain methyl and propyl parabens and potassium sorbate, with the following dye systems: for 5-mg capsules—FD&C yellow No. 6 plus D&C yellow No. 10, and either FD&C blue No. 1 or FD&C green No. 3; for 10-mg capsules—FD&C yellow No. 6 plus D&C yellow No. 10, and either FD&C blue No. 1 plus FD&C red No. 3 or FD&C green No. 3 plus FD&C red No. 40; for 25-mg capsules—D&C yellow No. 10 and either FD&C green No. 3 or FD&C blue No. 1.

Chlordiazepoxide Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
5.00	1	Chlordiazepoxide hydrochloride	5.10
114.00	2	Starch dried	114.00
26.00	3	Dicalcium phosphate	26.00
40.00	4	Talc	40.00

Manufacturing Directions

1. Charge all ingredients in a suitable mixer after passing through a No. 60 mesh and mix for 30 minutes.
2. Fill 185 mg in size 4 capsules.

Chloroxylenol and Chlorhexidine Topical Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Chloroxylenol	10.00
10.00	2	Chlorhexidine diacetate	10.00
30.00	3	Magnesium-L-lactate	30.00
10.00	4	Allantoin	10.00
100.00	5	Zinc stearate	10.00
840.00	6	Cornstarch	840.00

Manufacturing Directions

1. Pass all items through a 100-mesh screen and blend.
2. Fill; for use as a topical anti-infective formulation.

Chlorpromazine Sustained-Release Capsules*

Each capsule, with opaque orange cap and natural body, contains chlorpromazine hydrochloride as follows: 30 or 75 or 150 mg. Inactive ingredients consist of benzyl alcohol, calcium sulfate, cetylpyridinium chloride, FD&C yellow No. 6, gelatin, glyceryl distearate, glyceryl monostearate, iron oxide, povidone, silicon dioxide, sodium lauryl sulfate, starch, sucrose, titanium dioxide, wax, and trace amounts of other inactive ingredients.

Cimetidine Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
275.00	1	Cimetidine	275.00
525.00	2	Sodium alginate	525.00
QS	3	Calcium chloride 2%	QS
QS	4	Poly-L-glycine 0.05%	QS

Manufacturing Directions

1. Item 2 is dissolved in 17.5 L of distilled water at 25°C and item 1 is added to this solution with constant mixing.
2. This preparation is added drop-wise to a 2% calcium chloride solution through a small orifice that delivers droplets that are 1 mm in diameter. The spherical beads of cimetidine-containing calcium alginate thus formed are collected by filtration and washed 3 times with distilled water.
3. The beads are then immersed in a 0.05% aqueous solution of poly-L-lysine (molecular weight 14000) for 4 hours, then washed again 3 times with distilled water, collected by filtration, and dried under vacuum for 24 hours. The beads thus produced are filled into gelatin capsules (800 mg per capsule, providing a dose of 275 mg of cimetidine).
4. This dosage form for the delivery of cimetidine over an extended time period allows for through-the-night protection for patients who suffer from excess gastric acidity without the high bedtime dose that conventional dosage forms require for this duration of protection. The high bedtime dose otherwise required for such protection is associated with untoward side effects, which are reduced through use of the dosage form described in this example.

Citrate Effervescent Powder

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/kg (g)
0.50	1	Oil lemon terpeneless	0.50
10.00	2	Lemon flavor (natural microseal)	10.00
QS	3	Alcohol dehydrated (absolute, doubly rectified)	6.50
440.33	4	Sodium bicarbonate	440.33
0.35	5	Saccharin sodium	0.35
157.50	6	Anhydrous sodium citrate	157.50
178.82	7	Anhydrous citric acid (powder)	178.82
222.50	8	Acid tartaric	222.50

Manufacturing Directions

1. All processing should be done in controlled humidity at a maximum relative humidity of 40% at 25°C.
2. Sodium citrate and citric acid are anhydrous.
3. Dissolve lemon oil in dehydrated alcohol with stirring in a suitable container (do not follow this step if using powdered lemon flavor).
4. Sift sodium bicarbonate, if necessary, through a 595-μm screen.
5. Charge into a suitable mixer and mix for 10 minutes.
6. Very slowly add solution from first step to the mixer while mixing; continue mixing for at least 10 minutes and up to a total of 30 minutes, depending on equipment.
7. Screen the massed granulation mixture through a 595-μm screen and divide approximately in half.
8. Premix saccharin sodium into sodium citrate (and lemon powder, if used) and sift through a 595-μm screen or mill fitted with a 595-μm screen (knives forward, medium speed).
9. Sift both citric acid and tartaric acid separately through a 595-μm screen or mill separately using a comminuting mill with a 595-μm aperture (knives forward, medium speed).
10. Load materials into a suitable blender, preferably in the following order: milled tartaric acid, milled citric acid, half of granulation mixture, milled saccharin sodium, sodium citrate, and remaining granulation mixture.
11. Blend for 20 minutes and pack into double plastic bags inside fiber drums.
12. Provide silica gel protection to maintain low humidity in drums.
13. If blended material is lumpy, pass through a 1.2-mm screen before bagging.

Clindamycin Capsules*

Clindamycin hydrochloride capsules contain clindamycin hydrochloride equivalent to 150 mg of clindamycin. The inactive ingredients are cornstarch, FD&C blue No. 1, FD&C yellow No. 5, gelatin, lactose, magnesium stearate, talc, and titanium dioxide.

Clindamycin Capsules (150 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
150.00	1	Clindamycin, USE clindamycin hydrochloride	163.00
12.00	2	Lactose	12.00
3.00	3	Magnesium stearate	3.00
24.00	4	Talc	24.00
2.00	5	Aerosil 200	2.00
65.00	6	Starch dried	65.00

Manufacturing Directions

1. Pass all items through a No. 60 mesh and mix well for 30 minutes.
2. Fill 270 mg in size 2 capsules.

Clofibrate Capsules

Each capsule contains 500 mg of clofibrate for oral administration. Capsules also contain the following inactive ingredients: D&C red No. 28, D&C red No. 30, D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 28, FD&C red No. 40, FD&C yellow No. 6, and gelatin.

Clonidine Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
0.10	1	Clonidine hydrochloride (equivalent to 0.087 mg clonidine base) 100 μm or finer	0.10
70.00	2	Methocel® E4M[a]	70.00
129.90	3	Lactulose[b]	129.90

[a]This formulation is intended to provide an 8-hour release pattern; for an extended release pattern of 12 hours, use Methocel® K100M.
[b]Cornstarch can be used in place of lactulose.

Manufacturing Directions

1. This is a low-dose product that requires a careful geometric dilution of item 1 with portions of item 3.
2. Add the triturate in step 1 in one-half of item 3 and mix well.
3. Add item 2 and mix well; add balance of item 3.
4. Fill 200 mg in an appropriate capsule size.

Clorazepate Dipotassium Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
7.50	1	Clorazepate dipotassium	7.50
10.00	2	Potassium carbonate dried	10.00
0.45	3	Silicon dioxide colloidal	0.45
168.00	4	Talc	168.00
QS	5	Sodium chloride granules (for cleaning)	QS

Manufacturing Directions

Note: Avoid exposing clorazepate to light and moisture; process in low humidity area (46 grains, 35% RH at 76°F).

1. Blending
   a. Determine LOD (1 hour Brabender or equivalent at 105°C) of potassium carbonate dried (NMT 0.5%), silicon dioxide (NMT 2.5%), and talc (NMT 0.3%).
   b. Mill while mixing the potassium carbonate and silicon dioxide through a 60-mesh (250-mm aperture) screen using a Fitz mill or a similar mill, impact forward, high speed.
   c. Premix screened clorazepate with the milled mixture of potassium carbonate and silicon dioxide in a suitable container. Pass the mix through a 40-mesh (420-mm) screen by hand. Clean the screen with a small portion of talc (approximately 0.63 g). Use rubber gloves when handling clorazepate.
   d. Charge about half of the remaining talc into a V-blender or a similar blender. Add the preblend from step C and, finally, the remaining talc. Blend for 30 minutes. Discharge into polyethylene-lined drums, tightly tie, and seal.
2. Filling
   a. Fill blended material into hard gelatin capsules; fill weight for 10 caps is 1.85 g (±0.06 g). Sort capsules on sort vibrator, clean with sodium chloride, and store in polyethylene-lined drums.
3. Printing
   a. Print capsules using edible ink.

Coated Spheroids

Uncoated spheroids (24% w/w vinpocetine)	3.00 kg
Hydroxypropyl methylcellulose 2910, 4000 cps	0.075 kg
Methylene chloride	4.98 kg
Methanol anhydrous	2.96 kg
Eudragit E30D aqueous dispersion	1.00 kg
Calcium stearate	0.03 kg
Simethicone emulsion	0.0025 kg
Water purified	0.50 kg

Manufacturing Directions

1. Vinpocetine hydrochloride (10 kg), microcrystalline cellulose (Avicel-PH-101, 80 kg), and citric acid monohydrate (10 kg) are blended together in a 450-L planetary mixer. Water (100 kg) is added and the mixer is run for 10 minutes until a homogeneous plastic mass is obtained. The mass is extruded under pressure through a perforated cylinder to give cylindrical extrudates of nominally 1 mm in diameter.
2. The damp extrudates (in batches of 15–20 kg) are placed in a spheronizer in which the rotating disc (diameter 68 cm) is rotated at 300 to 400 rpm. The rotation is continued for 20 minutes and the resulting spheroids are then dried at 80°C in a fluidized bed drier. The dried spheroids are passed over a 1.2-mm screen and those that passed through are subjected to a 0.5-mm screen. The over- and undersized spheroids are discarded.
3. The finished dosage form consists of a hard gelatin capsule containing a powder blend of vinpocetine and two types of spheroids. The formulation particulars are based on 30 mg per capsule, although they can be designed to provide other dosage strengths.
4. The vinpocetine powder blend (or first group of spheroids) provides the loading dose (e.g., 5 mg of vinpocetine).
   a. Blend the vinpocetine, lactose microcrystalline cellulose, starch, glutamic acid, sodium starch glycolate, talc triturate, and the sodium lauryl sulfate into the PK® blender for 20 minutes with intensifier bar running.
   b. Pass the step 1 blend through a Fitz mill using a No. 1B screen, medium speed, knives forward.
   c. Return the granulation from step 2 to the PK blender and add the magnesium stearate and blend for 2 minutes without the intensifier bar on.
5. The second and third types of spheroids are categorized as
   a. pH-sensitive coated spheroids to provide a second dose (pH >6.5) (e.g., 12 mg vinpocetine). Uncoated spheroids are placed in a fluidized bed coater. The Eudragit S solution is applied using a peristaltic pump. The spheroids are dried.
   b. Coated spheroids to provide a third dose 4 to 10 hours post ingestion (e.g., 13 mg vinpocetine). Process for applying undercoat: The uncoated spheroids are placed in a fluidized bed coater. Methocel E4MP solution is

sprayed using a peristaltic pump. The spheroids are dried. Process for applying overcoat: Eudragit E30D suspension containing calcium stearate is sprayed on the Methocel E4MP-coated spheroids using a peristaltic pump. The spheroids are dried.

6. Capsules are filled with the powder blend, pH-sensitive coated spheroids, and coated spheroids on an encapsulating machine capable of dual filling powders and spheroids.

Crospovidone Water-Dispersible Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
1000.00	1	Crospovidone M (BASF)	1000.00
50.00	2	Aerosil 200	50.00
250.00	3	Sucrose (crystalline)	250.00
5.00	4	Saccharin sodium	5.00
2.00–3.00	5	Flavors	2.00–3.00
380.00	6	Water	380.00
5.00	7	Magnesium stearate	5.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with item 6, dry, and pass through a sieve.
2. Mix the dry granules with item 7 and press with low compression force.
3. The dosage may be increased to 2000 mg crospovidone by increasing the tablet weight to 2600 mg.
4. Compress 1280-mg tablets using 20-mm biplanar punches.

Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50.00 μg	1	Cyanocobalamin; use gelatin-coated cyanocobalamin (0.1%)	50.00
150.00	2	Ludipress®	150.00
1.50	3	Magnesium stearate	1.50
2.00	4	Sicovit Quinoline lake, yellow	2.00
3.00	5	Sicovit yellow lake, orange	3.00

Manufacturing Directions

1. Prepare a premix of item 1 and 2 and add to items 3 to 5.
2. Pass through a 0.5-mm sieve and press with low compression force.
3. Compress into 209-mg tablets using 8-mm biplanar punches.

Cyclosporin A Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Cyclosporin A	100.00
300.00	2	Cremophor RH (or Tween)	300.00

Manufacturing Directions

Mix ingredients and fill in hard gelatin capsules of a type that will not interact with ingredients. Optionally, the composition may contain ethanol 8%, propylene glycol 8%, or polyethylene glycol 300, 30% by weight.

Dantrolene Sodium Capsules*

It is supplied in capsules of 25, 50, and 100 mg. Each capsule contains the following inactive ingredients: edible black ink, FD&C yellow No. 6, gelatin, lactose, magnesium stearate, starch, synthetic iron oxide red, synthetic iron oxide yellow, talc, and titanium dioxide.

Dextroamphetamine Sulfate Capsules*

Each sustained-release capsule is so prepared that an initial dose is released promptly, and the remaining medication is released gradually over a prolonged period. Each capsule containing 5 to 15 mg of active and inactive ingredients consist of cetyl alcohol, D&C yellow No. 10, dibutyl sebacate, ethylcellulose, FD&C blue No. 1, FD&C blue No. 1 aluminum lake, FD&C red No. 40, FD&C yellow No. 6, gelatin, hydroxypropyl methylcellulose, propylene glycol, povidone, silicon dioxide, sodium lauryl sulfate, sugar spheres, and trace amounts of other inactive ingredients.

Diclofenac and Misoprostol Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Diclofenac delayed-release beads (47% diclofenac)	214.00
0.20	2	Misoprostol (dilute 1:100 on HPMC)	20.00
150.00	3	Microcrystalline cellulose	150.00
4.00	4	Stearic acid	4.00
9.00	5	Talc	9.00

Manufacturing Directions

1. Item 1 beads are prepared by spray coating a suspension or solution of diclofenac sodium onto a nonpareil sugar core, together with a binder (e.g., polyvinylpyrrolidone or hydroxypropyl methylcellulose).
2. The beads are subsequently coated with a delayed-release coating (e.g., methylmethacrylate, e.g., Eudragit). Mixtures of beads with various levels of coating are used to give the required therapeutic release pattern.
3. In a fluidized-bed apparatus, uniform spherical inert sugar sphere cores are coated with a first layer consisting of the compounds, an inert water-soluble polymer, such as hydroxypropyl methylcellulose or hydroxypropyl cellulose, and talc.
4. The second layer consists of an inert water-soluble polymer, such as hydroxypropyl methylcellulose or hydroxypropyl cellulose, talc, and a pigment, such as titanium dioxide.
5. The third and enteric coating layer consists of an enteric coating polymer, such as copolymerized methacrylic acid/methacrylic acid methyl esters, a plasticizer, such as triethyl acetate or similar plasticizers, and talc.
6. The layers are applied by conventional fluidized bed coating techniques using aqueous solutions or dispersions. Pseudozero release is obtained by the use of a mixture of beads.
7. The beads in item 1 contain 47% diclofenac, giving a dose per capsule of 75 mg.
8. The mixture of items 1 to 4 is filled into suitable hard gelatin capsules.

Diclofenac Spheronized Pellets for Sustained-Release Coating (30%)

Formulation

Diclofenac sodium, 300 g; Avicel PH101 (5), 438 g; granulac 230 (8), 237 g; Kollidon VA64 (1), 25 g; water, approximately 580 g.

Manufacturing Directions

1. Granulate the mixture (I) in a Diosna granulator with water (II) and press the humid granules through a sieve of 1.5 mm. Form pellets in a spheronizer during 10 minutes with the rotation speed of 380 to 420 rpm. Dry the pellets in a fluidized bed at 70°C.
2. Fill at relative humidity that does not exceed 45% and a temperature of 20°C to 25°C.
3. Calculate exact amount based on quantity of active ingredient in uncoated beads.
4. Fill 192.5 mg based on 100% potency basis.

Diclofenac Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Diclofenac, USE diclofenac sodium pellets (520 mg/g)	192.50

Diclofenac Granules

1. Preparation of uncoated granules:
   a. 800 g of diclofenac sodium, 200 g of citric acid, and 200 g of cornstarch are mixed and pulverized.
   b. The fine powders thus prepared are processed to produce spherical granules, using 600 g of purified sucrose that was obtained by shifting through 20 to 28 mesh as a core, while spraying a solution of 25 g of hydroxypropyl cellulose in 475 g of ethyl alcohol.
   c. The granules are then dried for 3 hours at 55°C.
   d. These dried granules are then passed through a 14 mesh, followed by passage through a 28 mesh. The granules that do not go through the 28 mesh are taken as uncoated granules A. The formulation of uncoated granules A is as follows.

Component	% by weight
Diclofenac sodium	43.7
Citric acid	11.0
Cornstarch	11.0
Purified sucrose	32.9
Hydroxypropyl cellulose	1.4
Total	100.0

   e. Alternate method of preparing uncoated granules:
      i. 1000 g of diclofenac sodium, 30 g of fumaric acid, and 170 g of cornstarch are mixed and pulverized.
      ii. The fine powders thus produced are processed to produce spherical granules, using 600 g of purified sucrose that is obtained by shifting through a 20 to 28 mesh as a core, while spraying a solution of 25 g of hydroxypropyl cellulose in 475 g of ethyl alcohol.
      iii. The granules are then dried for 3 hours at 55°C.
      iv. These dried granules are then passed through a 14 mesh followed by passage through a 28 mesh. The granules that do not go through the 28 mesh are taken as uncoated granules. The formulation of this uncoated granules B is as follows.

Component	% by weight
Diclofenac sodium	54.8
Fumaric acid	1.6
Cornstarch	9.3
Purified sucrose	32.9
Hydroxypropyl cellulose	1.4
Total	100.0

2. Preparation of long-acting granules:
   a. 600 g of uncoated granules are placed into a coating apparatus with a fluidized bed.
   b. The granules are spray-coated with 1263 g of a coating liquid having the following composition according to a conventional method to produce long-acting granules. The weight of the coat was approximately 8% of the weight of the uncoated granules.

Component	% by weight
Ethylcellulose	2.7
Polyvinyl pyrrolidine K30	0.9
Talc	0.2
Ethyl alcohol	96.2
Total	100.0

3. Preparation of long-acting granules, alternate method:
   a. 600 g of uncoated granules B are placed into a coating apparatus with fluidized bed.
   b. The granules are spray-coated with 1667 g of a coating liquid having the following composition according to a conventional method to produce long-acting granules. The amount of the coat is approximately 20% based on the weight of the uncoated granules.

Component	% by weight
Methacrylic acid copolymer S	6.5
Glycerin fatty acid ester	0.5
Talc	0.2
Ethyl alcohol	92.8
Total	100.0

4. Preparation of long-acting granules having an exterior rapid-releasing layer:
   a. 50.7 g of diclofenac sodium and 149.3 g of cornstarch are mixed and pulverized.
   b. The fine powders thus produced are processed to produce spherical granules, using 500 g of the long-acting granules (step 6) as a core, while spraying a solution of 4 g of hydroxypropyl cellulose in 76 g of ethyl alcohol.
   c. The granules are then dried for 2 hours at 55°C to produce long-acting granules. These granules have an exterior rapid-releasing layer.

Didanosine Delayed-Release Capsules*

The delayed-release capsules, which contain enteric-coated beadlets, are available for oral administration in strengths of 125, 200, 250, and 400 mg of didanosine. The inactive ingredients in the beadlets include carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium hydroxide, sodium starch glycolate, and talc. The capsule shells contain colloidal silicon dioxide, gelatin, sodium lauryl sulfate, and titanium dioxide. The capsules are imprinted with edible inks.

Didanosine Delayed-Release Capsules Enteric-Coated Beadlets*

Delayed-release capsules, containing enteric-coated beadlets, are available for oral administration in strengths of 125, 200, 250, and 400 mg of didanosine. The inactive ingredients in the beadlets include carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium hydroxide, sodium starch glycolate, and talc. The capsule shells contain colloidal silicon dioxide, gelatin, sodium lauryl sulfate, and titanium dioxide. The capsules are imprinted with edible inks.

Didanosine for Oral Suspension

The powder for oral solution is supplied for oral administration in single-dose packets containing 100, 167, or 250 mg of didanosine. Packets for each product strength also contain a citrate–phosphate buffer (composed of dibasic sodium phosphate, sodium citrate, and citric acid) and sucrose. Pediatric powder for oral solution is supplied for oral administration in 4- or 8-oz glass bottles containing 2 or 4 g of didanosine respectively. The chemical name for didanosine is 2c,3c-dideoxyinosine.

Diethyl Toluamide Topical Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
552.00	1	*N*, *N*-diethyl-m-toluamide (DEET)	600.00
368.00	2	2-Octyldodecanol	400.00
QS	3	Methylene chloride	QS
80.00	4	Cellulose triacetate	400.00

Manufacturing Directions

1. A liquefiable powder was prepared by spray evaporative drying. A liquid porogen was prepared from 60 parts by weight of *N*, *N*-diethyl-*m*-toluamide (DEET) and 40 parts by weight of 2-octyldodecanol, a heavy secondary alcohol commonly used in cosmetic formulations.
2. Cellulose triacetate (40 g) was dissolved in 3000 g of methylene chloride by moderate stirring for 4 hours. To that solution was added 460 g of the previously prepared porogen diluted with 1000 g of methylene chloride.
3. The resulting homogeneous solution was sprayed at 1000 psi from a 0.0135-in nozzle, downward into a tower (100 cm in diameter × 300 cm tall), through which 1250 L/min of solvent-free air was passing from top to bottom.
4. The evaporatively formed powder was collected on a fabric filter spanning the bottom of the tower and the solvent-laden air was passed through carbon beds to collect and recover solvent.
5. The product was transferred to a steel tray and exposed as a 1-cm deep layer in a ventilated hood for 25 minutes to remove residual solvent. Analysis showed 8% cellulose triacetate, 36.8% octyldodecanol, and 55.2% DEET, with less than 5 ppm or residual methylene chloride.
6. The resulting white powder could be readily dusted onto the skin and made to liquefy and vanish by gentle rubbing without any perceptible grit or stickiness.

Difluoromethylornithine-Alpha Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/2000 Caps (g)
		Rapid-release granules	
50.00	1	Difluoromethylornithine-alpha (DFMO)	100.00
50.00	2	Microcrystalline cellulose (MCC) Avicel PH101	100.00
QS	3	Water purified	QS
		Slow-release granules	
250.00	4	Difluoromethylornithine-alpha	500.00
250.00	5	Microcrystalline cellulose PH101	500.00
15–25.00	6	Eudragit RS 30D	30–50
QS	7	Triethyl citrate	QS
QS	8	Water purified	QS

Manufacturing Directions

1. Rapid-release granules: DFMO (100 g) and microcrystalline cellulose (MCC, Avicel PH101, 100 g) are mixed thoroughly. A sufficient amount of water to make a wet mass is added to the mixture, which is subsequently extruded and spheronized. The pellets are screened (size 14–20 mesh) and dried at 40°C for 24 hours. Polyvinyl pyrrolidine (PVP, 2% by weight of total mass) can optionally be included in the formulation. Increasing PVP will generally lengthen the release profile of the formulation.
2. Slow-release granules: DFMO (500 g), MCC (500 g), and Eudragit (35–50 g) are mixed. To this mixture is added sufficient water to yield a 30% weight suspension. To the suspension is added triethylcitrate (10% weight based on dry polymer weight of Eudragit) to yield a dispersion that is wet granulated and dried to remove as much water as possible. The particles are then ground into a fine powder.
3. Fill the rapid-release granules (500 g prepared according) and slow-release granules (750 g prepared) after thoroughly mixing.
4. Gastric-release granules: A slow gastric-release granule can be prepared as follows. DFMO (600 g), MCC (350 g), and HPC (50 g) are mixed thoroughly. To the mixture is added sufficient water to make a wet mass that is extruded and then spheronized using procedures well known in the art. The particles are then dried and ground.
5. Enteric-release granules: A latex dispersion is prepared as follows. To Eudragit L 30D–55 (1000 g, 15% weight in water) is added a plasticizer (15% weight of dry polymer weight in the Eudragit) while mixing for 1 to 24 hours. Plasticizers, such as triethylcitrate, tributylcitrate, acetyl-tributylcitrate, or dibutylsebacate, can be used. To this mixture is added talc (50% weight of dry polymer in the Eudragit) or glycerylmonostearate (10% weight of dry polymer in the Eudragit) to form a dispersion. The rapid-release granules are coated in a fluidized bed with the latex dispersion until a 10% to 15% weight increase in granule weight is achieved. The fluidized bed inlet air temperature is adjusted to approximately 40°C to 45°C and the outlet air temperature is adjusted to approximately 30°C to 35°C with a spray rate of about 2 g/min.
6. Slow-release granules: Granules previously prepared are coated with Eudragit L 30D (10–12% weight) or Aquateric (CAP, 10% weight, plasticized with TEC) until a 25% to 30% weight increase in granule weight is achieved.
7. Colorectal-release granules: A dispersion is prepared as follows. To Eudragit S100 (1000 g, 10% weight in water) is added a plasticizer (10% weight of dry polymer weight in the Eudragit) while mixing for 1 to 24 hours. Plasticizers, such as triethylcitrate, tributylcitrate, acetyl-tributylcitrate, or dibutylsebacate, can be used. To this mixture is added talc (50% weight of dry polymer in the Eudragit) to form a dispersion. The rapid-release granules previously prepared are coated in a fluidized bed with this dispersion until a 15% weight increase in granule weight is achieved.
8. Slow-release granules: A mixture is prepared as follows. Eudragit RS 30D (1000 g, 15% weight aqueous dispersion, Aquacoat® or Surelease®) is plasticized with triethylcitrate (TEC, 20% wt of dry polymer in the Eudragit) for 1 to 24 hours. Talc (50% weight of dry polymer in the Eudragit) is added with mixing to form the mixture. The rapid-release granules are coated with this mixture until a 10% to 15% weight increase in granule weight is achieved. The coated granules are then coated with a Eudragit S100 dispersion as done immediately above until a 10% to 15% weight increase in granule weight is achieved.
9. Sustained-release granules: This procedure employs a double granulation. Thus, DFMO (500 g), MCC (500 g), and Eudragit RS 30D (75–100 g) are mixed. To this mixture is added sufficient water to yield a 30% weight suspension. To the suspension is added TEC (10% weight based on dry polymer weight of Eudragit) to yield a dispersion that is wet granulated and dried to remove as much water as possible. The granules are then ground into a fine powder. To the powder is added sufficient water to make a wet mass that is extruded, spheronized, dried, ground, and screened (size 14–20 mesh).
10. Gastric-, enteric-, and colorectal-release granules: The following procedure details the preparation of the dosage form. Rapid gastric-release granules (450 g, prepared previously), rapid enteric-release granules (100 g, prepared previously), and slow colorectal-release granules (450 g, prepared previously) are mixed thoroughly. Hard gelatin capsules are then filled with the mixture.

Diltiazem Hydrochloride Extended-Release Capsules*

The extended-release capsules contain diltiazem hydrochloride in extended-release beads in doses of 120, 180, 240, 300, 360, and 420 mg. They also contain microcrystalline cellulose, sucrose stearate, Eudragit, povidone, talc, magnesium stearate, hydroxypropyl methylcellulose, titanium dioxide, polysorbate, simethicone, gelatin, FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, FD&C green No, 3, black iron oxide, and other solids.

In another formulation, the 120-, 180-, 240-, and 300-mg capsules also contain black iron oxide, ethylcellulose, FD&C blue No. 1, fumaric acid, gelatin, sucrose, starch, talc, titanium dioxide, white wax, and other ingredients. The 360-mg capsule also contains black iron oxide, diethyl phthalate, FD&C blue No. 1, gelatin, povidone K17, sodium lauryl sulfate, starch, sucrose, talc, titanium dioxide, and other ingredients.

Manufacturing Directions

The rapid-release pellets of diltiazem can be manufactured by the following procedure: 2 kg of microgranules composed of sucrose and starch, with a particle size of 0.500 to 0.710 mm, are rotated in a trough with a stainless steel basket that is 450 mm in diameter. The rotating mass is sprayed, by means of a membrane-type proportioning pump, with 26 g of a 40% strength solution of shellac in ethanol and sprinkled with 80 g of diltiazem with a particle size of 40 to 80 mm.

The sustained-release pellets can be manufactured by following procedure: 2 kg of saccharose/starch pellets having a particle size between 0.500 and 0.710 mm are put in rotation in a suitable coating pan. The rotating mass is sprayed with 27.2 g of an ethanolic solution containing 9.79 g of shellac and 1.09 g of polyvinylpyrrolidone, and 80 g of diltiazem HCl are added. This operation is repeated 50 times. These pellets are then coated with the same amount of solution of ethylcellulose N100 and talc, respectively, 80 g of 0.5% solution of ethylcellulose N100, and 54 g of talc. This operation is repeated 25 times. The proportion of soluble versus insoluble coating materials can be altered to obtain the best release profile. All the formulations are tested for in vitro dissolution, in the range of pH between 1 and 7.5, using the method described in the USP, paddle apparatus.

Alternate methods of preparing coated beads include first preparing beads and then coating them. The plain beads are prepared by

Formula 1

Diltiazem hydrochloride	1120.00 g
Lactose	119.00 g
Microcrystalline cellulose (Avicel pH101)	140.00 g
Povidone K30	21.00 g

After introducing the powders into a planetary mixer and granulating same through the obtained plastic, mass is extruded through a cylinder with 1-mm diameter holes (Alexanderwork). The small cylinders are rounded, so as to obtain beads, by means of a spheronizer. After drying at 60°C for 12 hours, the beads are sifted and the fraction with size comprised between 0.7 and 1.4 mm are retained. 1179 g of beads was obtained yield (84%).

Formula 2

Diltiazem HCl	560.00 g
Crodesta F 160	59.50 g
Microcrystalline cellulose (Avicel pH101)	70.00 g
Povidone K30	10.50 g

The ingredients are introduced in a planetary mixer and dry mixed for approximately 15 minutes. Thereafter, 100 mL purified water is added, and the mixing is pursued for 10 minutes more until a plastic mass is obtained. This mass is then extruded through a Fuji Paudal® extruder equipped with a 1-mm screen to obtain "spaghetti." A spheronizer-type caleva is used to transform the extruded product into beads. After drying for 12 hours on trays in an oven at 60°C, the beads are sieved to eliminate the ones with a size larger than 1.4 mm and with a size smaller than 0.7 mm. The amount of beads obtained with sizes between 0.7 and 1.4 mm was 639.1 g (yield 91.3%).

The beads prepared previously are then coated in a STREA-1 (Aeromatic-Fielder) fluidized bed using the "top spraying" technique, and 440 g of coating suspension from the following composition is applied on 500 g of beads. Thereafter, the coated beads are dried at 50°C for 16 hours.

Coating Suspension Composition

Magnesium stearate	12.50 g
Titanium dioxide	5.00 g
Povidone K30	5.00 g
Eudragit NE30D	620.00 g
Talc	17.50 g
Water	338.00 g
Simethicone	1.00 g
Tween 80	0.80 g

Diphenhydramine Hydrochloride Capsules*

Each capsule contains diphenhydramine hydrochloride 25 mg. Each capsule contains lactose and magnesium stearate. The banded capsule shell contains D&C red No. 28, FD&C red No. 3, FD&C red No. 40, FD&C blue No. 1, gelatin, glyceryl monooleate, and titanium dioxide.

Dipyridamole and Aspirin Extended-Release Capsules*

This is a combination antiplatelet agent intended for oral administration. Each hard gelatin capsule contains 200 mg of dipyridamole in an extended-release form and 25 mg of aspirin as an immediate-release sugar-coated tablet. In addition, each capsule contains the following inactive ingredients: acacia, aluminum stearate, colloidal silicon dioxide, cornstarch, dimethicone, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide, and triacetin. Each capsule shell contains gelatin, red iron oxide and yellow iron oxide, titanium dioxide, and water.

Divalproex Sodium Capsules*

The sprinkle capsules are for oral administration and contain specially coated particles of divalproex sodium equivalent to 125 mg of valproic acid in hard gelatin capsules. The inactive ingredients in the 125-mg sprinkle capsules are cellulosic polymers, D&C red No. 28, FD&C blue No. 1, gelatin, iron oxide, magnesium stearate, silica gel, titanium dioxide, and triethyl citrate.

Divalproex Sodium Coated Particle Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
125.00	1	Valproic acid, USE divalproex sodium-coated particles	134.50
0.53	2	Magnesium stearate	0.53
1.00	3	Silica gel (Syloid 244)	1.00

Manufacturing Directions

1. Prepare coated particles of divalproex sodium by coating with ethylcellulose (34.34 mg), triethyl citrate (5.8 mg), and magnesium citrate (35 mg), using a mixture of alcohol and acetone in an air suspension system; screen particles using 20- and 40-mesh screens; particles larger than 20 and smaller than 40 must be reworked.
2. Make the granules by wet granulation of divalproex sodium and silica gel, using alcohol.
3. Collect 20- to 40-mesh granules after drying NMT 50°C to LOD of NMT 0.5%.

Dofetilide Capsules*

Each capsule contains the following inactive ingredients: microcrystalline cellulose, cornstarch, colloidal silicon dioxide, and magnesium stearate. It is supplied for oral administration in three dosage strengths: 125 μg (0.125 mg) orange and white capsules, 250 μg (0.25 mg) peach capsules, and 500 μg (0.5 mg) peach and white capsules.

Doxepin Hydrochloride Capsules*

Inert ingredients for the capsule formulations are hard gelatin capsules (which may contain blue No. 1, red No. 3, red No. 40, yellow No. 10, and other inert ingredients), magnesium stearate, sodium lauryl sulfate, and starch.

Doxycycline Capsules*

Available as 100- and 50-mg capsules, they contain doxycycline monohydrate equivalent to 100 or 50 mg of doxycycline for oral administration. The inert ingredients are colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate.

Doxycycline Hyclate Capsules*

These capsules contain specially coated pellets of doxycycline hyclate for oral administration. They also contain lactose, microcrystalline cellulose, and povidone. The capsule shell and band contain FD&C blue No. 1, FD&C yellow No. 6, D&C yellow No. 10, gelatin, silicon dioxide, sodium lauryl sulfate, and titanium dioxide.

Doxycycline Hyclate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
122.00	1	Doxycycline hyclate (22% excess)	122.00
26.00	2	Microcrystalline cellulose (Avicel PH 102)	26.00
4.00	3	Starch (cornstarch dried)	4.00
0.60	4	Sodium lauryl sulfate	0.60
0.60	5	Colloidal silicon dioxide (Aerosil 200)	0.60
2.00	6	Magnesium stearate	2.00
–	7	Hard gelatin capsules, Size 3	1000.00

Manufacturing Directions

Note: Processing should be conducted in a controlled room temperature and humidity area. The limits are room temperature 20°C to 27°C, RH 40% to 45%.

1. Mix items 1, 2, and 4 in a stainless steel drum. Pass the mixed material through a 500-µm sieve using a sifter. Collect in stainless steel drum.
2. Mix items 3, 5, and 6 in a polyethylene bag. Pass the mixed material through a 250-µm sieve using a sifter. Pass two times. Collect in the polyethylene bag and transfer to step 1 in a stainless steel drum.
3. Mix the material in a drum mixer for 3 minutes.
4. Take a sample for assay and moisture content.
5. Load the empty capsule shells (size 3) in the hopper; cap and body are ivory opaque.
6. Run the machine and check the locking of shells. Run the machine. Check the fill weight (155 mg) and locking of the capsules. Collect the filled capsules from polyethylene-lined stainless steel container in silica bags and close tightly.
7. Store the containers in a controlled room temperature and humidity area. The limits are RH 45% to 50% at a temperature of 25°C to 27°C.

Doxycycline Hydrochloride Capsules and Oral Suspension*

Inert ingredients in the capsule formulations are hard gelatin capsules (which may contain blue 1 and other inert ingredients; magnesium stearate; microcrystalline cellulose; and sodium lauryl sulfate).

Efavirenz Capsules*

It is available as capsules for oral administration containing either 50, 100, or 200 mg of efavirenz as well as the following inactive ingredients: lactose monohydrate, magnesium stearate, sodium lauryl sulfate, and sodium starch glycolate. The capsule shell contains the following inactive ingredients and dyes: gelatin, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide. The capsule shells may also contain silicon dioxide. The capsules are printed with ink containing carmine 40 blue, FD&C blue No. 2, and titanium dioxide.

Enalapril Maleate Capsules

Inactive ingredients: magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. Inert ingredients for the oral suspension formulation are carboxymethylcellulose sodium, blue 1, methylparaben, microcrystalline cellulose, propylparaben, raspberry flavor, red 28, and simethicone.

Enalapril Maleate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
10.00	1	Enalapril maleate	10.00
235.00	2	Lactose anhydrous	235.00
1.25	3	Magnesium stearate	1.25

Manufacturing Directions

1. Pass all items through No. 60 mesh into blender; mix for 10 minutes.
2. Fill 250 mg in size 00 capsules.

Eplerenone Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
10.00	1	Eplerenone	10.00
306.80	2	Lactose hydrous NF	306.80
60.00	3	Microcrystalline cellulose NF	60.00
10.00	4	Talc	10.00
1.20	5	Croscarmellose sodium NF	1.20
2.00	6	Sodium lauryl sulfate NF	2.00
2.00	7	Colloidal silicon dioxide NF	2.00
1.20	8	Magnesium stearate NF	1.20

*adjust for higher dose fill.

Directions

Total capsules fill weight 400 mg, hard gelatin capsules, size
250 mg, white opaque.

Erythromycin and Bromhexine Powder for Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/l (g)
21.00	1	Sodium carboxymethylcellulose	0.42
6.55	2	Dye red	0.131
4735.00	3	Sugar granular 39075 mesh	94.70
2650.00	4	Sodium citrate dihydrate	53.00
659.00	5	Sodium carboxymethylcellulose high viscosity	13.18
393.50	6	Magnesium aluminum silicate Veegum F	7.87
78.50	7	Saccharin sodium dihydrate	1.57
200.00	8	Erythromycin, USE erythromycin ethylsuccinate[a] citrate washed	123.58
0.80	9	Bromhexine, USE bromhexine hydrochloride	2.10
QS	10	Flavor	3.95
QS	11	Water purified, ca	67 mL

[a]Erythromycin ethylsuccinate is factored = (123.58 × 850)/potency, μg/g.

Manufacturing Directions

1. Granulation
   a. Dissolve the sodium carboxymethylcellulose (item 1) and the dye in approximately 67 mL of purified water with heat while stirring. Allow to cool. Ensure that the sodium carboxymethylcellulose is completely in solution.
   b. Pass sugar cane through a 2.38-mm aperture screen using an oscillating granulator.
   c. Pass the following through a 1.27-mm aperture or similar screen: sodium CMC (item 5), Veegum F, sodium saccharin, bromhexine HCl, and erythromycin ethylsuccinate. Use a Fitz mill or a similar mill, high speed, impact forward.
   d. Load the ingredients from steps B and C into the mixer and blend for 30 minutes.
   e. Mass with the solution from step A. If necessary, add purified water to form a cohesive granule with even color dispersion.
   f. If necessary, pass the wet mass through a 4.76-mm aperture screen and spread on stainless steel trays.
   g. Load trays of granulation into the oven and dry at 49°C to LOD of less than 0.5% (60°C/5 mm). *Note:* Stir granulation during drying.
   h. Allow granulation to cool in low humidity area before passing through a 1.7-mm aperture screen.
   Note: Precooling in a low humidity area prevents condensation when later packed in polyethylene-lined bags.
   i. Request samples.
   j. Charge part of dry granulation and sodium citrate into a mixer. Slowly add flavor while mixing. Mix for a few minutes. Hand screen through a 1.2-mm aperture screen.
   k. Charge the screened granulation into a suitable blender and add flavor mixture from step J. Mix well (approximately 30 minutes).
   l. Take samples.
   m. Discharge blended granulation into tared polyethylene-lined drums; seal and weigh. Store until needed for filling.
2. Finishing
   a. At filling, weight for a 60-mL bottle should be 22.85 g, weight for a 100-mL bottle should be 39.08 g.

Erythromycin and Sulfisoxazole Granules for Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/kg (g)
180.63	1	Sodium citrate dihydrate	66.90
600.00	2	Sulfisoxazole, USE sulfisoxazole acetyl	222.30
13.50	3	Sodium carboxymethylcellulose high viscosity	5.00
10.80	4	Magnesium aluminum silicate Veegum F	4.00
5.40	5	Citric acid	2.00
0.54	6	Polaxamer 188 (Pluronic F68)	0.20
200.00	7	Erythromycin, USE erythromycin ethylsuccinate citrate washed[a] (850 μg/mg) 5% excess	75.29
1661.28	8	Sucrose	615.29
QS	9	Water purified	55 mL
7.56	10	Flavor	2.80
3.24	11	Flavor	1.20
10.80	12	Flavor	4.00
2.70	13	Ammonium glycyrrhizinate	1.00

[a]Factored according to potency. Adjust with sugar.

Manufacturing Directions

I. Premixing
Note: This milling step is hazardous. *Caution:* Equipment must be grounded or bonded.
A. Mill sodium citrate, sodium carboxymethylcellulose, magnesium aluminum silicate, citric acid, poloxamer, and erythromycin ethylsuccinate through a No. 2 band (1.59-mm aperture) using a Fitz mill or similar mill, at high speed, impact forward.
B. Load milled materials from step A into a suitable blender. Mix for 15 minutes.
C. Screen the sulfisoxazole acetyl through a 4.76-mm aperture screen and add to the blender. Blend for 15 minutes.
D. Discharge blender into polyethylene-lined drums.

II. Granulation
A. Load mass mixer with the premix blend. Add the sucrose to mixer by hand screening through a 2.00-mm aperture screen. Dry mix for not less than 5 minutes.
B. QS to mass using approximately 51 mL of purified water.
C. Granulate the wet mass through a $\frac{5}{8}$-in band (15.88-mm aperture or similar) on a rotary granulator or similar granulator. Spread on paper-lined trays, no more than one scoopful per tray. Place granulation in oven set at 49°C.
D. Dry to NMT 0.7% LOD.
E. Sift dried granulation through a 1.19-mm aperture screen and grind coarse granulation through a No. 2 AA band (1.98-mm aperture or similar) in a Fitz mill or a similar mill, medium speed, knives forward into polyethylene-lined drums.

III. Blending
A. Load approximately one-half of the granulation from step II-E into a suitable blender.
B. Screen flavors and ammonium glycyrrhizinate through a 600-μm aperture screen into a portion of the granulation; mix and add to the blender.
C. Add the remaining granulation into the blender. Blend for 20 minutes.
D. Discharge mixture into polyethylene-lined drums.

IV. Finishing
A. Fill into suitable approved bottles at a theoretical weight of 62.5 g/100 mL, requiring approximately 50 mL of water for reconstitution.

Erythromycin Delayed-Release Capsules*

Erythromycin delayed-release capsules contain enteric-coated pellets of erythromycin base for oral administration. Each erythromycin delayed-release capsule contains 250 mg of erythromycin base. The inactive ingredients are cellulosic polymers, citrate ester, D&C red No. 30, D&C yellow No. 10, magnesium stearate, and povidone. The capsule shell contains FD&C blue No. 1, FD&C red No. 3, gelatin, and titanium dioxide.

Erythromycin Delayed-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Erythromycin, USE erythromycin 66.7% pellets (label claim is 667 mg/g)	375.00[a]
–	2	Empty hard gelatin capsules, Size 0	1000.00

[a]Quantity of pellets for 1000 capsules will be adjusted based on the pellets assay results.

Manufacturing Directions

Note: Processing should be done under controlled room temperature and relative humidity. The limits are room temperature 20°C to 25°C, RH 40% to 45%.

1. Load the empty capsule shells (size 0) in the hopper.
2. Fill.

Erythromycin Ethylsuccinate for Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/1 kg (19 units) (g)
125.00	1	Erythromycin ethylsuccinate[a]	55.860
2168.00	2	Sucrose[b]	823.840
250.25	3	Sodium citrate	95.095
2.97	4	Saccharin sodium	1.128
0.27	5	FD&C red No. 40	0.104
1.43	6	Carmellose sodium (sodium CMC 7 MFD)	0.543
21.45	7	Simethicone emulsion 30% (simethicone M30)	8.151
12.98	8	Xanthan gum	4.932
6.27	9	Cherry dry flavor	2.382
–	10	Purified water	15.200

[a]Potency: 850 μg/mg, as is.
[b]Sucrose quantity to be adjusted accordingly. The weight of sucrose may be adjusted to compensate for potency variation of erythromycin ethylsuccinate to maintain the standard batch size (1 kg). Fill weight: 52.5 g for 100-mL pack.

Manufacturing Directions

Precautions: Handle erythromycin ethylsuccinate carefully to avoid any cross-contamination. The processing area must be under controlled room temperature and humidity. The limits are RH: 45% to 55%, temperature: 23°C to 25°C.

1. Preparation of solution: Dissolve item 5 in item 10 (25–30°C). Add item 6 slowly while stirring with stirrer at medium speed until gel is formed. Check the weight; theoretical weight is 15.84 g. If required, adjust with item 10.
2. Dry mixing: Pass item 2 (calculated quantity) through sifter using a 900-μm sieve. Crush the larger crystals of item 2 using a Fitz mill, impact forward, high speed.
3. Load item 2 from step 2 into the mixer and start mixing at high speed. Add item 7 while mixing. Mix for 10 minutes with the mixer and chopper at high speed.
4. Mix items 3, 4, 8, 1, and the mixture from step 3 in a clean, dry stainless steel container using a clean, dry stainless steel scoop.
5. Pass the material through a Fitz mill, impact forward, high speed.
6. Add the milled material to the mixer; mix for 5 minutes with the mixer and chopper at high speed.
7. Scrap down the sides and blades and again mix for 2 minutes with the mixer and chopper at high speed.
8. Wet granulation: Very slowly add the solution from step 1 to step 5 in mixer. Mix at low speed, until a satisfactory mass is obtained. Mix and chop for 1 minute only. Do not overwet the mass.
9. Drying: Dry the wet granules in the fluid-bed dryer at 55°C to reach an LOD of no more than 0.4%.
10. Grinding: Pass the dried granules through a 1-mm sieve using Frewitt® granulator. Collect in a stainless steel drum.
11. Final mixing: Pass item 9 through 250-μm sieve using a sifter. Collect in a polyethylene-lined bag.
12. Load sieved material from step 8 into the blender.
13. Add sieved flavor (item 9) from step 11 to the blender.
14. Blend the powders for 5 minutes.
15. Unload the blended powder in stainless steel drums.

Erythromycin Ethylsuccinate for Oral Suspension (200 mg/5 mL)

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/1 kg (18 Units) (g)
200.00	1	Erythromycin, USE erythromycin ethylsuccinate[a]	89.3700
1342.00	2	Sucrose	483.1200
880.00	3	Sucrose[b]	316.8000
250.25	4	Sodium citrate	90.0900
2.97	5	Saccharin sodium	1.0692
0.27	6	FD&C red No. 40	0.0990
1.43	7	Carmellose sodium (Sodium CMC 7 MFD)	0.5148
21.45	8	Simethicone emulsion 30% (simethicone M30)	7.7220
12.98	9	Xanthan gum	4.6728
6.27	10	Cherry dry flavor	2.2572
–	11	Purified water	15.8400

[a]Potency: 850 μg/mg, as is.
[b]The weight of sucrose may be adjusted to compensate for potency variation of erythromycin ethylsuccinate to maintain the standard batch size (1 kg). Fill weight: 55 g for 100-mL pack.

Erythromycin Stearate for Oral Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
25.00	1	Erythromycin stearate 600 μg/mg, 5% excess	43.75
1.00	2	Methyl paraben	1.00
0.20	3	Propyl paraben	0.20
10.00	4	Magnesium aluminum silicate	10.00
1.15	5	Sodium carboxymethylcellulose (CMC), low viscosity	1.15
4.00	6	Alcohol 190 proof	4.00
120.00	7	Sodium citrate dihydrate	120.00
0.20	8	Saccharin sodium	0.20
700.00	9	Sugar granular	700.00
0.07	10	Yellow dye	0.07
2.76	11	Chocolate flavor	2.76
0.54	12	Orange flavor	0.54
1.25	13	Sodium lauryl sulfate	1.25
QS	14	Water purified	QS

Manufacturing Directions

I. Mixing
   A. Place sodium CMC and 40 g of sugar in a mixing drum. (If using alcohol, add it to the drum to wet the mixture and indicate use on the work order.) Roll for 2 hours to blend.
   B. Measure 350 mL of purified water into a jacketed mixing tank and heat the water to 95°C. Maintain at this temperature.
   C. Add methyl paraben to the water at 95°C. Stir until completely dissolved.
   D. Add propyl paraben to the solution at 95°C. Stir until completely dissolved.
   E. Cool to 60°C and maintain temperature. Stir the solution and slowly sprinkle in Veegum. Stir until Veegum is completely dispersed. Check by passing quantity of the batch through a 350-μm aperture or similar screen and watch for any undissolved residue.
   F. While stirring, add the blended powders from step A slowly to the solution. Stir until completely dissolved. Screen a quantity through a 350-μm aperture or similar screen to check for undissolved sodium CMC.
   G. Maintain the batch at 50°C to 55°C and gradually add the remaining sugar (item 9) with stirring. Stir until completely dissolved. Check for any undissolved sugar by passing a quantity of the bulk through a 350-mm aperture or similar screen.
   H. Dissolve the saccharin sodium in approximately 5 mL of purified water and add the solution to the batch.
   I. While stirring, add the sodium citrate to the batch. Stir under maximum vacuum until completely dissolved. Check by passing a quantity of the bulk through a 350-mm aperture or similar screen.
   J. Dissolve FD&C yellow No. 6 in approximately 5 mL of purified water and add the solution to the batch. Cool the batch to 30°C (chilled water may be used).
   K. In a separate tank, stir approximately 85 mL of purified water and slowly, taking care to avoid a vortex, add and dissolve sodium lauryl sulfate. When dissolved, gradually sprinkle in the erythromycin stearate and mix into a smooth slurry. Mix for half hour.
   L. While stirring the batch from step J, slowly add the slurry from step K. Take care not to aerate the batch. Wash thoroughly into the batch with approximately 10 mL of purified water.
   M. With continual stirring, add the flavors (items 11 and 12) to the batch.
   N. Pass the whole batch through a homogenizing mill using a suitable setting such that crystal fracture is minimized. Rinse the mill with purified water and add the rinsing to the batch.
   O. Return the milled batch back into the mixing tank. Gradually increase the application of vacuum as allowed by the level in the tank. Stir under a 28-in Hg vacuum for 1 hour. Adjust the batch volume to 1 L using purified water.
   P. Repeat step O until the volume is constant and specific gravity meets specifications.

Erythromycin Stearate for Oral Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/l (g)
25.00	1	Erythromycin stearate 600 μg/mg, 5% excess	43.75
1.00	2	Methyl paraben	1.00
0.20	3	Propyl paraben	0.20
2.00	4	Xanthan gum	2.00
120.00	5	Sodium citrate dihydrate	120.00
0.20	6	Saccharin sodium	0.20
100.00	7	Sorbitol solution	100.00
4.50	8	Antifoam emulsion Dow Corning	4.50
0.07	9	Dye yellow	0.07
2.76	10	Flavor chocolate	2.76
700.00	11	Sugar granular	700.00
0.54	12	Flavor orange	0.54
1.25	13	Sodium lauryl sulfate	1.25
QS	14	Water purified	QS

Manufacturing Directions

I. Mixing
   A. Heat 600 mL of purified water in a jacketed mixing tank to 95°C to 100°C.
   B. Add the methyl paraben and propyl paraben and mix to dissolve.
   C. Withdraw the following preserved purified water:
      1. 200 mL and dissolve the sodium citrate.
      2. 150 mL and dissolve the sodium lauryl sulfate.
      3. 5 mL and dissolve the sodium saccharin and the dye yellow.
   D. In a plastic bag, mix together the xanthan gum and 20 g of sucrose (item 11) for 10 minutes.
   E. Maintaining the batch at 50°C to 60°C while mixing, slowly add the dry mixture from step D until a clear gel is obtained.
   F. Add the sorbitol and mix.
   G. While mixing, slowly add the solution obtained from step C-1.
   H. Add the disperse 380 g of sucrose (item 11) while mixing. Make sure that the temperature will not go over 60°C. Stop heating when all dissolved.
   I. Without producing the vortex, add erythromycin stearate to the solution from step C-2 and continue mixing until smooth slurry is formed. Continue mixing for 15 to 30 minutes and then pass slurry through a homogenizer. Add the antifoam C to the slurry and mix; rinse the homogenizer with purified water and add the rinsings to the slurry. Mix.
   J. While mixing, add the slurry obtained from step I to the batch; rinse the vessel with 5 mL of purified water and add the rinsings to the batch.
   K. Add and disperse the solution from step C-3 and continue mixing.
   L. Mix under vacuum for 1 hour. Release the vacuum and record the volume. *Caution*: Do not adjust volume at this stage.
   M. Repeat step L until no further volume change is noticed.
   N. Add the flavors (items 10 and 11) and bring to volume with purified water.

Erythropoietin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
14000 IU	1	Erythropoietin[a]	140000000 IU
0.047	2	Dimyristoyl phosphatidyl choline	0.047
3.42	3	Aprotinin[b]	3.42
3.78	4	Hydroxypropyl cellulose-LF	3.78
3.78	5	Polyoxy-40 stearate Myrj-52®	3.78
141.1	6	Polyethylene glycol 400	141.1
15.72	7	Propylene glycol	15.72
8.83	8	Phosphate buffer	8.83
31.49	9	Cholesterol	31.49
17.72	10	Tween 80	17.72
63.68	11	Egg yolk lecithin	63.68
28.15	12	Glyceryl amino oleate	28.15
19.78	13	d-Alpha Tocopherol	19.78
251.42	14	Oleic acid	251.42

[a]Erythropoietin: 1000 IU = 8 μg
[b]Aprotinin: 7500 KIU = 1 mg

Manufacturing Directions

1. Erythropoietin is a 165-amino acid glycoprotein of approximately 34000 daltons. It is an endogenous protein, which is involved in the production of red blood cells. It is indicated for the treatment of anemia associated with chronic renal failure, in AIDS patients, and also to maintain or elevate the red blood cell level in the human body. In its preparations, there can be no use of heat or alcohol that can denature it.
2. The overall method is as follows: The high HLB surfactant polyoxy-40 stearate is slowly dispersed into the mixture of polyethylene glycol 400 and propylene glycol. Once it dissolves, hydroxypropyl cellulose as a stabilizer is also added which is dispersed slowly into the above mixture. A separate solution of the proteinaceous material along with the phospholipid and the protease inhibitor is made in a portion of the above solvent mixture. The solution can then be added to the PEG/PG mixture at room temperature. The amount of any water is limited to 5% of the polyol solvent. When the water solution is used, citrate buffer is used to maintain the pH at a point where the protein is most stable. For erythropoietin, pH can be adjusted to 7.0 to 7.5 with a phosphate buffer. The amount of aqueous buffer solution would still be 5% of the hydrophilic phase. At a pH of 7.0 to 7.5, erythropoietin has its maximum stability. It is known that in formulating proteins, the pH of the formulation should be distant from the isoelectric point of the protein, which would not precipitate the protein from the solution. Separately, the ingredients of the lipid solvent are mixed together. Under gentle and constant stirring, the polyol solution is dispersed with the lipid solution.
3. The surfactant (polyoxy-40 stearate) is slowly dispersed into a mixture of polyethylene glycol and propylene glycol. Once it is dissolved, small amounts of hydroxypropyl cellulose are then added and dispersed into the same mixture. Erythropoietin is dissolved in the phosphate buffer/water/saline, along with aprotinin and dimyristoyl phosphatidyl choline. The aqueous solution is then added to the polyethylene glycol mixture at room temperature. The pH of the solution should be adjusted at 7.5 for maximum stability.
4. In a separate vessel, dissolve all the lipid-liking ingredients in oleic acid. Cholesterol is added slowly to achieve faster dissolution. Once both the phases are ready, the lipid solution is added slowly to polyol solution while mixing at low speed. Preferably, the vessel should be ice jacketed because mixing produces heat. Once the mixing is achieved, a transparent yellowish-brown preemulsion solution is obtained.
5. The preemulsion solution is filled in a size 0 hard gelatin capsule and the capsule is sealed with a band of gelatin solution. The banding helps to coat the capsule uniformly.
6. The capsule is then coated with a 10% hydroxypropyl methylcellulose solution as an undercoat. The amount of coat required is sufficient just enough to cover the capsule uniformly with a thin layer of the polymer coat. Usually, a 3.5% to 4.5% weight gain of the capsule is a good indication of the amount required as an undercoat.
7. Once the capsule is coated with an undercoat, enteric coating is applied. For enteric coating purposes, different polymers, such as hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and cellulose acetate phthalate, are used.
8. Anionic copolymers that are based on methacrylic acid and methyl methacrylate, commercially available as Eudragit, are also suitable polymers for enteric coating purposes. The polymer is dissolved in organic solvents such as ethyl alcohol, methyl alcohol, acetone, isopropyl alcohol. A combination of two solvents can also be used. The amount of enteric coating solution required is 5% to 6% of the weight gain of the capsules from the original weight of the capsules before applying an enteric coat.

A typical enteric coating solution is made as follows: methacrylic acid and Methacrylate copolymer 10% w/w, diethyl butyl phthalate (plasticizer) 2% w/w, acetone 22% w/w, isopropanol 66% w/w.

9. Mix acetone and isopropanol. Add the polymer slowly with constant mixing. Once the polymer is dissolved, add the plasticizer slowly and let it dissolve.
   For a size 0 capsule, the previously mentioned enteric coating solution can be sprayed using fluidizing bed techniques. The fluid bed sprayer/dryer is operated with the following parameters.
   Flow rate: 1.5 mL/min
   Inlet air temperature: 25°C
   Outlet air temperature: 25°C
   Air flap: 35
   Atomizer: 2 bar
   A size 0 capsule after the enteric coating will typically have the following composition: preemulsion solution: 0.589 g, undercoat polymer: 0.027 g, enteric coat polymer: 0.032 g, 0.648 g.

Esomeprazole Magnesium Capsules*

Each delayed-release capsule contains 20 or 40 mg of esomeprazole (present as 22.3 or 44.5 mg esomeprazole magnesium trihydrate) in the form of enteric-coated pellets with the following inactive ingredients: glyceryl monostearate 40 to 50, hydroxypropyl cellulose, hydroxypropyl methylcellulose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, *N*-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidine, and D&C yellow No. 10.

Estramustine Phosphate Capsules*

The capsules are white and opaque, each containing estramustine phosphate sodium as the disodium salt monohydrate that is equivalent to 140 mg estramustine phosphate for oral administration. Each capsule also contains magnesium stearate, silicon dioxide, sodium lauryl sulfate, and talc. Gelatin capsule shells contain titanium dioxide.

Ethosuximide Capsules*

Each capsule contains 250 mg ethosuximide and the inactive ingredient polyethylene glycol. The capsule contains D&C yellow No. 10; FD&C red No. 3, gelatin, glycerin, and sorbitol.

Etodolac Capsules*

The inactive ingredients in the capsules are cellulose, gelatin, iron oxides, lactose, magnesium stearate, povidone, sodium lauryl sulfate, sodium starch glycolate, and titanium dioxide.

Felbamate for Oral Suspension*

The inactive ingredients for felbamate suspension (600 mg/5 mL) are sorbitol, glycerin, microcrystalline cellulose, carboxy methylcellulose sodium, simethicone, polysorbate 80, methylparaben, saccharin sodium, propylparaben, FD&C yellow No. 6, FD&C red No. 40, flavorings, and purified water.

Fenofibrate Capsules*

Each capsule contains 67, 134, or 200 mg of micronized fenofibrate. Each capsule also contains the following inactive ingredients: crospovidone, iron oxide, lactose, magnesium stearate, pregelatinized starch, sodium lauryl sulfate, and titanium dioxide.

Fenofibrate Capsules

1. According to the preparation example I in Japanese Examined Patent Publication No. Hei 7–14876 (hereinafter referred to "PREPARATION I"), granules are prepared via a co-micronizing process of fenofibrate and sodium lauryl sulfate.
2. The formulation used is as follows (in a capsule; total amount: 250 mg): Fenofibrate 200 mg, sodium lauryl sulfate 7 mg, lactose 3 mg, magnesium stearate 3 mg, alpha, modified starch 30 mg, crospovidone 7 mg.
3. The granules thus obtained were filled into size No. 2 capsules.

Fenofibrate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Fenofibrate micronized (5 mm)	100.00
2.00	2	Sodium lauryl sulfate	2.00
100.00	3	Polyvinylpyrrolidone K 25, 100–400 mm	100.00
QS	4	Water purified	1750.00
114.28	5	Lactose monohydrate, 100–400 mm	114.28

Note: This formulation is expected to provide enhanced bioavailability of item 1, thus the dose may be reduced by 33% for all strengths.

Manufacturing Directions

1. Examine item 1 using a Coulter® counter to make sure 90% of particles are within the 5-mm range.
2. Add and dissolve item 2 in item 4; item 1 is then added to make a smooth suspension using a high-speed stirrer and then passing it through a high-speed mill.
3. Add item 3 while agitating until it is dissolved and ensure that no agglomerates are present.
4. Pass step 3 through a 350-μm sieve.
5. Separately, item 5 is charged in a fluid-bed granulator and brought into suspension and the temperature is raised to 40°C.
6. Add step 3 into step 5 gradually at a spraying pressure of 2.1 bar, air throughput of 70 m^3/h, air inlet temperature of 45°C, air outlet temperature of 33°C, product temperature of 34°C, and a spraying duration of 3 hours.
7. The granulate thus obtained is filled in a suitable size capsule.

Fexofenadine Hydrochloride Capsules*

Each capsule contains 60 mg of fexofenadine hydrochloride and the following excipients: croscarmellose sodium, gelatin, lactose, microcrystalline cellulose, and pregelatinized starch. The printed capsule shell is made from gelatin, iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and other ingredients.

Fexofenadine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
60.00	1	Fexofenadine hydrochloride[a]	60.00
141.00	2	Microcrystalline cellulose	141.00
141.00	3	Lactose	141.00
40.00	4	Pregelatinized starch	40.00
20.00	5	Croscarmellose sodium	20.00
14.70	6	Gelatin capsules	14.70

[a]Particle surface area of 2–4 m^2/g.

Manufacturing Directions

1. Combine fexofenadine hydrochloride (item 1), microcrystalline cellulose (item 2), lactose (item 3), and pregelatinized starch (item 4) and blend in a mixer for 5 minutes.
2. To this mixture, add a solution of gelatin (item 6) in purified water (prepared by adding the gelatin to the water and heating the dispersion with mixing until solution of the gelatin is attained) and continue mixing until a good granulation is formed.
3. Pass the granulation through a 0.375-in screen and dry at 60°C until moisture content of less than 3.0% is achieved as determined by a Computrac moisture balance at 125°C.
4. Mill the dried granulation through a 0.065-in screen.
5. To the granulation, add croscarmellose sodium and mix for approximately 10 minutes.
6. Fill the granulation into size 0 hard gelatin capsules to a total fill weight of 416.7 mg granulation per capsule.

Fluconazole for Oral Suspension*

The oral suspension contains 350 or 1400 mg of fluconazole and the following inactive ingredients: sucrose, sodium citrate dihydrate, citric acid anhydrous, sodium benzoate, titanium dioxide, colloidal silicon dioxide, xanthan gum, and natural orange flavor. After reconstitution with 24 mL of distilled water or purified water, each milliliter of reconstituted suspension contains 10 or 40 mg of fluconazole.

Flucytosine Capsules*

Each capsule also contains cornstarch, lactose, and talc. Gelatin capsule shells contain parabens (butyl, methyl, propyl) and sodium propionate, with the following dye systems: 250-mg capsules contain black iron oxide, FD&C blue No. 1, FD&C yellow No. 6, D&C yellow No. 10, and titanium dioxide; 500-mg capsules contain black iron oxide and titanium dioxide.

Fluoxetine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Fluoxetine, USE fluoxetine hydrochloride	22.36
80.14	2	Starch (cornstarch)	80.14
10.00	3	Simethicone, USE simethicone M30	35.00
42.00	4	Starch (cornstarch dried)	42.00
0.50	5	Colloidal Silicon dioxide (Aerosil 200)	0.50
1.00	6	Empty hard gelatin capsule, shell size 3	1000.00

Manufacturing Directions

Note: The processing area must be under controlled room temperature and humidity. The limits are RH 40% to 50%, temperature NMT 27°C.

1. Dry powder mixing
   A. Sift items 1 and 2 through a stainless steel sieve (630 μm) in a sifter.
   B. Load the powder mix in the mixer. Mix for 5 minutes at low speed.
2. Wet massing
   A. Add item 3 suspension into the powder mix while mixing at low speed for 3 minutes. Scrape sides and blades. Mix for another 3 minutes at low speed.
3. Drying and grinding
   A. Spread the moist mass thinly on stainless steel trays. Break the big lumps if any.
   B. Dry the mass in oven at 55°C for 10 hours.
   C. Check LOD (limit between 1.5% and 2.0%). If required, dry further for 1 hour.
   D. Grind the dried granules through a granulator using a stainless steel sieve (1 mm). Collect in a stainless steel drum.
4. Lubrication
   A. Sift items 4 and 5 through a stainless steel sieve (500 μm) using a sifter. Collect in a stainless steel drum. Add into the drum blender (step III-D). Mix for 5 minutes.
   B. Unload the final blend.
5. Take sample for analyzing fluoxetine hydrochloride content in the granules to fill. *Note:* Encapsulation is recommended within 7 days after lubrication.

Fluoxetine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Fluoxetine, USE fluoxetine hydrochloride	22.40
160.00	2	Talc	160.00
100.00	3	Starch dried	100.00
4.00	4	Magnesium stearate	4.00
1.00	5	Aerosil 200	1.00

Manufacturing Directions

1. Charge items 1 to 5 in a suitable blender after passing through a No. 60 mesh.
2. Mix for 30 minutes.
3. Fill 350 mg in size 2 capsules.

Fluoxetine Hydrochloride Instant and Weekly Capsules*

Each capsule contains fluoxetine hydrochloride equivalent to 10 mg (32.3 mmol), 20 mg (64.7 mmol), or 40 mg (129.3 mmol) of fluoxetine. The Pulvules also contain starch, gelatin, silicone, titanium dioxide, iron oxide, and optionally other inactive ingredients. The 10- and 20-mg Pulvules also contain FD&C blue No. 1 and the 40-mg Pulvule also contains FD&C blue No. 1 and FD&C yellow No. 6. The capsules intended for weekly administration, a delayed-release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 mmol) of fluoxetine. The capsules also contain FD&C yellow No. 10, FD&C blue No. 2, gelatin, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and optionally other inactive ingredients.

Flutamide Capsules*

Each capsule contains 125 mg of flutamide. The inactive ingredients include cornstarch, lactose, magnesium stearate, povidone, and sodium lauryl sulfate. Gelatin capsule shells may also contain benzyl alcohol, butylparaben, colloidal silicon dioxide, edetate calcium disodium, methylparaben, propylparaben, and sodium propionate, as well as the following dye systems: FD&C blue No. 1, FD&C red No. 3, FD&C yellow No. 6, titanium dioxide, and black ink.

Fluticasone Propionate and Salmeterol Xinafoate Inhalation Powder*

This is a combination of fluticasone propionate and salmeterol xinafoate. These are specially designed plastic devices containing a double-foil blister strip of a powder formulation of fluticasone propionate and salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 100, 250, or 500 μg of microfine fluticasone propionate and 72.5 μg of microfine salmeterol xinafoate salt, equivalent to 50 μg of salmeterol base, in 12.5 mg of formulation containing lactose. Each blister contains one complete dose of both medications. After a blister containing the medication is opened by activating the device, the medication is dispersed into the air stream created by the patient inhaling through the mouthpiece. Under standardized in vitro test conditions, it delivers 93, 233, and 465 μg of fluticasone propionate and 45 μg of salmeterol base per blister, respectively, when tested at a flow rate of 60 L/min for 2 seconds.

Fluvastatin Sodium Capsules*

It is supplied in capsules containing fluvastatin sodium, equivalent to 20 or 40 mg of fluvastatin, for oral administration. The inactive ingredients in the capsules are gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, and yellow iron oxide. Capsules may also include benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, and sodium propionate.

Fluvastatin Sodium Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Fluvastatin	20.00
62.84	2	Calcium carbonate heavy precipitated	62.84
2.00	3	Sodium bicarbonate	2.00
23.35	4	Microcrystalline cellulose Avicel PH102	23.35
20.95	5	Pregelatinized starch (starch 1500)	20.95
QS	6	Water purified	QS
33.88	7	Microcrystalline cellulose	33.38
20.95	8	Pregelatinized starch	20.95
9.43	9	Talc	9.43
1.05	10	Magnesium stearate	1.05

Manufacturing Directions

1. Fluvastatin (item 1), sodium bicarbonate (item 3), calcium carbonate (item 2), microcrystalline cellulose (item 4), and pregelatinized starch (item 5) are mixed for 5 minutes and the mixture is passed through a 40-mesh screen and blended for another 3 minutes.
2. Water is added to the mixture while blending for about 4 minutes to form a wet granulation.
3. The wet granulation is dried in a fluid bed dryer at 50°C inlet temperature to a loss on drying of 1.59%.
4. The dried granules are passed through a 20-mesh screen and blended with the microcrystalline cellulose and pregelatinized starch set-asides (items 7 and 8) for approximately 10 minutes.
5. Talc and magnesium stearate (each prescreened on a 60-mesh bolting cloth) are added to the mixture while blending for approximately 5 minutes. The resulting composition has a loss on drying of 2.65%.
6. A blue opaque capsule is filled with the composition and polished manually with salt.

Formoterol Fumarate Inhalation Powder*

This consists of a capsule dosage form containing a dry powder formulation of formoterol fumarate intended for oral inhalation only with the AerolizerJ® inhaler. Each clear, hard gelatin capsule contains a dry powder blend of 12 μg of formoterol fumarate and 25 mg of lactose as a carrier. The active component is formoterol fumarate—a racemate.

Formoterol Fumarate Inhaler Capsules*

The inhaler consists of a capsule dosage form containing a dry powder formulation of formoterol fumarate intended for oral inhalation only with the AerolizerJ inhaler. Each clear, hard gelatin capsule contains a dry powder blend of 12 μg of formoterol fumarate and 25 mg of lactose as a carrier.

Fosfomycin Tromethamine Sachets*

Fosfomycin tromethamine sachet contains fosfomycin tromethamine, a synthetic, broad-spectrum bactericidal antibiotic for oral administration. It is available as a single-dose sachet, which contains white granules consisting of 5.631 g of fosfomycin tromethamine (equivalent to 3 g of fosfomycin) and the following inactive ingredients: mandarin flavor, orange flavor, saccharin, and sucrose.

Gabapentin Capsules*

Gabapentin capsules are supplied as imprinted hard shell capsules containing 100, 300, and 400 mg of gabapentin. The inactive ingredients for the capsules are lactose, cornstarch, and talc. The 100-mg capsule shell contains gelatin and titanium dioxide. The 300-mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400-mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C blue No. 2 and titanium dioxide.

Gabapentin Capsules

Ingredients	Percent (w/w)
Gabapentin (Kemprotec)	75.00%
StarCap 1500® (Colorcon)	24.75%
Magnesium stearate NF (Mallinckrodt)	0.25%
Total:	100.00%
Hard gelatin capsule shell No. 0, White/White	QS

Manufacturing Directions

1. Mix all ingredients.
2. Fill 400 mg in size 0 capsule.

Ganciclovir Capsules*

Each capsule contains 250 or 500 mg ganciclovir respectively and the following inactive ingredients: croscarmellose sodium, magnesium stearate, and povidone. Both hard gelatin shells consist of gelatin, titanium dioxide, yellow iron oxide, and FD&C blue No. 2.

Ganciclovir Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Ganciclovir	250.00
3.00	2	Magnesium stearate	3.00
30.00	3	Cornstarch	30.00
116.00	4	Lactose	116.00
4.00	5	Polyvinylpyrrolidone	3.00
QS	6	Methanol	QS

Manufacturing Directions

1. Items 1, 3, and 4 are granulated in a solution of item 5 in item 6.
2. Granules are dried, lubricated with item 2, and filled in capsules or tablets.

Gemfibrozil Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Gemfibrozil	100.00
248.80	2	Lactose anhydrous[a]	248.80
100.00	3	Cornstarch	100.00
25.00	4	Sodium starch glycolate	25.00
5.00	5	Povidone	5.00
15.00	6	Polysorbate 80	15.00
1.25	7	Colloidal silicon dioxide	1.25
5.00	8	Magnesium stearate	5.00
QS	9	Water purified	QS

[a]The quantity of lactose can be reduced to compensate if additional quantities of glycine 12.5 mg and citric acid 2.5 mg are used.

Manufacturing Directions

1. An aqueous wet granulation process is used whereby the respective active ingredients of lactose, cornstarch, sodium starch glycolate, colloidal silicon dioxide, and povidone are mixed and subsequently granulated with polysorbate dissolved in purified water.
2. Additional purified water is then added until granules form and no dry powder remains.
3. Wet granules are dried at 60°C until the loss on drying is NMT 2%.
4. The dried granules are milled with the sodium starch glycolate, blended, and lubricated with screened magnesium stearate in a twin-shell blender.
5. Size 0 capsules are used to fill 500 mg of granules.

Glycoprotein IIa/IIb Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
0.23	1	Glycoprotein IIa/IIb	0.23
53.77	2	Lactose anhydrous	53.77
2.70	3	Crospovidone	2.70
1.20	4	Povidone	1.20
1.50	5	Disodium citrate	1.50
0.60	6	Magnesium stearate	0.60
QS	7	Water purified	QS

Manufacturing Directions

1. Triturate item 1 with item 2 (portion) in a small mixing vessel or mortar.
2. Charge the balance of item 2 and two-thirds of the quantity of item 3 in a shear granulator and add step 1 into it with fast mixing.
3. Granulate step 2 using aqueous solution of balance of item 4 and item 5 (9.3% solids in item 7 and pH adjusted to 4 using 1 *N*-hydrochloric acid).
4. Screen the granulation through a No. 8 mesh and dry in vacuum at 40°C to moisture content of 0.7%.
5. Blend the granulation with remaining amount of items 3 and 6.
6. Fill 60 mg in size 3 capsules.

Guaifenesin Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
150.00	1	Guaifenesin	150.00
26.60	2	Carbopol 934P (B. F. Goodrich)	26.60
172.10	3	PVP C-15 (GAF Corporation)	172.10
3.50	4	Talc	3.50
1.80	5	Zinc stearate	1.80

Manufacturing Directions

1. Carbopol 934P, PVP C-15, talc, and zinc stearate are combined in a mortar and triturated well.
2. The guaifenesin is added to this mixture in the mortar and triturated well until a substantially uniform particulate mixture is achieved.
3. The resulting particulate mixture is filled 354 mg into size 1 hard gelatin capsule shells.

Herbal AIDS Treatment Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
32.00	1	*Combretum quadrangulare*	32.00
20.00	2	*Houttuynia cordata*	20.00
20.00	3	*Mimusops elengi*	20.00
20.00	4	*Randia siamensis*	20.00
308.00	5	*Borassus flabellifer*	308.00

Manufacturing Directions

1. Items 1 to 5 are prepared by first making a powdered form of herbs, extracting them in water or hydroalcoholic solution, and drying the extract.
2. Powdered extracts 1 to 5 are admixed and filled in a gelatin capsule. Add magnesium stearate 1%, if necessary, to improve flow.

Histidine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Histidine	240.00
QS	2	Lactose	QS

Manufacturing Directions

1. Mix items 1 and 2 (using desired quantity of item 2 to fit the capsule size chosen) by process of trituration.
2. Fill in appropriate capsule.

Human Growth Hormone Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
28.00 IU	1	Human growth hormone[a]	28000 IU
0.047	2	Dimyristoyl phosphatidic acid	0.047
3.38	3	Aprotinin[b]	3.38
3.47	4	Sodium cholate	3.47
3.70	5	Polyoxy-23 lauryl ether	3.70
138.60	6	Polyethylene glycol 400	138.60
13.71	7	Propylene glycol	13.71
8.67	8	Water/pH adjuster	8.67
30.92	9	Cholesterol	30.92
17.40	10	Tween 80	17.40
62.53	11	Egg yolk lecithin	62.53
19.43	12	D-alpha-tocopherol	19.43
27.64	13	Sorbitan monooleate	27.64
246.90	14	Isostearic acid	246.90

[a]Human growth hormone 2.6 IU = 1 mg.
[b]Aprotinin: 7500 KIU = 1 mg.

Manufacturing Directions

1. Polyoxy-23 lauryl ether (commercially available as Brij™ 35) is dispersed in the solvent mixture of polyethylene glycol 400 and propylene glycol.
2. Sodium cholate is also separately dispersed in the mixture.
3. A water solution containing recombinant human growth hormone, phospholipid, and aprotinin is then added to the solvent mixture in step 1 and the pH is adjusted to 7.5 to 7.8 with the help of a phosphate buffer.
4. The lipid solution is made separately in another beaker.
5. To the oil solution, the polyol solution is added drop-wise while mixing continuously. While mixing, it is suggested that the vessel be ice jacketed to prevent the denaturation of the protein in the formulation.
6. A clear transparent liquid, which is called the preemulsion solution, is obtained after approximately 5 minutes of mixing at low speed. An in situ emulsion can be made by mixing any ratio of the preemulsion solution with the simulated intestinal fluid.
7. The preemulsion solution is filled in a size 0 hard gelatin capsule and the capsule is sealed with a band of gelatin solution. The banding helps to coat the capsule uniformly.
8. The capsule is then coated with a 10% hydroxypropyl methylcellulose solution as an undercoat. The amount of coat required is sufficient just enough to cover the capsule uniformly with a thin layer of the polymer coat. Usually 3.5% to 4.5% weight gain of the capsule is a good indication of the amount required as an undercoat.
9. Once the capsule is coated with an undercoat, enteric coating is applied. For enteric coating purposes, different polymers such as hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and cellulose acetate phthalate are used.
10. Anionic copolymers, which are based on methacrylic acid and methyl methacrylate, commercially available as Eudragit, are also suitable polymers for enteric coating purposes. The polymer is dissolved in organic solvents such as ethyl alcohol, methyl alcohol, acetone, and isopropyl alcohol. A combination of two solvents can also be used. The amount of enteric coating solution required is 5% to 6% weight gain of the capsules from the original weight of the capsules before applying enteric coat. A typical enteric coating solution is made as follows:
    Methacrylic acid and methyl methacrylate copolymer 10% w/w
    Diethyl butyl phthalate (plasticizer) 2% w/w
    Acetone 22% w/w
    Isopropanol 66% w/w
11. Mix acetone and isopropanol. Add the polymer slowly with constant mixing. Once the polymer is dissolved, add the plasticizer slowly and let it dissolve.
12. For a size 0 capsule, the previously mentioned enteric coating solution can be sprayed using fluidizing bed techniques.
    The fluid bed sprayer/dryer is operated with the following parameters:
    Flow rate: 1.5 mL/min
    Inlet air temperature: 25°C
    Outlet air temperature: 25°C
    Air flap: 35
    Atomizer: 2 bar
    A size 0 capsule, after the enteric coating, will typically have the following composition:
    Preemulsion solution: 0.589 g
    Undercoat polymer: 0.027 g
    Enteric coat polymer: 0.032 g, 0.648 g

Hydrochlorothiazide and Triamterene Capsules*

This is a combination capsule with an opaque red cap and an opaque white body. It contains hydrochlorothiazide (25 mg) and triamterene (37.5 mg). Inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C red No. 33, FD&C yellow No. 6, gelatin, glycine, lactose, magnesium stearate, microcrystalline cellulose, povidone, polysorbate 80, sodium starch glycolate, titanium dioxide, and trace amounts of other inactive ingredients. These capsules meet Drug Release Test 3 as published in the USP monograph for triamterene and hydrochlorothiazide capsules.

Hydrochlorothiazide Capsules*

It is supplied as 12.5-mg capsules for oral use. Each capsule contains the following inactive ingredients: colloidal silicon dioxide, cornstarch, D&C red No. 28, D&C yellow No. 10, FD&C blue No. 1, gelatin, lactose monohydrate, magnesium stearate, titanium dioxide, and other optional ingredients.

Hydroxyzine Pamoate Capsules and Oral Suspension*

The inert ingredients for the capsule formulations are hard gelatin capsules (which may contain FD&C yellow No. 10, FD&C green No. 3, FD&C yellow No. 6, FD&C red No. 33, and other inert ingredients), magnesium stearate, sodium lauryl sulfate, starch, and sucrose. The inert ingredients for the oral suspension formulation are carboxymethylcellulose sodium, lemon flavor, propylene glycol, sorbic acid, sorbitol solution, and water.

Hyoscyamine Sulfate Capsules*

The sustained-release capsules contain 0.375 mg hyoscyamine sulfate in an extended-release formulation designed for oral bid dosage. Each capsule also contains the following inactive ingredients: FD&C blue No. 1, D&C red No. 28, FD&C red No. 40, FD&C yellow No. 6, gelatin, lactose monohydrate, sodium lauryl sulfate, magnesium stearate, silicon dioxide, titanium dioxide, and other optional ingredients.

Ibuprofen Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
450.00	1	Ibuprofen	450.00
450.00	2	Sodium alginate	450.00
4.50 mL	3	Zinc chloride solution 2%	451.00
QS	4	Hydrochloric acid	QS
0.22 mL	5	Glycerin	225.00 mL
–	6	Water purified	22.5 L

Manufacturing Directions

1. A mixture consisting of item 1, previously triturated in 225 mL of glycerin, is added with rapid stirring to an aqueous solution consisting of 450 g (w/v) of sodium alginate in 22.5 L of purified water.
2. This solution is then added to 45 L of a 2% (w/v) zinc chloride solution, which has previously been adjusted to pH 3 by the addition of HCl while the rapid stirring is continued for 10 minutes.
3. The preparation is then allowed to stand at room temperature for 4 hours, after which the drug-entrapped zinc alginate precipitate is collected by filtration, washed 3 times with distilled water, and dried under vacuum for 24 hours.
4. After drying, the residue is granulated using minimal amounts of glycerin/water and processed into 0.5-mm diameter microspheres by mechanical extrusion and spheronization (Nica Extruder®; Aeromatic Ltd., Bubendorf, Switzerland), into which the slightly flexible mass represented by the above residue is fed and which produces therefrom a continuous flow of cylindrical extrudate that is 0.5 mm in diameter.
5. This extrudate falls onto the spinning plate of a Nica Spheronizer® (Aeromatic Ltd.), where it is broken into cylinders of approximately 1:1 length:diameter ratio. Interaction then between the spinning disc and the wall of the spheronizer causes the cylinders to be worked into spheres of 0.5 mm diameter.
6. The spheres are then filled into gelatin capsules (1 g of spheres per size 0 capsule, which represents a total dose of 450 mg of ibuprofen). The capsules of spheres thus produced represent a sustained-release dosage form for analgesic–antipyretic activity with less propensity for gastrointestinal side effects than the conventional tablet form of ibuprofen. Upon ingestion, the spheres begin to release the incorporate drug almost immediately, but begin erosion in 3 to 5 hours. Total erosion time is approximately 8 hours.

Ibuprofen and Domperidone Maleate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
200.00	1	Ibuprofen	200.00
10.00	2	Domperidone maleate	10.00
100.00	3	Lactose	100.00
20.00	4	Croscarmellose	20.00

Manufacturing Directions

Items 1 to 4 are formed into a homogeneous blend and filled into a conventional hard gelatin capsule containing 200 mg ibuprofen and 10 mg domperidone.

Ibuprofen and Domperidone Maleate Effervescent Granules

Bill of Materials			
Scale (mg/10 g sachet)	Item	Material Name	Qty/kg (g)
20.00	1	Domperidone	2.00
400.00	2	Ibuprofen	40.00
250.00	3	Microcrystalline cellulose	25.00
5120.00	4	Pulverized sugar	512.00
2550.00	5	Malic acid	255.00
770.00	6	Sodium bicarbonate anhydrous	77.00
260.00	7	Sodium carbonate	26.00
10.00	8	Sodium lauryl sulfate	1.00
QS	9	Water	QS

Manufacturing Directions

1. The domperidone, ibuprofen, microcrystalline cellulose, and sugar are granulated with water and then thoroughly dried. The remaining ingredients are added to form a powder mixture.
2. Fill 10 g into sachets each containing 400 mg ibuprofen and 20 mg domperidone maleate.

Ibuprofen Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
800.00	1	Ibuprofen	800.00
8.00	2	Aerosil R972	8.00
8.00	3	Beeswax	8.00

Manufacturing Directions

1. Charge items 1 and 3 in a jacketed kettle and heat to melt; stir until uniformly melted.
2. Add item 2, with stirring, to form a homogeneous suspension. Allow to cool.
3. Pass through sieve. If needed, a lubricant may be added to facilitate flow (1% magnesium stearate).
4. Fill size 00 capsules.
5. The 50% dissolution time is approximately 15 hours.

Given below are guidelines on controlling release rates of ibuprofen using different compositions of excipients. In all instances, ibuprofen is melted with the ingredient, allowed to congeal, sized, and filled in appropriate size capsules. T_{50} represents time for 50% dissolution. A combination of these granules can be used to provide a wide range of ibuprofen release patterns that are particularly useful in arthritis therapy.

	Amount of		
	Ibuprofen (% w/w)	Excipient (% w/w)	T_{50} (hours)
None	100	—	2.9
Arachis oil	90	10	4.1
Beeswax	90	10	>24.0
Beeswax	90[a]	10	9.5
Colloidal silicon dioxide (Aerosil 200)	99	1	4.7
	97	3	6.6
	95	5	10.0
Colloidal silicon dioxide (Aerosil R972)	99	1	5.9
	95	5	20.5
Croscarmellose sodium (Ac-Di-Sol)	99	1	0.4
	97.5	2.5	0.13
Glycerides	95	5	3.0
(Gelucire 50/13)	90	10	7.4
(Gelucire 50/13)	90[a]	10	2.9
Liquid paraffin	90	10	4.8
Cornstarch	99	1	3.5
	95	5	1.6
	90	10	0.16
Copolymer (Pluronic F68)	95	5	3.0
PEG 400	90	10	3.5
PEG 4000	90	10	3.3
PEG 6000	90	10	4.2
Polyvinylpyrrolidone (crospovidone)	90	10	4.0
Sodium starch glycolate (Explotab®)	99	1	1.8
	95	5	0.3
Stearic acid	99	1	4.2
	95	5	7.8
	90	10	>24.0
Stearyl alcohol	99	1	10.0
	95	5	14.0
	90	10	>24.0

[a]Indicates S(+)ibuprofen.

Ifosfamide Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Ifosfamide	250.00
83.50	2	Microcrystalline cellulose, Avicel PH105	83.50
1.50	3	Colloidal silicon dioxide	1.50
0.50	4	Magnesium stearate	0.50

Manufacturing Directions

1. Pass items 1 to 3 through a 0.8-mm sieve into a blender.
2. Blend for 4 minutes.
3. Add item 4, which has been sieved through a 0.8-mm sieve, to step 2; mix for another 1 minute.
4. Fill 340 mg in size 1 capsules. For a 500-mg capsule, fill 680 mg in size 00 capsules.
5. To impart enteric resistance to capsules, coat using a coating suspension. For example, to coat 2500 size 1 capsules containing 250 mg ifosfamide, use 3 kg of suspension containing 1440 g anionic polymerizate of methacrylic acid and methacrylic acid esters with a mean molecular weight of, for example, 150000, to which a conventional softener has been added, 18 g of 1,2-propandiol, 36 g of magnesium stearate, and 1506 g of isopropanol. The copolymerizate of methacrylic acid and methylmethacrylate that may, for example, be considered is Eudragit® L, particularly in the form of a 12.5% solution in isopropanol (Eudragit® L/12.5%). Copolymerizates for this type are soluble in neutral to weak alkaline medium through salt formation with alkalis.

Imatinib Mesylate Capsules*

The capsules contain imatinib mesylate equivalent to 100 mg of imatinib freebase. The inactive ingredients are colloidal silicon dioxide, crospovidone, magnesium stearate, and microcrystalline cellulose. The capsule shell contains gelatin; iron oxide; red (E172); iron oxide, yellow (E172); and titanium dioxide (E171).

Indinavir Sulfate Capsules*

Capsules are formulated as a sulfate salt and are available for oral administration in strengths of 100, 200, 333, and 400 mg of indinavir (corresponding to 125, 250, 416.3, and 500 mg indinavir sulfate, respectively). Each capsule also contains the inactive ingredients anhydrous lactose and magnesium stearate. The capsule shell has the following inactive ingredients and dyes: gelatin, titanium dioxide, silicon dioxide, and sodium lauryl sulfate.

Indinavir Sulfate Capsules

Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
400.00	1	Indinavir sulfate, USE indinavir sulphate	400.00
7.00	2	Sodium lauryl sulphate	7.00
1.50	3	Colloidal silicon dioxide (Aerosil 200)	1.50
6.50	4	Magnesium stearate	6.50
650.00	5	Lactose monohydrate dense	QS to 650.00
1.00	6	Empty hard gelatin capsule, size 00	1000.00

Manufacturing Directions

1. Sift indinavir sulphate, lactose anhydrous, and Aerosil 200 through a specified sieve.
2. Load the sifted powder into a blender and blend well.
3. Sift magnesium stearate and sodium lauryl sulphate through a specified sifter.
4. Mix step 3 with step 2 and blend well.
5. Encapsulate the powder to get the stated amount of indinavir per capsule.

Indomethacin Capsules

Directions

1. Granules (per 100 mg), indomethacin 25 (mg), DL-tryptophan 35, hardened oil (hydrogenate soybean oil) 38, ethyl cellulose, total 100 mg.
2. A blender was charged with 750 g of indomethacin, 1050 g of DL-tryptophan, and 1140 g of the hardened oil (hydrogenated soybean oil) and mixing was conducted for 10 minutes.
3. Thereafter, 600 g of an ethanol solution of 10% ethyl cellulose (Ethocel 10CPS) was added and blending was conducted for an additional 10 minutes.
4. The blend was granulated in a rotary granulator equipped with a net (1 mm), dried at 45°C in a tray dryer for 6 hours, and classified on a 12-mesh sieve to make granules.
5. 2500 g of the granules prepared in step 4 were coated with 15% (w/w), based on the granules, of 6% hydroxypropyl methyl cellulose phthalate (HP-55) dissolved in a 1:1 mixture of methylene chloride and ethanol.
6. 300 g of the granules prepared in step 4 and 805 g of the enteric granules obtained in example 4 were mixed in a polyethylene bag and charged in No. 2 capsules in such a manner that each capsule contained 110.5 mg of the mixed granules.

Indomethacin Capsules*

Capsules for oral administration contain either 25 or 50 mg of indomethacin and the following inactive ingredients: colloidal silicon dioxide, FD&C blue No. 1, FD&C red No. 3, gelatin, lactose, lecithin, magnesium stearate, and titanium dioxide. Suspension for oral use contains 25 mg/5 mL of indomethacin, alcohol 1%, and sorbic acid 0.1% added as a preservative. The suspension also contains the following inactive ingredients: antifoam AF emulsion, flavors, purified water, sodium hydroxide or hydrochloric acid to adjust pH, sorbitol solution, and tragacanth.

Indomethacin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
25.00	1	Indomethacin micronized	26.25
1.00	2	Lecithin (liquid)	1.00
–	3	Trichlorotrifluoroethane	17.00
218.25	4	Lactose monohydrate (dense)	218.25
1.50	5	Colloidal silicon dioxide (Aerosil 200)	1.50
2.00	6	Sodium lauryl sulfate	2.00
1.00	7	Magnesium stearate	1.00
1.00	8	Empty hard gelatin capsule, size 3	1000.00

Manufacturing Directions

1. Precautions
   A. The processing area must be under controlled room temperature and humidity. The limits are RH: 40% to 50%, temperature: 21°C to 27°C.
   B. Trichlorotrifluoroethane is a volatile substance when kept in open air. Always keep in covered containers.
   C. Do not expose the granules for a long time to light, as discoloration will occur.
   D. Mix item 2 with item 3 in a clean stainless steel container. Firmly cover to avoid any vaporization.
2. Blending
   A. Mix item 1 and 0.25 g of item 5 in a drum mixer.
   B. Sift the "mix" through 1250-μm sieve using sifter. Collect in stainless steel drum and transfer to the mixer.
   C. Add item 2 solution from step 1 to the item 1 powder in mixer while mixing at high speed. When the addition is over, mix the moist mass at highest speed for 5 minutes.
   D. Scrape the sides of mixer and mix at highest speed for 5 minutes.
   E. Again scrape the sides of mixer and mix at highest speed for 10 minutes.
3. Drying
   A. Spread the moist mass thinly on stainless steel trays. Break the big lumps if any.
   B. Dry the mass in oven using only cold air (without temperature) for 6 hours.
4. Sifting
   A. Sift 168.25 g of item 4 through 630-mm sieve using a sifter. Collect in stainless steel drum. Keep aside.
5. Mixing
   A. Mix 50.0 g of item 4, the indomethacin–lecithin mixture (dried) and 1.25 g of item 5 in a drum mixer, for 10 minutes.
   B. Sift the mixture twice through 630-mm stainless steel sieve using a sifter.
   C. Use item 4 (approximately 2–4 g) to prevent the clogging of the sifter sieve, if required.
   D. Load sieved item 4 from step 4 into the blender.
   E. Add lactose–indomethacin–Aerosil mixture from step V-B to the blender. Mix for 10 minutes.
6. Lubrication
   A. Sift items 6 and 7 through a 630-mm sieve using a sifter.
   B. Add to the powder in blender. Mix for 2 minutes.
   C. Unload the granules in stainless steel drums.
7. Loading of empty shells
   A. Load the empty capsule shells (size 3) in the hopper.
   B. Run the machine and check the locking of shells.
8. Filling of powder
   A. Calculation: A fill weight of one capsule = 250 mg.

Indomethacin Capsules (25 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
25.00	1	Indomethacin	25.00
0.50	2	Lecithin Swiss	0.50
1.25	3	Colloidal silicon dioxide	1.25
1.67	4	Magnesium stearate	1.67
200.00	5	Lactose	200.00
–	6	Chloroform	QS

Manufacturing Directions

1. Mix indomethacin with about one-half of the quantity of lactose and micronize.
2. Dissolve lecithin in chloroform and wet this solution with the remaining half of the lactose.
3. Dry the chloroform mixture in a drying oven at 4°C for 4 hours.
4. Pass the dried granulate through a Fitz mill sieve No. 24228 at a low speed; add the mixture of indomethacin and lactose from step 1; add colloidal silicon dioxide and magnesium stearate and mix for 15 minutes.
5. Fill into size 3 capsules as 200 mg ± 5%. For 50 mg capsules, fill into capsules as 325 mg ± 5%.

Indomethacin Capsules (50 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
50.00	1	Indomethacin	50.00
1.00	2	Lecithin Swiss	1.00
3.00	3	Colloidal silicon dioxide	3.00
4.00	4	Magnesium stearate	4.00
325.00	5	Lactose	325.00
–	6	Chloroform	QS

Manufacturing Directions

1. Mix indomethacin with about one-half of the quantity of lactose and micronize.
2. Dissolve lecithin in chloroform and wet this solution with the remaining half of the lactose.
3. Dry the chloroform mixture in a drying oven at 4°C for 4 hours.
4. Pass the dried granulate through a Fitz mill sieve No. 24228 at a low speed; add the mixture of indomethacin and lactose from step 1; add colloidal silicon dioxide and magnesium stearate and mix for 15 minutes.
5. Fill into size 3 capsules as 200 mg ± 5%. For 50 mg capsules, fill into capsules as 325 mg ± 5%.

Indomethacin Powder for Hard Gelatin Capsules (160 mg)

Formulation

Indomethacin, 160 g; Kollidon CL, 320 g; Aerosil 200, QS.

Manufacturing Directions

Mix the components for approximately 10 minutes and fill in hard gelatin capsules to obtain 160 mg indomethacin in each capsule.

Indomethacin Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
45.00	1	Indomethacin	45.00
45.00	2	Sodium alginate	45.00
4.50 mL	3	Zinc chloride solution 2%	45 L
QS	4	Hydrochloric acid	QS
0.22	5	Glycerin	22.5 mL
–	6	Water purified	2.25

Manufacturing Directions

1. A mixture consisting of item 1 previously triturated in 22.5 mL glycerin is added with rapid stirring to an aqueous solution consisting of 45.00 g (w/v) of sodium alginate in 2.25 L of purified water.
2. This solution is then added to 4.5 L of a 2% (w/v) zinc chloride solution, which has previously been adjusted to pH 3 by the addition of HCl, while the rapid stirring is continued for 10 minutes.
3. The preparation is then allowed to stand at room temperature for 4 hours, after which the drug-entrapped zinc alginate precipitate is collected by filtration, washed 3 times with distilled water and dried under vacuum for 24 hours.
4. After drying, the residue is granulated using minimal amounts of glycerin/water and processed into 0.5-mm diameter microspheres by mechanical extrusion and spheronization (Nica Extruder; Aeromatic Ltd., Bubendorf, Switzerland), into which the slightly flexible mass represented by the above residue is fed and which produces therefrom a continuous flow of cylindrical extrudate that is 0.5 mm in diameter.
5. This extrudate falls onto the spinning plate of a Nica Spheronizer (Aeromatic Ltd.), where it is broken into cylinders of approximately 1:1 length:diameter ratio. Interaction between the spinning disc and the wall of the spheronizer then causes the cylinders to be worked into spheres of 0.5 mm in diameter.
6. The spheres are then filled into gelatin capsules (100 mg of spheres per size 1 capsule, which represents a total dose of 45.0 mg indomethacin). The capsules of the spheres thus produced represent a sustained-release dosage form for analgesic–antipyretic activity with less propensity for gastrointestinal side effects than the conventional tablet form of indomethacin Upon ingestion the spheres begin to release the incorporate drug almost immediately, but begin to erode in 3 to 5 hours. Total erosion time is approximately 8 hours.

Indomethacin Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
75.00	1	Indomethacin	75.00
110.20	2	Sucrose	110.20
39.75	3	Cornstarch	39.75
36.20	4	Lactose	36.20
10.95	5	Polyvinylpyrrolidone	10.95
19.65	6	Talc	19.65
5.15	7	Magnesium stearate	5.15
1.10	8	Eudragit L	1.10
2.00	9	Eudragit S	2.00
–	10	Ethyl alcohol	98.55
–	11	Acetone	27.90

Manufacturing Directions

1. Pellets
   A. Weigh and mix in a stainless steel mixer suitable quantities of sucrose and cornstarch in the proportion of 3:1 w/w. Sift through a screen of suitable size to break up possible lumps.
   B. Transfer the mixture to a stainless steel coating pan and adjust rotary speed between 20 and 30 rpm so as to obtain good tumbling action.
   C. By means of a suitable spray gun, spray over the powder a quantity of water equal to 15% w/w in very minute drops.
   D. Place the wet pellets over a thermostatic tray dryer and dry at 37°C to complete evaporation of water.
   E. Pass the dried pellets through sieves of suitable screens to ensure removal of dust and selection of cores of desirable size.
2. Active pellets
   A. Dissolve polyvinylpyrrolidone in ethyl alcohol and add indomethacin previously mixed with lactose (No. 3) to it.
   B. Transfer 149.95 kg of neutral pellets obtained from step I-E to a stainless steel coating pan and adjust the rotary speed between 20 and 30 rpm so as to obtain good tumbling action.
   C. Spray over the neutral pellets the result of step II-A.
   D. Keep the pan rotating to allow partial evaporation of the solvent.
   E. Complete evaporation of the solvent by drying the pellets in a thermostat at 35°C for 3 days.
3. Film-coated pellets
   A. Dissolve Eudragit L and Eudragit S in acetone.
   B. Transfer the active pellets obtained from step II-E to a stainless steel coating pan and adjust the rotary speed to obtain a good tumbling action.
   C. Spray the pellets as uniformly as possible with the solution obtained from step II-E.
   D. Spray the wet pellets with talc and magnesium stearate to prevent agglutination.
   E. Keep the pan rotating to achieve solidification of the film coating and partial evaporation of the solvent.
   F. Complete evaporation of the solvent by drying the pellets in a thermostat for 35°C for 3 days.
4. Blending of pellets
   A. Transfer the film-coated pellets obtained from step III-F to a stainless steel pan and add a suitable quantity of neutral pellets obtained from step I-E so as to obtain the required dosage.
   B. Add 0.5% w/w of talc to eliminate electrostatic charges and mix for 30 to 35 minutes.
5. Filling
   A. Fill the blended pellets obtained from step IV-B into capsules (size 2) at the dose of 300 mg each.

Insulin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
140.00 IU	1	Insulin[a]	140000 IU
0.047	2	Dimyristyl phosphatidyl choline	0.047
3.39	3	Aprotinin[b]	3.39
3.76	4	Hydroxypropyl cellulose-LF	3.76
3.76	5	Polyoxy-40 stearate Myrj-52	3.76
139.80	6	Polyethylene glycol 400	139.80
15.57	7	Propylene glycol	15.57
8.75	8	Water-citrate buffer for pH adjustment	8.75
31.20	9	Cholesterol	31.20
17.56	10	Tween 80	17.56
63.10	11	Egg yolk lecithin	63.10
27.90	12	Glyceryl amino oleate	27.90
19.60	13	D-alpha-tocopherol	19.60
249.10	14	Oleic acid	249.10

[a]Insulin: 26 IU = 1 mg.
[b]Aprotinin: 7500 KIU = 1 mg.

Manufacturing Directions

1. Insulin is a biologically active proteinaceous material. Insulin is a polypeptide consisting of 65 amino acids with an approximate molecular weight of 6000. In its preparations, there can be no use of heat or alcohol that can denature it.
2. The overall method is as follows: The surfactant Myrj-52 is slowly dispersed into the mixture of polyethylene glycol 400 and propylene glycol. Once it dissolves, hydroxypropyl cellulose as a stabilizer is also added, which is dispersed slowly into the preceding mixture. A separate solution of the proteinaceous material along with the phospholipid and the protease inhibitor is made in a portion of the preceding solvent mixture. The solution can then be added to the PEG/PG mixture at room temperature. The amount of any water is limited to 5% of the polyol solvent. When the water solution is used, citrate buffer is used to maintain the pH at a point where the protein is most stable. In this particular example, if insulin is used, it is suggested that the pH be maintained with a citrate buffer at or around 2.5. Separately, the ingredients of the lipid solvent are mixed together. Under gentle and constant stirring, the polyol solution is dispersed with the lipid solution.
3. The surfactant (polyoxy-40 stearate) is slowly dispersed into a mixture of polyethylene glycol and propylene glycol.
4. Once it is dissolved, small amounts of hydroxypropyl cellulose are then added and dispersed into the same mixture.
5. Insulin is dissolved in water and citric acid is dissolved in water for maintaining the pH at 2.5.
6. The water solution is added to the polyethylene glycol mixture. In a separate vessel, dissolve all the ingredients of the oil phase in oleic acid.
7. Cholesterol is added slowly to achieve faster dissolution.
8. Once both the phases are ready, the polyol solution is added slowly to lipid phase while mixing at low speed. The vessel should be preferably ice jacketed because heat may be produced. Once the addition is achieved, a transparent yellowish-brown solution is obtained.
9. The preemulsion solution is filled in a size 0 hard gelatin capsule and the capsule is sealed with a band of gelatin solution. The banding helps to coat the capsule uniformly.
10. The capsule is then coated with a 10% hydroxypropyl methylcellulose solution as an undercoat. The amount of coat required is sufficient just enough to cover the capsule uniformly with a thin layer of the polymer coat. Usually, 3.5% to 4.5% weight gain of the capsule is a good indication of the amount required as an undercoat.
11. Once the capsule is coated with an undercoat, enteric coating is applied. For enteric coating purposes, different polymers such as hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, and cellulose acetate phthalate are used.
12. Anionic copolymers that are based on methacrylic acid and methyl methacrylate, commercially available as Eudragit, are also suitable polymers for enteric coating purposes. The polymer is dissolved in organic solvents such as ethyl alcohol, methyl alcohol, acetone, and isopropyl alcohol. A combination of two solvents can also be used. The amount of enteric coating solution required is 5% to 6% weight gain of the capsules from the original weight of the capsules before applying enteric coat. A typical enteric coating solution is made as follows:
    Methacrylic acid and methyl methacrylate copolymer 10% w/w
    Diethyl butyl phthalate (plasticizer) 2% w/w
    Acetone 22% w/w
    Isopropanol 66% w/w
13. Mix acetone and isopropanol. Add the polymer slowly with constant mixing. Once the polymer is dissolved, add the plasticizer slowly and let it dissolve.
14. For a size 0 capsule, the previously mentioned enteric coating solution can be sprayed using fluidizing bed techniques. The fluid bed sprayer/dryer is operated with the

following parameters: Flow rate: 1.5 mL/min, inlet air temperature: 25°C, outlet air temperature: 25°C, air flap: 35, atomizer: 2 bar.

15. A size 0 capsule after the enteric coating will typically have the following composition: Preemulsion solution: 0.589 g, undercoat polymer: 0.027 g, enteric coat polymer: 0.032 g, 0.648 g.

Iron–Polysaccharide Complex Capsules*

Each bead-filled capsule contains 150 mg elemental iron as polysaccharide–iron complex, as cell-contracted akaganeite. Each capsule also contains the following inactive ingredients: D&C red No. 7, D&C red No. 28, D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6, gelatin, hydrogenated castor oil, polysorbate 80 pharmaceutical glaze, povidone, sodium lauryl sulfate, starch, sucrose, and titanium dioxide. Each capsule may contain silicon dioxide.

Isometheptene Mucate, Dichloralphenazone, and Acetaminophen Capsules*

Each red capsule with a pink band contains isometheptene mucate (65 mg), dichloralphenazone (100 mg), and acetaminophen (325 mg). Capsules contain FD&C yellow No. 6 as a color additive.

Isosorbide Mononitrate Capsules (20 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Isosorbide-5-mononitrate	20.00
60.00	2	Lactose	60.00
60.00	3	Sucrose and cornstarch microgranules	60.00
5.85	4	Shellac	5.85
1.20	5	Eudragit L 100	1.20
1.20	6	Eudragit RS 100	1.20
11.75	7	Talc	11.75
–	8	Alcohol	QS
–	9	Acetone	QD

Manufacturing Directions

1. Charge neutral microgranules of item 3 in a coating pan.
2. Prepare a 40% solution of shellac in alcohol together with item 1.
3. Maintain the temperature of microgranules at 25°C ± 5°C. Apply step 2 and dry granules and repeat the process until the entire drug has been incorporated.
4. Sieve granules using a 1-mm aperture and dry at 20°C to 30°C for 8 hours.
5. Prepare a 12.5% solution of equal parts of items 5 and 6 in acetone. Spray the microgranules from step 4 and incorporate.
6. Sieve the microgranules using a 1-mm aperture sieve.
7. Dry microgranules at 20°C to 30°C for 8 hours.
8. Spray the microgranules with balance of alcoholic shellac solution adding talc simultaneously.
9. Adjust fill weight of granules based on assay.

Isradipine Capsules*

The inactive ingredients are colloidal silicon dioxide, D&C red No. 7 calcium lake, FD&C red No. 40 (5-mg capsule only), FD&C yellow No. 6 aluminum lake, gelatin, lactose, starch (corn), titanium dioxide, and other optional ingredients. The 2.5- and 5-mg capsules may also contain benzyl alcohol, butylparaben, edetate calcium disodium, methylparaben, propylparaben, and sodium propionate.

Itraconazole Capsules*

The capsules contain 100 mg of itraconazole coated on sugar spheres. The inactive ingredients are gelatin, hydroxypropyl methylcellulose, polyethylene glycol (PEG) 20000, starch, sucrose, titanium dioxide, FD&C blue No. 1, FD&C blue No. 2, D&C red No. 22, and D&C red No. 28.

Itraconazole Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Itraconazole (used as pellets)	100.00
–	2	Empty hard gelatin capsule, size 0	1000
280.00	3	Sugar spheres	280.00
32.00	4	Hydroxypropyl cellulose	32.00
2.00	5	Polyethylene glycol 6000	2.00
30.00	6	Cornstarch	30.00
6.00	7	Titanium dioxide	6.00

Manufacturing Directions

1. Check the assay of pellets to calculate the exact amount needed. Calculate the dose per capsule to fill.
2. Charge items 1 and 3 to 7 in a suitable blender; mix for 10 minutes.
3. Set the capsule-filling machine with empty shells.
4. Fill the pellets as per assay.
5. Polish the capsules.

Ketoprofen and Misoprostol Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Ketoprofen delayed-release beads (40% Ketoprofen)	250.00
0.20	2	Misoprostol (dilute 1:100 on HPMC)	20.00
160.00	3	Lactose anhydrous	160.00
4.00	4	Hydrogenated vegetable oil	4.00

Manufacturing Directions

1. Item 1 beads are prepared by spray coating a suspension or solution of ketoprofen onto a nonpareil sugar core, together with a binder (e.g., polyvinyl pyrrolidine or hydroxypropyl methylcellulose). The beads are subsequently coated with a delayed release coating (e.g., methyl methacrylate, for instance, Eudragit). Mixtures of beads with various levels of coating were used to give the required therapeutic release pattern.
2. In a fluidized bed apparatus, uniform spherical inert sugar cores were coated with a first layer consisting of the compounds, an inert water-soluble polymer, such as hydroxypropyl methylcellulose or hydroxypropyl cellulose, and talc. The second layer consists of an inert water-soluble polymer, such as hydroxypropyl methylcellulose or hydroxypropyl cellulose, talc, and a pigment, such as titanium dioxide. The third and enteric coating layer consists of an enteric coating polymer such as copolymerized methacrylic acid/methacrylic acid methyl esters, a plasticizer, such as triethylacetate or similar plasticizers, and talc. The layers were applied by conventional fluidized bed coating techniques using aqueous solutions or dispersions. Pseudo-zero release is obtained by the use of a mixture of beads.
3. The beads in item 1 contain 40% ketoprofen, giving a dose per capsule of 100 mg. The mix of items 1 to 4 is filled into suitable hard gelatin capsules.

Ketoprofen Capsules*

Capsules contain 25, 50, or 75 mg of ketoprofen for oral administration. The inactive ingredients present are D&C yellow No. 10, FD&C blue No. 1, FD&C yellow No. 6, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25-mg dosage strength also contains D&C red No. 28 and FD&C red No. 40. Each 100-, 150-, or 200-mg capsule contains ketoprofen in the form of hundreds of coated pellets. The dissolution of the pellets is pH-dependent, with optimum dissolution occurring at pH 6.5 to 7.5. There is no dissolution at a pH of 1. In addition to the active ingredient, each 100-, 150-, or 200-mg capsule of Oruvail contains the following inactive ingredients: D&C red No. 22, D&C red No. 28, FD&C blue No. 1, ethyl cellulose, gelatin, shellac, silicon dioxide, sodium lauryl sulfate, starch, sucrose, talc, titanium dioxide, and other optional ingredients. The 100- and 150-mg capsules also contain D&C yellow No. 10 and FD&C green No. 3.

Lansoprazole Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
30.00	1	Lansoprazole	30.00
93.50	2	Neutral pellets	93.50
22.86	3	Magnesium carbonate	22.86
66.00	4	Sucrose	66.00
37.14	5	Cornstarch	37.14
46.34	6	Hydroxypropyl cellulose	46.34
79.68	7	Eudragit L	79.68
13.68	8	Talc	13.86
4.36	9	Titanium dioxide	4.36
4.36	10	Polyethylene glycol 6000	4.36
1.80	11	Polysorbate 80	1.80
–	12	Water purified	QS

Manufacturing Directions

1. Charge items 1 and 3 to 5 and half of item 6 in a suitable mixer and confirm homogeneity of mixture.
2. In a separate mixer, add and dissolve balance of item 6 and dissolve.
3. In rotary fluid bed dryer, charge item 2 and incorporate step 2 into it.
4. Prepare a suspension with item 9 in item 12 and items 8, 10, and 11 and keep agitating until dissolved or well dispersed.
5. Add item 7 and mix until well suspended.
6. Start spraying it onto the pellets from step 3 after passing the suspension before a fine mill.
7. Fill 370 mg in capsules.

Lansoprazole Delayed-Release Capsules*

Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole (30 mg), hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C red No. 28, FD&C blue No. 1, and FD&C red No. 40.

Lincomycin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
500.00	1	Lincomycin, USE lincomycin hydrochloride	560.00
7.00	2	Lactose	7.00
2.00	3	Aerosil 200	2.00
2.00	4	Magnesium stearate	2.00
12.00	5	Sodium starch glycolate	12.00

Manufacturing Directions

1. Charge all items after passing through No. 60 mesh in a low humidity room (NMT 40%).
2. Mix for 30 minutes.
3. Fill 590 mg in size 0 capsules.

Linezolid Oral Suspension

The oral suspension is supplied as an orange-flavored granule/powder for constitution into a suspension for oral administration. Following constitution, each 5 mL contains 100 mg of linezolid. The inactive ingredients are sucrose, citric acid, sodium citrate, microcrystalline cellulose and carboxymethylcellulose sodium, aspartame, xanthan gum, mannitol, sodium benzoate, colloidal silicon dioxide, sodium chloride, and flavors. The sodium (Na^+) content is 8.52 mg/5 mL (0.4 mEq/5 mL).

Lipase, Amylase, and Protease Capsules

The pancrelipase capsules are orally administered and contain enteric-coated mini-tablets of porcine pancreatic enzyme concentrate, predominantly pancreatic lipase, amylase, and protease. Each capsule contains lipase (12000 USP units), amylase (39000 USP units), and protease (39000 USP units). Other combinations are 18000/58500/58500 or 20000/65000/65000. The capsules contain an amount of pancrelipase equivalent to but NMT 125% of the labeled lipase activity expressed in USP units. The inactive ingredients are hydrogenated castor oil, silicon dioxide, sodium carboxymethylcellulose, magnesium stearate, microcrystalline cellulose, methacrylic acid copolymer (type C), talc, simethicone, triethyl citrate, iron oxides, and titanium oxide.

Lithium Carbonate Capsules

Each capsule for oral administration contains lithium carbonate (150, 300, or 600 mg). The capsules contain talc, gelatin, FD&C red No. 40, titanium dioxide. The imprinting ink contains FD&C blue No. 2, FD&C yellow No. 6, FD&C red No. 40 , synthetic black iron oxide, and pharmaceutical glaze.

Loperamide and Trimebutine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 capsules (g)
2.00	1	Loperamide	2.00
200.00	2	Trimebutine	200.00
122.47	3	Cornstarch	122.47
30.00	4	Talc	30.00
60.00	5	Lactose monohydrate	60.00

Manufacturing Directions

Mix and fill using into No. 2 size capsule.

Lopinavir–Ritonavir Capsules*

This is a coformulation of lopinavir and ritonavir. Capsules are available for oral administration in a strength of 133.3 mg lopinavir and 33.3 mg ritonavir with the following inactive ingredients: FD&C yellow No. 6, gelatin, glycerin, oleic acid, polyoxyl 35 castor oil, propylene glycol, sorbitol special, titanium dioxide, and water.

Loracarbef Capsules and Oral Suspension*

Each Pulvule contains loracarbef equivalent to 200 mg (0.57 mmol) or 400 mg (1.14 mmol) anhydrous loracarbef activity. They also contain cornstarch, dimethicone, FD&C blue No. 2, gelatin, iron oxides, magnesium stearate, titanium dioxide, and other inactive optional ingredients. After reconstitution, each 5 mL of Lorabid for oral suspension contains loracarbef equivalent to 100 mg (0.286 mmol) or 200 mg (0.57 mmol) anhydrous loracarbef activity. The suspensions also contain cellulose, FD&C red No. 40, flavors, methylparaben, propylparaben, simethicone emulsion, sodium carboxymethylcellulose, sucrose, and xanthan gum.

Loxapine Succinate Capsules

Each capsule for oral administration contains loxapine succinate 6.8, 13.6, 34.0, or 68.1 mg equivalent to 5, 10, 25, or 50 mg of loxapine base respectively. It also contains the following inactive ingredients: gelatin, silicon dioxide, sodium lauryl sulfate, anhydrous lactose, D&C yellow No. 10, FD&C blue No. 1, polacrilin potassium, magnesium stearate, talc, and titanium dioxide. Additionally, the 5-mg capsule contains D&C red No. 33, the 10-mg capsule contains D&C red No. 28 and D&C red No. 33, and the 25-mg capsule contains FD&C yellow No. 6.

Magaldrate Instant Powder or Dry Syrup

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
800.00	1	Magaldrate, USP	800.00
640.00	2	Kollidon CL-M	640.00
200.00	3	Sorbitol (crystalline)	200.00
40.00	4	Orange flavor	40.00
40.00	5	Kollidon 90 F	40.00
4.00	6	Coconut flavor	4.00
4.00	7	Banana flavor	4.00
0.80	8	Saccharine sodium	0.80
QS	9	Water	~280.00 mL

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with solution of items 5 to 9 and pass through a 0.8-mm sieve to obtain free-flowing granules.
2. Fill 2 g in sachets or 20 g in a 100-mL flask.
3. Instant granules in sachets: Suspend 2 g (=one sachet) in a glass of water (=800 mg magaldrate).

Magaldrate Instant Powder or Dry Syrup

Bill of Materials			
Scale (mg/sachet)	item	Material Name	Qty/1000 Sachets (g)
800.00	1	Magaldrate	800.00
640.00	2	Kollidon CL-M	640.00
200.00	3	Sorbitol, crystalline	200.00
40.00	4	Orange flavor	40.00
40.00	5	Kollidon 90 F	40.00
4.00	6	Coconut flavor	4.00
4.00	7	Banana flavor	4.00
0.80	8	Saccharin sodium	0.80
QS	9	Water	~280 mL

Manufacturing Directions

1. Granulate a mixture of items 1 to 4 with solution of items 5 to 9 and pass through a 0.8-mm sieve to obtain free-flowing granules.
2. Fill 2 g in sachets or 20 g in a 100-mL flask. For instant granules in sachets, suspend 2 g (=1 sachet) in a glass of water (=800 mg magaldrate).

Magnesium Oxide Capsules

Each capsule contains magnesium oxide [140 mg USP (heavy)] or 84.5 mg of elemental magnesium (6.93 mEq).

Mefenamic Acid Capsules

Mefenamic acid is a member of the fenamate group of nonsteroidal anti-inflammatory drugs (NSAIDs). Each blue-banded ivory capsule contains 250 mg of mefenamic acid for oral administration. Each capsule also contains lactose. The capsule shell and band contain citric acid, D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 3, FD&C yellow No. 6, gelatin, glycerol monooleate, silicon dioxide, sodium benzoate, sodium lauryl sulfate, and titanium dioxide.

Mesalamine Capsules*

Each capsule contains 250 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains D&C yellow No. 10, FD&C blue No. 1, FD&C green No. 3, gelatin, titanium dioxide, and other optional ingredients.

Mesalamine Colonic Delivery Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Mesalamine (5-ASA)	250.00
45.00	2	Lactose	45.00
5.20	3	Polyvinylpyrrolidone	5.20
10.80	4	Sodium starch glycolate	10.80
3.60	5	Magnesium stearate	3.60
36.80	6	Talc	36.80
18.40	7	Eudragit S100	18.40
43.20	8	Eudragit NE 30D	43.20
0.40	9	Antifoam emulsion SE 2	0.40

Manufacturing Directions

1. Add items 1 and 2 to a blending vessel; mix well.
2. Add item 4 and blend.
3. Prepare an aqueous solution of item 3 and granulate step 2.
4. Dry and compress; reduce size by passing through a 0.5- to 1.2-mm sieve.
5. The granules in step 4 are loaded into a fluid bed coater and then spray-coated with an aqueous suspension to provide a 20% or 25% dry weight gain based on an uncoated granule weight of a mixture of Eudragit S100 and Eudragit NE 30D (Rohm Pharma GmbH, Darmstadt, Germany) in the ratio of 3:7. Eudragit S100 is a copolymer of methacrylic acid and methylmethacrylate in the ratio of 1:2 in powder form and Eudragit NE 30D is a 30% aqueous dispersion of a copolymer of ethylacrylate and methylmethacrylate in the ratio 2:1.
6. Coated granules are packed into size 00 hard gelatin capsules in an amount of 400 mg granules per capsule.
7. The capsules are then spray-coated with a coating solution of the following formula:
   Eudragit L powder 3 g
   Diethyl phthalate 0.75 mL
   Silicone fluid 200 cs 0.75 mL
   Acetone 100 mL

Methsuximide Capsules*

Each capsule contains 150 or 300 mg methsuximide as well as starch. The capsule contains colloidal silicon dioxide, D&C yellow No. 10, FD&C yellow No. 6, gelatin, and sodium lauryl sulfate.

Methylphenidate Capsules

It contains 20 mg of methylphenidate hydrochloride for oral administration. The extended-release capsules comprise both immediate-release (IR) and extended-release (ER) beads such that 30% of the dose (6 mg) is provided by the IR component and 70% of the dose (14 mg) is provided by the ER component. It also contains the following inert ingredients: sugar spheres, povidone, hydroxypropyl methylcellulose and polyethylene glycol, ethylcellulose aqueous dispersion, dibutyl sebacate, gelatin, titanium dioxide, and FD&C blue No. 2.

Methylphenidate Capsules

Manufacturing Directions

1. Methylphenidate HCl (200 g) is slowly added to an aqueous solution (approximately 15% solids) of polyvinylpyrrolidone (10 g povidone K-30) and mixed well.
2. About 25- to 30-mesh sugar spheres (770 g) were coated with the drug solution in a fluid bed granulator. The drug-containing pellets are dried and a seal coat of Opadry Clear® (20 g) is first applied to produce instant-release or IR beads.
3. ER beads are produced by taking IR beads and coating with the dissolution rate controlling polymer. A plasticized ethyl-cellulose coating is applied to the methylphenidate particles (893 g) by spraying Aquacoat ECD-30® (233 g) and dibutyl sebacate (16.8 g).
4. An outer seal coating formulation (20 g) of Opadry® is sprayed onto the coated active particles. The coated particles are cured at 60°C for 12 hours so that polymer particles coalesce to form a smooth membrane on ER beads. The IR and ER beads are then filled into hard gelatin capsules with dual bead-filling hoppers.

Methylphenidate Immediate- and Extended-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
25.00	1	Methylphenidate	25.00
1.25	2	Polyvinylpyrrolidone K-30	1.25
96.25	3	Sugar spheres 25–30 mesh	96.25
2.25	4	Opadry clear	2.25
29.12	5	Aquacoat ECD-30	29.12
2.10	6	Dibutyl sebacate	2.10
2.25	7	Opadry clear	2.25
–	8	Alcohol	QS

Manufacturing Directions

1. This product consists of two types of beads: IR and ER. The ER beads are formed by further coating of IR beads.
2. IR beads are produced by preparing a 15% solution of item 2 in item 8 and adding item 1 to it slowly.
3. Charge item 3 in a fluid bed granulator and load drug solution in step 2 onto sugar pellets. Dry and apply seal coat of item 4. This completes the process of preparing IR beads.
4. Take an appropriate quantity (893 g) of beads in step 3 and apply a coating of item 6 in item 8.
5. Apply item 7 seal coat (as 15% aqueous solution), and cure at 60°C for 12 hours for polymer particles to coalesce into a uniform film.
6. Fill in gelatin capsules using a 20:80, 30:70, or 40:60 mixture of IR to ER beads. Use equipment that is capable of filling beads simultaneously.

Methyltestosterone Capsules*

Each capsule contains 10 mg of methyltestosterone. Each capsule, for oral administration, contains 10 mg of methyltestosterone. In addition, each capsule contains the following inactive ingredients: cornstarch, gelatin, FD&C blue No. 1, FD&C red No. 40. Each capsule also contains the following inactive ingredients: cornstarch, gelatin, FD&C blue No. 1, and FD&C red No. 40.

Metoclopramide Hydrochloride Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Metoclopramide, USE metoclopramide hydrochloride	21.00
183.90	2	Sucrose and cornstarch microgranules, size 20	183.90
0.12	3	Disodium edetate	0.12
0.19	4	Stearic acid	0.19
1.30	5	Methacrylic acid copolymer Eudragit L100	1.30
0.42	6	Cornstarch	0.42
9.07	7	Shellac, bleached wax-free	9.07
15.00	8	Talc	15.00
1.00	9	Gelatin capsules, size 3	1000.00
–	10	Alcohol	QS
–	11	Water purified	11.00

Manufacturing Directions

1. The neutral microgranules (item 2) are placed in an appropriate coating pan and the pan is rotated.
2. In a separate vessel, prepare an alcoholic solution of item 5. Spray in step 1.
3. Prepare alcohol solution of item 4 in alcohol and spray into step 2.
4. Prepare aqueous solution of item 3 and spray into step 3.
5. Mix item 1 with item 6 and add to step 4 alternating with an alcoholic solution of Eudragit until the entire drug has been incorporated.
6. Sieve the microgranules.
7. Apply aqueous solution of item 3 followed by an alcohol solution of Eudragit L and microgranules dried.
8. Apply alcoholic solution of shellac alternating with talc until all shellac solution is used.
9. Lubricate and fill in capsules; sieve and dry microgranules.

Metyrosine Capsules*

It is supplied as capsules for oral administration. Each capsule contains 250 mg of metyrosine. The inactive ingredients are colloidal silicon dioxide, gelatin, hydroxypropyl cellulose, magnesium stearate, and titanium dioxide. The capsules may also contain any combination of D&C red No. 33, D&C yellow No. 10, FD&C blue No. 1, and FD&C blue No. 2.

Miconazole Nitrate Foot and Itch Powder

Spray powder for athlete's foot contains miconazole nitrate 2%. It also contains alcohol SD-40 (10% w/w), isobutane, starch/acrylates/acrylamide copolymer, stearalkonium hectorite, and talc. Spray powder for jock itch contains miconazole nitrate 2%. It also contains alcohol SD-40 (10% w/w), isobutane, stearalkonium hectorite, and talc. Spray deodorant powder contains miconazole nitrate 2%. It also contains isobutane, alcohol SD-40 (10% w/w), talc, starch/acrylates/acrylamide copolymer, stearalkonium hectorite, and fragrance. Powder contains miconazole nitrate 2%. It also contains benzethonium chloride, cornstarch, kaolin, sodium bicarbonate, starch/acrylates/acrylamide copolymer, and zinc oxide.

Midodrine Capsules

1. The midodrine controlled-release product is prepared by manufacturing one type of pellet, which afterward is coated with different types of film coatings. The capsule ends up with three different types of pellets (noncoated pellet, CR-coated pellet, and EC-pellet).
2. The pellet is prepared by the use of an extrusion/spheronization technique.
3. Microcrystalline 2135.0 g, cellulose lactose monohydrate 1207.5 g, carmellose sodium 70.0 g, midodrine hydrochloride 87.50 g, purified water qs to 2000.
4. The above ingredients are mixed and wetted in a Fielder high shear mixer in which the water is applied by a nozzle.
5. The wetted mass is extruded in a Nica E 140 extruder with a screen size of 600 micron (those pellets which is being used for noncoated pellets and for CR-coating) or 800 micron (those pellets used for EC-coating). The extrudate is spheronized in a laboratory unit for 5 minutes. The pellets were dried in a laboratory scala fluid bed for approximately 75 minutes at 50°C.
6. The dried pellets used for noncoated pellets and for CR-coating were screened through a screen of 700 micron and the dried pellets used for EC coating were fractionated with a lower screen of 500 micron and a upper screen of 1000 micron.
7. One batch of these pellets is not coated because it is used as an immediate-release unit. The pellets are a part of the content in the capsule.
8. One batch of these pellets is coated with an inner coat and an outer coat in a fluid bed (GPCG3) with a 0.8-mm spray nozzle and a spray pressure of 2.5 bar.
9. Inner coat (batchsize 2000 g), hypromellose (viscosity 13.1 5 cps), purified water 1094.0 g, magnesium stearate 2.7 g, talc 26.2 g, polyacrylate dispersion 864.0 g, 30% Eudragit g, talc 40.0 g. In the coating process, the following amount of inner and outer coat was applied. The amount of dry matter applied calculated in percentage of the core weight also appears from below. Inner coat: 1788.1 g per 3000.0 g pellets (dry matter: 9% of the core weight). Outer coat: 375.0 g per 3000.0 g pellets (dry matter: 1% of the core weight). Throughout the coating process the bed temperature is maintained substantially in the interval from 20°C to 25°C by adjustment of the liquid flow rate or the inlet temperature. The inlet air temperature is kept at approximately 32°C. After the application of the coatings the coated pellets were cured at a bed temperature of approximately 70°C for 30 minutes. Then the pellets were screened through a screen 1 mm. Oversized material is discarded.
10. One batch of these pellets is coated with an EC-coat in a fluid bed (Wurster technique) with a 0.8-mm spray nozzle and a spray pressure of 2.5 bar.

Ingredients	Amount (g/batch size)
Isopropyl alcohol	3852.0
Talc	100.0
Acetyltributyl citrate	99.2
Methacrylic acid/Methyl methacrylate	3948.8
Copolymer	1:2
Eudragit S	12.5

In the coating process the following amount of the coat were applied. The amount of dry matter applied calculated in percentage of the core weight also appears from below. 15517.2 g per 3000 g pellets (dry matter: 45% of the core weight). Throughout the coating process, the bed temperature is maintained substantially in the interval from 30°C to 38°C by adjustment of the liquid flow rate or the inlet temperature. The inlet air temperature is kept at approximately 49°C. After the application of the coating the pellets were screened through a screen 1.3 mm. Oversized material is discarded.

11. The three different pellets (steps 1, 2, and 3) were filled into capsules : Unit amount (mg) per capsule capsule approx. 76.3 pellets step 1 approx. 50.4 corresp. to 1.25 mg midodrine hydrochloride Pellets step 2 approx. 110.6 corresp. to 2.5 mg midodrine hydrochloride Pellets step 3 approx. 72.7 corresp. to.25 mg midodrine hydrochloride Total weight of capsule approx. 310 corresponding to 5.0 mg midodrine hydrochloride

Mineral Powder for Topical Herpes Simplex

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
14.00	1	Calcium carbonate	14.00
14.00	2	Sodium carbonate	14.00
14.00	3	Sodium dihydrogen phosphate anhydrous	14.00
80.00	4	Calcium hypochlorite	80.00
818.00	5	Cornstarch	818.00

Manufacturing Directions

1. Mix all ingredients after passing through an 80-mesh screen.
2. Pack in bottles.

Minocycline Hydrochloride Capsules*

Each minocycline hydrochloride capsule for oral administration contains the equivalent of 50, 75, or 100 mg of minocycline. In addition, each capsule contains the following inactive ingredients: magnesium stearate and starch (corn). The 50-, 75-, and 100-mg capsule shells contain gelatin, silicon dioxide, sodium lauryl sulfate, and titanium dioxide. The 75- and 100-mg capsule shells also contain black iron oxide.

Mixed Amphetamine Salt Capsules*

It is a once-daily, extended-release single-entity amphetamine product. It combines the neutral sulfate salts of dextroamphetamine and amphetamine, with the dextro isomer of amphetamine saccharate and *d*,*l*-amphetamine aspartate monohydrate. The capsule contains two types of drug-containing beads designed to give a double-pulsed delivery of amphetamines, which prolongs the release of amphetamine compared to the conventional immediate-release tablet formulation. Each capsule contains equal quantities of four salts of amphetamine to give a total of 10, 20, or 30 mg of content (total amphetamine base equivalence of 6.3, 12.5, and 18.8 mg): dextroamphetamine saccharate, amphetamine aspartate monohydrate, dextroamphetamine sulfate, amphetamine sulfate. The inactive ingredients in the capsules include gelatin capsules, hydroxypropyl methylcellulose, methacrylic acid copolymer, Opadry beige, sugar spheres, talc, and triethyl citrate. The gelatin capsules contain edible inks, kosher gelatin, and titanium dioxide. The 10-mg capsules also contain FD&C blue No. 2. The 20- and 30-mg capsules also contain red iron oxide and yellow iron oxide.

Mixed Amphetamine Salts Enteric-Release Capsules

Bill of Materials		
Item	Material Name	Qty/kg (g)
Immediate-release beads		
1	Amphetamine mixed salts[a]	88.00
2	Nonpareil seeds (30/35 Mesh, Paulaur)	6.80
3	Hydroxypropyl methylcellulose E5 premium	0.60
4	Water purified	QS
Enteric-release pellets		
5	Immediate-release beads (see items 1–4)	40.00
6	Eudragit L30-D-55	24.88
7	Triethyl citrate	2.52
8	Talc	2.60
9	Water purified	QS

[a]Mixed salts include amphetamine sulfate, amphetamine aspartate, and dextroamphetamine sulfate.

Manufacturing Directions

1. Charge item 2 in a fluid-bed processor and fluidize at 60°C.
2. Prepare a suspension of item 3 (prepare a 1% solution) and item 1 using item 4; ensure it is free of agglomerates and contains no fines with a yield of at least 98%.
3. Apply binder solution to step 1 and load the drug.
4. Charge item 5 into a fluid bed processor.
5. Prepare the coating dispersion using items 6 to 8 in item 9 and mix for at least 30 minutes.
6. Spray the coating solution in step 5 onto step 1 until a target level of 20 μm is achieved.
7. Dry pellets at 30°C to 35°C for 5 minutes before stopping the processor.
8. Fill to contain in each capsule base equivalent 10, 20, and 30 mg (Adderall XR®).

Morphine Sulfate Capsules*

Each capsule for oral administration contains morphine sulfate 15 or 30 mg. The inactive ingredients are FD&C blue No. 1, FD&C blue No. 2, FD&C red No. 40, FD&C yellow No. 6, gelatin, hydroxypropyl methylcellulose, lactose, polyethylene glycol, polysorbate 80, polyvinylpyrrolidone, starch, sucrose, titanium dioxide, and other optional ingredients. In addition, the 30-mg capsule contains black iron oxide and D&C red No. 28.

Morphine Sulfate Controlled-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
40.00	1	Morphine hydrochloride	40.00
40.00	2	Lactose	40.00
20.00	3	Microcrystalline cellulose	20.00
QS	4	Water purified	QS
3.50–5.30	5	Ethyl cellulose	3.50–5.30
2.20–3.40	6	Hydroxypropyl methylcellulose	2.20–3.40
0.60–1.0	7	Triethyl citrate	0.60–1.00
QS	8	Ethanol	QS
QS	9	Methyl isobutyl ketone	QS

Manufacturing Directions

1. Mixing and granulating: Morphine hydrochloride (40% w/w), lactose (40% w/w), and microcrystalline cellulose (Avicel PH-101) (20% w/w) total 1500 g are dry-mixed in a planetary-type mixer (Kenwood Major®) at a low mixing speed (speed adjustment <1) for 10 minutes. Water (585 g) is added and the mass is granulated for 5 minutes at speed adjustment 2.
2. Extrusion: Extrusion is performed in a Nica™ E-140 Extruder (Lejus Medical AB, Sweden) through a perforated screen with drilled orifices of 1 mm in diameter. The speed of the agitator and the feeder is set on the lowest values.
3. Spheronization: Spheronization is conducted in a mammerizer (Ferro Mecano AB, Sweden). The speed of the Marumerizer™ plate is adjusted to 450 rpm. The number of spheronization rounds is 5 with about 400 g of wet extrudates on the plates at each run.
4. Drying: Drying is performed in a fluid bed dryer (Aeromatic AG®, West Germany) at an IN temperature of 50°C. The batch is divided into subbatches of 600 to 700 g wet particulate cores. Each subbatch is dried for 5 minutes at the air velocity adjustment 20 to obtain individual cores rather than aggregates. The subbatches are then mixed and the whole batch is dried at adjustment 12 for 65 minutes. The end OUT temperature is 36°C. The yield of dry cores after drying is 1437 g and 96% w/w.
5. Sieving: Sieving is performed by using analytical sieves with sieve sizes of 0.71 mm and 1.40 mm respectively. The yield of dry cores after sieving is 1337 g and 89% w/w. The yields are 96% and 89% w/w after drying and sieving respectively.
6. A sieving analysis before and after abrasion of the cores shows that about 93% of the cores have a size between 0.71 and 1.0 mm. A crushing strength analysis shows that the mean crushing strength of 1-mm particles is 4.71 N. A hardness value at this level makes it possible to coat the particles in small as well as in large equipment.
7. Morphine hydrochloride cores manufactured as above are coated with controlled-release membranes. Hydroxypropyl methylcellulose (HPMC) (E5) and ethyl cellulose (EC) (10 cps) were used as film formers together with triethyl citrate (TEC) as a plasticizer. The coating solution contains 99.5% ethanol and methyl isobutyl ketone (MIBK).
8. The coating is performed using a spray coating equipment (Nica™ FB-coater, Sweden). The spray gun used is a Binks&Bullows with a J92R liquid nozzle and a J930 air nozzle. A net device is placed in the top of the fluidized bed to avoid loss of cores to the cyclone output. The spray gun is mounted on a height over the bottom of the bed for 185 minutes. Ethanol/MIBK mixture is pumped through the system before to the start of the coating and there is consequently liquid present between the pump housing and the spray gun. The morphine hydrochloride cores prepared above are loaded. The cores are preheated at 55°C with an air velocity of 20 to 25 m^3/h for 4 minutes. At the start of the coating, the bed temperature is 32°C to 36°C. The coating is started using the following process parameters: atomizing pressure 500 kPa, air velocity 85 m^3/h, and a solution flow of about 24 mL/min The registered IN temperature varies between 53°C to 56°C, and the OUT temperature varies between 34°C and 38°C during the coating.
9. The coated spheres are sieved through a 1.4-mm sieve and spheres with size less than 1.4 mm are collected.
10. The collected spheres are filled into hard gelatin capsule (white) with a normal weight of 0.17 g (net 108 mg). The mean content of active component in the capsule is between 36 and 44 mg.

Morphine Sulfate Sustained-Release Capsules*

Each sustained-release capsule contains either 20, 30, 50, 60, or 100 mg of morphine sulfate and the following inactive ingredients that are common to all strengths: hydroxypropyl methylcellulose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, cornstarch, and sucrose. The 20-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C yellow No. 10, titanium dioxide, and black ink (SW-9009). The 30-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, FD&C red No. 3, FD&C blue No. 1, titanium dioxide, and black ink (S-1–8114 or S-1–8115).

The 50-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C red No. 28, FD&C red No. 40, FD&C blue No. 1, titanium dioxide, and black ink (SW-9009). The 60-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C red No. 28, FD&C red No. 40, FD&C blue No. 1, titanium dioxide, and black ink (S-1–8114 or S-1–8115). The 100-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C yellow No. 10, FD&C blue No. 1, titanium dioxide, and black ink (SW-9009).

Multivitamin Effervescent Granules

Bill of Materials			
Scale (mg/Sachet)	Item	Material Name	Qty/1000 Tabs (g)
2.600	1	Thiamin hydrochloride (BASF)	0.26
3.000	2	Riboflavin (BASF)	0.30
11.000	3	Nicotinamide	1.10
2.500	4	Pyridoxine hydrochloride (BASF)	0.25
15.000	5	Calcium D-pantothenate (BASF)	1.50
200.000	6	Ascorbic acid powder (BASF)	20.00
500.000	7	Citric acid	50.00
1300.000	8	Sucrose	130.00
800.000	9	Fructose	80.00
200.000	10	Kollidon CL-M	20.00
250.000	11	Flavors	25.00
20.000	12	Cyclamate sodium	2.00
1.000	13	Saccharine sodium	0.10
150.000	14	Kollidon VA 64	15.00
350.000	15	Isopropanol	35.00
15.000	16	Vitamin A acetate dry powder 325000 IU/g CWD (BASF)	1.50
8.000	17	Vitamin D_3 dry powder 100000 IU/g CWD (BASF)	0.80
21.000	18	Vitamin E acetate dry powder 50%	2.10
0.066	19	Cyanocobalamin gelatin coated 0.1% (BASF)	0.66
400.000	20	Sodium bicarbonate	40.00

Manufacturing Directions

1. Granulate mixture of items 1 to 13 with solution of items 14 and 15; pass through a 0.8-mm sieve, dry well, and mix with items 16 to 20.
2. Fill 4 g in sachets.

Multivitamin Effervescent Granules

Bill of Materials			
Scale (mg/Sachet)	Item	Material Name	Qty/1000 Sachet (g)
2.60	1	Thiamin hydrochloride	0.26
3.00	2	Riboflavin	0.30
11.00	3	Nicotinamide	1.10
2.50	4	Pyridoxine hydrochloride	0.25
15.00	5	Calcium D-pantothenate	1.50
200.00	6	Ascorbic acid (powder)	20.00
500.00	7	Citric acid	50.00
1300.00	8	Sucrose	130.00
800.00	9	Fructose	80.00
200.00	10	Kollidon CL-M	20.00
250.00	11	Flavors	25.00
20.00	12	Cyclamate sodium	2.00
1.00	13	Saccharine sodium	0.10
150.00	14	Kollidon VA 64	15.00
350.00	15	Isopropanol	35.00
5000 IU	16	Vitamin A acetate (dry powder; 325000 IU/g CWD)	1.50
800 IU	17	Vitamin D_3 (dry powder; 100000 IU/g CWD)	0.80
21.00	18	Vitamin E acetate (dry powder; 50%)	2.10
0.0660	19	Cyanocobalamin (gelatin-coated; 0.1%)	0.66
400.00	20	Sodium bicarbonate	40.00

Manufacturing Directions

1. Granulate mixture of items 1 to 13 with solution of items 14 and 15.
2. Pass through a 0.8-mm sieve, drywell, and mix with items 16 to 20.
3. Fill 4 g in sachets.

Multivitamin Instant Granules

Bill of Materials			
Scale (mg/6 g Sachet)	Item	Material Name	Qty/30 kg (g)
40.00	1	Vitamin A+D dry powder + 50000 IU/g CWD (BASF)	200.00
5.00	2	Thiamine mononitrate (BASF)	26.00
6.00	3	Riboflavin (BASF)	33.00
22.00	4	Nicotinamide	110.00
4.50	5	Pyridoxine hydrochloride (BASF)	22.00
30.00	6	Calcium D-pantothenate (BASF)	150.00
0.013	7	Cyanocobalamin, USE cyanocobalamin 0.1% gelatin coated (BASF)	66.00
230.00	8	Ascorbic acid powder (BASF)	1150.00
42.00	9	Vitamin E acetate dry powder	210.00
4000.00	10	Sucrose, finely ground	20000.00
1000.00	11	Kollidon CL-M	5000.00
200.00	12	Orange flavor	1000.00
400.00	13	Kollidon VA 64	2000.00
–	14	Ethanol or isopropanol	~7 L

Manufacturing Directions

1. Pass mixture through a 0.8-mm sieve and granulate with solution of items 13 and 14 in the fluidized bed.
2. Fill the granules in sachets. If the technology of a fluidized bed is not available, the dry powders of vitamin A, E, and B_{12} should be added after the granulation of the other components.
3. Suspend 6 to 12 g (=1 sachet) in a glass of water corresponding to 2 to 4 RDA of vitamins. Double-strength sachet filled at 12 g.

Multivitamin Instant Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/30 kg (g)
40.00	1	Vitamin A and vitamin D (dry powder + 50000 IU/g CWD)	200.00
5.00	2	Thiamine mononitrate	26.00
6.00	3	Riboflavin	33.00
22.00	4	Nicotinamide	110.00
4.50	5	Pyridoxine hydrochloride	22.00
30.00	6	Calcium D-pantothenate	150.00
0.013	7	Cyanocobalamin; use cyanocobalamin (gelatin-coated, 0.1%)	66.00
230	8	Ascorbic acid powder	1150.00
–	9	Vitamin E acetate dry powder	210.00
4000	10	Sucrose (finely ground)	20000.00
1000	11	Kollidon CL-M	5000.00
200	12	Orange flavor	1000.00
400	13	Kollidon VA 64	2000.00
–	14	Ethanol or isopropanol	~7.00 L

Manufacturing Directions

1. Pass mixture through a 0.8-mm sieve and granulate with solution of items 13 and 14 in the fluidized bed.
2. Fill 6 to 12 g of the granules in sachets.
3. If the technology of a fluidized bed is not available, the dry powders of vitamins A, E, and B_{12} should be added after granulation of the other components.
4. Suspend 6 to 12 g (=1 sachet) in a glass of water; corresponds to 2 to 4 RDA of vitamins.

Mycophenolate Mofetil Capsules and Oral Suspension*

The inactive ingredients in 250-mg capsules include croscarmellose sodium, magnesium stearate, povidone (K-90), and pregelatinized starch. The capsule shells contain black iron oxide, FD&C blue No. 2, gelatin, red iron oxide, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and yellow iron oxide. The inactive ingredients in CellCept oral suspension include aspartame, citric acid anhydrous, colloidal silicon dioxide, methylparaben, mixed fruit flavor, sodium citrate dihydrate, sorbitol, soybean lecithin, and xanthan gum.

Nanoparticle Polymer Particle Powders

1. Preparation of polymer nanoparticles of ketorolac: To 900 mg *N*-isopropyl acrylamide (NIPAAM), 100 mL freshly distilled vinyl pyrrolidone (VP) and 50 mL freshly distilled acrylic acid (AA) in 100 mL of water, and 300 mL methylene bis acrylamide (MBA; MBA = 0.049 g/mL) are added to cross-link the polymer chain. The dissolved oxygen is removed by passing nitrogen gas for 30 minutes; 50 mL of 0.5% w/v ferrous ammonium sulphate (FAS) and 50 mL saturated ammonium persulfate (APS) solutions are then added to initiate the polymerization reaction. The polymerization is done at 30°C for 24 hours in nitrogen atmosphere. Total aqueous solution of polymer is then dialyzed overnight using a spectrapore membrane dialysis bag (12 kD cutoff). The dialyzed aqueous solution of polymeric micelles is frozen in liquid nitrogen and is lyophilized immediately to obtain dry powder for subsequent use. The yield of micelle nanoparticles is more than 80%. The lyophilized powder is easily redispersible in aqueous buffer; 100 mg of lyophilized powder of polymeric micelles is dispersed in 10 mL of water and is stirred well to disperse the micelles. The free acid form of ketorolac is dissolved in absolute ethanol (ketorolac = 50 mg/mL) and the alcoholic solution is added in polymeric micelles slowly with constant stirring. Ketorolac got directly loaded into hydrophobic core of micelles. The drug-loaded polymeric micelles are then lyophilized to get dry powder for subsequent use.
2. Preparation of polymeric nanoparticles containing indomethacin: In 100 mg of the lyophilized powder of the polymeric micelle nanoparticles, an alcoholic solution of indomethacin (indomethacin = 33 mg/mL) is added with constant stirring to get clear solution of polymeric micelles containing the drug of desired concentration dispersed in aqueous buffer. Maximum 10% w/w of the drug can be dissolved in polymeric micelles at room temperature. The drug-loaded polymeric micelles are then lyophilized to get dry powder for subsequent use.
3. Preparation of polymeric micelles containing nimesulide: In 100 mg of dry powder of polymeric micelles, an alcoholic solution of nimesulide (nimesulide = 10 mg/mL) is added with constant stirring to get a clear solution. Maximum 8% w/w of nimesulide could be dissolved in polymeric micelles at room temperature. The drug-loaded micelles are then lyophilized to get dry powder for subsequent use.

Nelfinavir Mesylate Oral Powder*

Oral powder is available for oral administration in a 50-mg/g strength (as nelfinavir freebase) in bottles. The oral powder also contains the following inactive ingredients: microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hydroxypropyl methylcellulose, aspartame, sucrose palmitate, and natural and artificial flavors.

Nelfinavir Mesylate Oral Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Nelfinavir mesylate	50.00
50.00	2	Sodium carboxymethylcellulose	50.00
1.25 mL	3	Syrup	1.25 L
0.10 mL	4	Benzoic acid solution	0.10 L
QS	5	Flavor	QS
QS	6	Dye	QS
QS to 5 mL	7	Purified water	5 L

Manufacturing Directions

1. The active ingredient is passed through a No. 45 mesh sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste.
2. The benzoic acid solution, flavor, and color are diluted with a portion of the water and added with stirring. Sufficient water is then added to produce the required volume.

Nilvadipine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
14.00	1	Nilvadipine	14.00
166.00	2	Polyethylene glycol 400	166.00
20.00	3	Hydroxypropyl methylcellulose	10.00

Manufacturing Directions

1. Add and dissolve item 1 in item 2.
2. Add item 3 and fill 200 mg in a size 4 hard gelatin capsule.

Nitrofurantoin Capsules*

Each capsule contains edible black ink, gelatin, lactose, starch, talc, titanium dioxide, and may contain FD&C yellow No. 6 and D&C yellow No. 10. Nitrofurantoin is an antibacterial agent specific for urinary tract infections. Another formulation of nitrofurantoin capsule is a hard gelatin capsule shell containing the equivalent of 100 mg of nitrofurantoin in the form of 25 mg of nitrofurantoin macrocrystals and 75 mg of nitrofurantoin monohydrate. Inactive ingredients: Each capsule contains carbomer 934P, cornstarch, compressible sugar, D&C yellow No. 10, edible gray ink, FD&C blue No. 1, FD&C red No. 40, gelatin, lactose, magnesium stearate, povidone, talc, and titanium dioxide.

Nitrofurantoin Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
150.00	1	Nitrofurantoin monohydrate (Norwich Eaton Pharmaceuticals, Inc.)	150.00
17.70	2	Carbopol 934P (B. F. Goodrich)	17.70
181.00	3	PVP C-15 (GAF Corporation)	181.00
3.50	4	Talc	3.50
1.80	5	Zinc stearate	1.80

Manufacturing Directions

1. Carbopol 934P, PVP C-15 (mean molecular weight of approximately 8000), talc, and zinc stearate are combined in a mortar and triturated well.
2. The nitrofurantoin monohydrate is added to this mixture in the mortar and triturated well until a substantially uniform particulate mixture is achieved.
3. The resulting particulate mixture (354 mg) is filled into size 1 hard gelatin capsule shells.

Nizatidine Capsules*

Each capsule contains pregelatinized starch, dimethicone, starch, titanium dioxide, yellow iron oxide, 150 mg (0.45 mmol) or 300 mg (0.91 mmol) of nizatidine, and other inactive ingredients. The 150-mg capsule also contains magnesium stearate and the 300-mg capsule also contains croscarmellose sodium, povidone, red iron oxide, and talc.

Nizatidine Capsules*

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
150.00	1	Nizatidine	150.00
33.70	2	Cornstarch	33.70
15.00	3	Pregelatinized starch (starch 1500)	15.00
0.70	4	Magnesium stearate	0.70
0.60	5	Simethicone	0.60
	6	Empty hard gelatin shell, size 2 (bovine origin)	1000.00

Manufacturing Directions

1. Add and blend items 1 to 3 in a suitable blender and mix for 20 minutes.
2. Add item 4 and blend for 10 minutes
3. Add item 5 and blend for 4 minutes.
4. Fill in 200 mg of hard gelatin capsules.

Nystatin Powder*

Nystatin topical powder is for dermatologic use and contains 100,000 USP nystatin units per gram dispersed in talc.

Omeprazole and Piroxicam Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
95.70	1	Omeprazole enteric-coated pellets	95.70
122.70	2	Piroxicam enteric-coated pellets	122.70

Manufacturing Directions

1. This product requires preparation of enteric-coated pellets of omeprazole and piroxicam separately.
2. The omeprazole pellets are prepared by applying drug solution (in HPMC) on nonpareil sugar beads, applying a separating layer consisting of HPMC alone and then applying an enteric coating that comprises methylacrylic acid copolymer 30% suspension with triethyl citrate, mono- and diglycerides, and polysorbate 80 in purified water. Finally an overcoat is applied.
   Core material (omeprazole)
   Magnesium omeprazole: 5.00 kg
   Nonpareil cores: 10.00 kg
   Hydroxypropyl methylcellulose: 0.75 kg
   Water purified: 19.65 kg
   Separating layer (omeprazole)
   Core material (acc. to above): 14.60 kg
   Hydroxypropyl cellulose: 1.46 kg
   Talc: 2.5 kg
   Magnesium stearate: 0.21 kg
   Water purified: 29.2 kg
   Enteric coating layer (omeprazole)
   Pellets with separate layer (acc. to above): 9.00 kg
   Methacrylic acid copolymer (30% suspension): 15.00 kg
   Triethyl citrate: 1.35 kg
   Mono- and diglycerides: 0.22 kg
   Polysorbate 80: 0.02 kg
   Water purified: 8.8 kg
   Overcoating layer (omeprazole)
   Enteric coating layered pellets: 9.0 kg
   Hydroxypropyl methylcellulose: 0.18 kg
   Magnesium stearate: 0.005 kg
   Water purified: 3.6 kg
3. The piroxicam pellets are prepared by a similar method except using a hydroalcoholic solution in the first instance, not using a separating layer, and performing enteric coating using HPMC succinate.
   Core material (piroxicam)
   Piroxicam micronized: 35 g
   Sugar seeds: 100 g
   Hydroxypropyl methylcellulose: 6 cps, 25 g
   Water purified: 250 g
   Ethanol 99% (w/v): 250 g enteric coating layer (piroxicam)
   Piroxicam pellets (acc. to above): 100 g
   Hydroxypropyl methylcellulose acetate-succinate: 14.38 parts
   Triethyl citrate: 2.87 parts
   Sodium lauryl sulphate: 0.43 parts
   Talc: 4.32 parts
   Water purified: 183.3 parts
4. Coat with a suspension of the preceding composition to give a product with a content of 163 mg/g; suspension layering is performed in fluid bed equipment. Micronized piroxicam is sprayed onto inert nonpareil cores from a water suspension containing the dissolved binder.

Omeprazole Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
20.00	1	Omeprazole	20.00
5.33	2	Hydroxymethylcellulose	5.33
6.00	3	2910 hydroxypropyl cellulose	6.00
8.00	4	Lactose	8.00
0.64	5	Disodium phosphate anhydrous	0.64
0.50	6	Sodium lauryl sulfate	0.50
		Enteric coating layer	
21.00	7	HPMCAS	21.00
6.00	8	Triethyl citrate	6.00
0.66	9	Sodium lauryl sulfate	0.66
11.00	10	Talc	11.00
1.12	11	Sodium hydroxide	1.12

Directions

1. First, sugar spheres 20/25 (700–850 microns, 161.63 mg) were placed in a fluid bed coating chamber equipped with a Wurster bottom-spraying device.
2. A suspension of the ingredients in water is then prepared so that the concentration is approximately 20% of total solids in water.
3. This active coating suspension is sprayed onto the sugar spheres. A suspension of the enteric coating is then sprayed onto the substrate to form the finished pellets. The pellets were then placed in capsules.

Omeprazole Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
40.00	1	Omeprazole	40.00
68.00	2	Sucrose and cornstarch neutral microgranules, size 26	68.00
4.00	3	Sodium starch glycolate (Explotab)	4.00
6.00	4	Sodium lauryl sulfate	6.00
7.12	5	Polyvidone	7.00
5.96	6	Hydroxypropyl methylcellulose	5.96
36.15	7	Eudragit L30D	36.15
3.62	8	Triethyl citrate	3.62
15.40	9	Talc	15.40
–	10	Alcohol	QS

Omeprazole Delayed-Release Capsules*

Each delayed-release capsule contains either 10, 20, or 40 mg of omeprazole in the form of enteric-coated granules with the following inactive ingredients: cellulose, disodium hydrogen phosphate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, mannitol, sodium lauryl sulfate, and other ingredients. The capsule shells have the following inactive ingredients: gelatin NF, FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, titanium dioxide, synthetic black iron oxide, isopropanol, butyl alcohol, FD&C blue No. 2, D&C red No. 7, calcium lake, and, in addition, the 10- and 40-mg capsule shells also contain D&C yellow No. 10

Oral Rehydration Salt (45 mEq)

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
811.90	1	Cerelose powder	811.90
66.57	2	Sodium chloride	66.57
31.82	3	Sodium citrate dihydrate	31.82
70.14	4	Potassium citrate monohydrate/food grade	70.14
19.57	5	Povidone (K 29—32)	19.57
—	6	Alcohol	500.00 mL
—	7	Water purified	50.00 mL

Manufacturing Directions

1. Mill the dextrose through a 1.2-mm aperture screen or similar on a comminuting mill, medium speed, knives forward.
2. Individually mill the sodium chloride, sodium citrate, and potassium citrate through a 1.2-mm aperture screen on a comminuting mill, medium speed, knives forward.
   Note: Do not mix the milled items until ready to add them to the dextrose.
3. Charge the powders from steps above into a suitable mass mixer and mix for 10 minutes. Screen the povidone through a 1.2-mm aperture screen and transfer to the mixer. Mix all the powders for 5 minutes.
4. Mix 500 mL of alcohol with 50 mL of water and slowly add to the mixer while mixing. Continue to mix for 5 to 10 minutes. Do not overwet the mass.
5. Granulate the wet mass through a 4.76-mm aperture screen using an oscillating granulator and spread on stainless steel trays.
6. Dry the granules at 45°C for approximately 16 hours or until loss on drying is less than 0.8%.
7. Turn the granules over after 3 to 4 hours drying.
8. Screen dry granules through an 840-μm aperture screen.
9. Transfer the fine powder to a suitable blender.
10. Pass coarse granules through an 840-μm aperture screen using an oscillating granulator and transfer to the blender. Blend for 5 to 10 minutes.
11. Discharge into polyethylene-lined drums.
12. Fill 3.08 g for 100 mL, 7.70 g for 250 mL, and 30.80 g for 1000 mL of reconstituted solution; prorate weights for different volumes.

Orlistat Capsules*

Orlistat is available for oral administration in dark blue hard gelatin capsules, with light blue imprinting. Each capsule contains 120 mg of the active ingredient orlistat. The capsules also contain the inactive ingredients microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate, povidone, and talc. Each capsule shell contains gelatin, titanium dioxide, and FD&C blue No. 1, with printing of pharmaceutical glaze, titanium dioxide, and FD&C blue No. 1 aluminum lake.

Orlistat Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
120.00	1	Orlistat	120.00
93.60	2	Microcrystalline cellulose	93.60
7.20	3	Sodium starch glycolate	7.20
12.00	4	Polyvinylpyrrolidone	12.00
7.20	5	Sodium lauryl sulfate	7.20

Manufacturing Directions

1. Polyvinylpyrrolidone and sodium lauryl sulfate are dissolved in water.
2. Orlistat, microcrystalline cellulose, and sodium starch glycolate are mixed for 10 minutes and granulated with the solution of step 1.
3. Granules are dried at or below 30°C and passed through a No. 20 mesh screen.
4. Granules are filled in a size 1 hard gelatin capsule.

Oseltamivir Phosphate Capsules and Oral Suspension*

Oseltamivir phosphate is available as a capsule containing 75 mg oseltamivir for oral use, in the form of oseltamivir phosphate, and as a powder for oral suspension, which when constituted with water as directed contains 12 mg/mL oseltamivir. In addition to the active ingredient, each capsule contains pregelatinized starch, talc, povidone K 30, croscarmellose sodium, and sodium stearyl fumarate. The capsule shell contains gelatin, titanium dioxide, yellow iron oxide, black iron oxide, and red iron oxide. Each capsule is printed with blue ink, which includes FD&C blue No. 2 as the colorant. In addition to the active ingredient, the powder for oral suspension contains xanthan gum, monosodium citrate, sodium benzoate, sorbitol, saccharin sodium, titanium dioxide, and tutti-frutti flavoring.

Oxcarbazepine Oral Suspension*

The oral suspension contains the following inactive ingredients: ascorbic acid, dispersible cellulose, ethanol, macrogol stearate, methyl parahydroxybenzoate, propylene glycol, propyl parahydroxybenzoate, purified water, sodium saccharin, sorbic acid, sorbitol, yellow-plum-lemon aroma.

Oxycodone Hydrochloride and Acetaminophen Capsules

Each capsule contains oxycodone hydrochloride USP 5 mg and acetaminophen 500 mg. Inactive ingredients: Docusate sodium, gelatin, magnesium stearate, sodium benzoate, sodium metabisulfite, cornstarch, FD&C blue No. 1, FD&C red No. 3, FD&C red No. 40, and titanium dioxide.

Oxytetracycline Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Oxytetracycline, USE oxytetracycline HCl BP 80	275.00
30.00	2	Starch (cornstarch dried)	30.00
1.00	3	Colloidal silicon dioxide (Aerosil 200)	1.00
3.00	4	Magnesium stearate	3.00
3.00	5	Talc (fine powder)	3.00
1	6	Empty hard gelatin capsule, size 1	1000.00

Manufacturing Directions

Note: The processing area must be under controlled room temperature and humidity. The limits are RH 50% to 55%, temperature 22°C to 27°C.

1. Pass item 1 through a 630-μm sieve using a sifter. Collect in stainless steel drum.
2. Mix items 5, 3, and 2 in stainless steel drum. Pass through a 250-μm sieve using a sifter. Collect in a stainless steel drum.
3. Add 66.67 g of sieved item 1 (from step 1) to the drum at step 2 and mix for 5 minutes in drum blender.
4. Pass the mix through a 630-μm stainless steel sieve using a sifter. Collect in stainless steel drum.
5. Pass item 4 through a 250-μm sieve using a sifter. Collect in stainless steel drum.
6. Add 8.0 g of sieved item 1 (from step 1) to the drum at step 4 and mix for 5 minutes by rolling.
7. Pass the mix through a 630-μm stainless steel sieve using a sifter. Collect in stainless steel drum.
8. Load the sieved powders to the blender. Mix for 5 minutes.
9. Unload the powder in stainless steel drum.
10. A fill weight of one capsule is 312 mg.

Oxytetracycline Hydrochloride, Sulfamethizole, and Phenazopyridine Hydrochloride Capsules*

Each capsule contains tetracycline hydrochloride equivalent to 250 mg oxytetracycline, sulfamethizole 250 mg, phenazopyridine hydrochloride 50 mg. Inert ingredients in the formulation are hard gelatin capsules (which may contain FD&C green No. 3, FD&C yellow No. 6, D&C yellow No. 10, and other inert ingredients); magnesium stearate, sodium lauryl sulfate, and starch.

Pancrelipase Capsules

The delayed-release microsphere capsules for delayed release of pancrelipase, which is of porcine pancreatic origin, contain lipase (5000 USP units), protease (18750 USP units), and amylase 16600 (USP units) or pancrelipase (10000 USP units), protease (37500 USP units), and amylase (33200 USP units) or contain lipase (20000 USP units), protease (75000 USP units), and amylase (66400 USP units). Inactive ingredients include dibutyl phthalate, dimethicone, hydroxypropyl methylcellulose phthalate, light mineral oil, and polyethylene glycol. The capsule shells contain gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The capsule shell contains FD&C blue No. 2. In addition, the 10000-unit capsule shell contains black iron oxide and the imprinting ink contains dimethicone, 2-ethoxyethanol, shellac, soya lecithin, and titanium dioxide.

Pancrelipase Capsules Enteric-Coated Microspheres

Pancrelipase capsules are orally administered capsules containing enteric-coated microspheres of porcine pancreatic enzyme concentrate, predominantly pancreatic lipase, amylase, and protease. The inactive ingredients are povidone, talc, sugar, methacrylic acid copolymer (type C), triethyl citrate, and simethicone emulsion.

Penicillamine Capsules*

Capsules of penicillamine for oral administration contain either 125 or 250 mg of penicillamine. Each capsule contains the following inactive ingredients: D&C yellow No. 10, gelatin, lactose, magnesium stearate, and titanium dioxide. The 125-mg capsule also contains iron oxide.

Pentosan Polysulfate Sodium Capsules

It is supplied in white opaque hard gelatin capsules containing 100 mg of pentosan polysulfate sodium, microcrystalline cellulose, and magnesium stearate. It is formulated for oral use.

Pentostatin Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
5.00	1	Pentostatin	5.00
25.00	2	Gelatin	25.00
100.00	3	Lactose	100.00
2.00	4	Iron oxide red	2.00

Manufacturing Directions

1. Pass items 1 to 3 through an 80 mesh and blend.
2. Add item 4 and mix for 10 minutes.
3. Fill 132 mg in a size 1 capsule.

pH-Sensitive Coated Spheroids

Uncoated spheroids (60% w/w propranolol hydrochloride)	3.00 kg
Methacrylic acid copolymer type B Eudragit S	0.75 kg
Triacetin	0.112 kg
Isopropyl alcohol	1.64 kg
Methylene chloride	1.99 kg
Water	0.50 kg
Coated Spheroids	
Uncoated spheroids (60% w/w propranolol hydrochloride)	3.00 kg
Hydroxypropyl methylcellulose 2910, 4000 cps, Methocel	0.075 kg
Methylene chloride	4.98 kg
Methanol anhydrous	2.96
Eudragit E 30D aqueous dispersion	1.00 kg
Calcium stearate	0.03 kg
Simethicone emulsion	0.0025 kg
Water purified	0.50 kg

Manufacturing Directions

1. The finished dosage form consists of a hard gelatin capsule containing a powder blend of propranolol hydrochloride and two types of spheroids. The formulation particulars are based on 160 mg of propranolol hydrochloride per capsule, although they can be designed to provide other dosage strengths.
2. The propranolol hydrochloride powder blend (or first group of spheroids) provides the loading dose (e.g., 25 mg of propranolol HCl). The second and third types of spheroids are categorized as
   a. Propranolol hydrochloride (60 kg) and microcrystalline cellulose (Avicel-PH101; 40 kg) are blended together in a 450 L planetary mixer. Water (50 kg) is added and the mixer is run for 10 minutes until a homogeneous plastic mass is obtained. The mass is extruded under pressure through a perforated cylinder to give cylindrical extrudates of nominally 1 mm in diameter. The damp extrudates (in batches of 15–20 kg) are placed in a spheronizer in which the rotating disc (diameter 68 cm) rotated at 300 to 400 rpm. The rotation is continued for 10 minutes and the resulting spheroids are then dried at 60°C in a fluidized bed dryer. The dried spheroids are passed over a 1.4-mm screen, and those which passed through are subjected to a 0.7-mm screen. The over- and undersized spheroids are discarded.
   b. pH-sensitive coated spheroids are used to provide a second dose (pH 6.5) (e.g., 65 mg propranolol HCl). Uncoated spheroids are placed in a fluidized bed coater. The Eudragit S solution is applied using a peristaltic pump. The spheroids are dried.
   c. Coated spheroids are used to provide a third dose (4–10 hours post ingestion; e.g., 70 mg propranolol HCl). The uncoated spheroids are placed in a fluidized bed coater. Methocel E4MP® solution is sprayed using a peristaltic pump. The spheroids are dried.
3. Process for applying overcoat: Eudragit E 30D suspension containing calcium stearate is sprayed on the Methocel E4MP coated spheroids using a peristaltic pump.
4. The spheroids are dried.
5. Capsules are filled with the powder blend, pH-sensitive coated spheroids, and coated spheroids on an encapsulating machine capable of dual filling powders and spheroids.

Phenobarbital and Hyoscyamine Sulfate Capsules

Each capsule contains phenobarbital (16.2 mg) and hyoscyamine sulfate (0.1037 mg). The inactive ingredients include cornstarch, edible ink, D&C yellow No. 10 and FD&C green No. 3, or FD&C blue No. 1 and FD&C yellow No. 6, FD&C blue No. 2 aluminum lake, gelatin, lactose, sucrose. Capsules may contain FD&C red No. 40 and yellow No. 6 aluminum lake.

Phenoxybenzamine Hydrochloride Capsules

Each capsule with a red cap and a red body contains phenoxybenzamine hydrochloride (10 mg). Inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C red No. 33, FD&C red No. 3, FD&C yellow No. 6, gelatin, lactose, sodium lauryl sulfate, and trace amounts of other inactive ingredients.

Phentermine Capsules

Each capsule contains 15 or 30 mg of phentermine as the cationic exchange resin complex. Phentermine is alpha, alpha-dimethyl phenethylamine (phenyl-tertiary-butylamine). The inactive ingredients are D&C yellow No. 10, dibasic calcium phosphate, FD&C yellow No. 6, gelatin, iron oxides (15-mg capsules only), lactose, magnesium stearate, and titanium dioxide.

Phentermine Hydrochloride Capsules

It is available as a capsule or tablet containing 37.5 mg of phentermine hydrochloride (equivalent to 30 mg of phentermine base). The capsules contain the following inactive ingredients: cornstarch, gelatin, lactose monohydrate, magnesium stearate, titanium dioxide, black iron oxide, FD&C blue No. 1, FD&C red No. 40, and D&C red No. 33.

Phenytoin Sodium Extended-Release Capsules*

Each extended phenytoin sodium capsule contains 30 or 100 mg phenytoin sodium. The capsule also contains lactose, confectioner's sugar, talc, and magnesium stearate. The capsule shell and band contain colloidal silicon dioxide, FD&C red No. 3, gelatin, glyceryl monooleate, and sodium lauryl sulfate. The 30-mg capsule shell and band also contain citric acid, FD&C blue No. 1, sodium benzoate, and titanium dioxide. The 100-mg capsule shell and band also contain FD&C yellow No. 6, purified water, and polyethylene glycol 200. Product in vivo performance is characterized by a slow and extended rate of absorption with peak blood concentrations expected in 4 to 12 hours as contrasted with prompt phenytoin sodium capsules with a rapid rate of absorption with peak blood concentration expected in $1^1/_2$ to 3 hours.

Piroxicam and Beta-Cyclodextrin Topical Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Piroxicam	100.00
900.00	2	Beta-cyclodextrin	900.00

Manufacturing Directions

1. Items 1 and 2 are screened through a 60-mesh screen and fed into the grinding chamber of a high-energy vibration mill together.
2. While maintaining the mill at its minimum vibrational frequency, the powders are exposed for 15 minutes to a flow of steam by opening a connection valve between the chamber and a steam reservoir (mixing and activation stage).
3. After this operation, the true cogrinding stage is continued for 4 hours.
4. On termination, the product is discharged, screened through a 60-mesh screen, and homogenized by mixing.

Piroxicam Capsules

Each maroon and blue capsule contains 10 mg of piroxicam; each maroon capsule contains 20 mg of piroxicam for oral administration. The inactive ingredients in Feldene capsules include FD&C blue No. 1, FD&C red No. 3, lactose, magnesium stearate, sodium lauryl sulfate, and starch.

Piroxicam Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Piroxicam	20.00
233.23	2	Lactose	233.23
48.75	3	Cornstarch	48.75
1.36	4	Magnesium stearate	1.36
0.15	5	Sodium lauryl sulfate	0.15

Note: For 5- and 10-mg strength, adjust with item 2.

Manufacturing Directions

1. Charge items 1 to 3 in a suitable blender in a low humidity area.
2. Compress to make slugs; reduce slugs by passing through a No. 20 sieve.
3. Add and blend items 4 and 5 and blend for 10 to 15 minutes.
4. Fill 305 mg in hard gelatin capsules.

Piroxicam Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
50.00	1	Piroxicam	50.00
124.40	2	Lactose anhydrous	124.40
50.00	3	Cornstarch	50.00
12.50	4	Sodium starch glycolate	12.50
2.50	5	Povidone	2.50
7.50	6	Polysorbate 80	7.50
0.625	7	Colloidal silicon dioxide	0.625
6.25	8	Glycine	6.25
1.25	9	Citric acid	1.25
QS	10	Water purified	QS

Manufacturing Directions

1. An aqueous wet granulation process is whereby item 1, lactose, cornstarch, sodium starch glycolate, colloidal silicon dioxide, and povidone are mixed and subsequently granulated with polysorbate dissolved in purified water.
2. Additional purified water is then added until granules form and no dry powder remains.
3. Glycine and citric acid are dissolved in the additional purified water.
4. Wet granules are dried at 60°C until loss on drying is NMT 2%.
5. The dried granules are milled with the sodium starch glycolate, blended and lubricated with screened magnesium stearate in a twin-shell blender.
6. Fill 250 mg in size 2 capsules.

Polyethylene Glycol 3350 Powder for Reconstitution

Each dose consists of 17 g of polyethylene glycol 3350.

Polythiazide Capsules

Inert ingredients in the formulations are hard gelatin capsules (which may contain FD&C blue No. 1, FD&C green No. 3, FD&C red No. 3, and other inert ingredients), magnesium stearate, sodium lauryl sulfate, starch, and sucrose.

Potassium Chloride Extended-Release Capsules

The extended-release capsules contain microencapsulated potassium chloride 600 and 750 mg, respectively, of potassium chloride USP equivalent to 8 and 10 mEq of potassium. Dispersibility of potassium chloride (KCl) is accomplished by microencapsulation and a dispersing agent. The resultant flow characteristics of the KCl microcapsules and the controlled release of K^+ ions by the microcapsular membrane are intended to avoid the possibility that excessive amounts of KCl can be localized at any point on the mucosa of the gastrointestinal tract. Each crystal of KCl is microencapsulated by a patented process with an insoluble polymeric coating which functions as a semipermeable membrane; it allows for the controlled release of potassium and chloride ions over an 8- to 10-hour period. Fluids pass through the membrane and gradually dissolve the potassium chloride within the microcapsules. The resulting potassium chloride solution slowly diffuses outward through the membrane. The inactive ingredients present are edible ink, ethylcellulose, FD&C blue No. 2 aluminum lake, FD&C yellow No. 6, gelatin, magnesium stearate, sodium lauryl sulfate, and titanium dioxide. The capsules may contain FD&C red No. 40 and yellow No. 6 aluminum lake.

Potassium Chloride for Oral Solution

Natural fruit-flavored potassium chloride for oral solution, USP is an oral potassium supplement offered in individual packets as a powder for reconstitution. Each packet of powder contains potassium 20 mEq and chloride 20 mEq provided by potassium chloride 1.5 g. It is an electrolyte replenisher. Inactive ingredients: FD&C yellow No. 6, maltodextrin (contains corn derivative), malic acid, saccharin, silica gel, and natural flavoring.

Potassium Chloride Microencapsulated Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
600.00	1	Potassium chloride	600.00
900.00	2	Gelatin	900.00
QS	3	Water purified	1.5 L
QS	4	Corn oil	QS
QS	5	Petroleum ether	QS
QS	6	Isopropyl alcohol	QS
QS	7	Glutaraldehyde 1%	QS

Manufacturing Directions

1. Item 2 is added to 1.5 L of item 3 and the mixture is allowed to stand at 25°C for 1 hour while the gelatin hydrates and swells.
2. To this mixture is added item 1 and the preparation is heated to 60°C while it is stirred at 300 rpm for 30 minutes to effect dissolution of the gelatin and to ensure even suspension of the calcium carbonate. Additional distilled water previously heated to 60°C is then added to bring the total volume to 100°C while the stirring is continued.
3. This preparation is slowly poured into 12 L of a mixture consisting of 20% by volume of corn oil in petroleum ether, which has previously been heated to 60°C while the petroleum ether solution is stirred at 500 rpm. This preparation is then cooled to 5°C with continued stirring and the stirring is continued at 500 rpm for 1 hour after the lower temperature is reached.
4. Isopropanol (6 L) is then added while stirring of the preparation at 5°C is continued. The solid microspheres are then collected by filtration and washed 3 times with isopropyl alcohol. The capsules are then immersed in 1.5 L of a 1% solution of glutaraldehyde in isopropyl alcohol for 8 hours at 5°C, then washed again 3 times with isopropyl alcohol, filtered, and vacuum dried for 24 hours.
5. The microspheres, which average between 200 and 300 μm in diameter, are filled into gelatin capsules for administration as a long-acting antacid product (1.5 g of the microsphere mix, which contains 600 mg of potassium chloride, are filled into each size 00 capsule). This final dosage form delivers a total dose of 600 mg of KCl, but over a sustained time period of 1 to 4 hours and in such a way that the potassium chloride is in the solution state, rather than the more injurious solid state, when it contacts the gastrointestinal mucosa. Total dissolution of the microspheres occurs from 1 to 5 hours after the drug content is depleted.

Potassium Chloride Powder (20 mEq)

Bill of Materials			
Scale (g/3 g pack)	Item	Material Name	Qty/kg (g)
1.50	1	Potassium chloride powder	500.00
0.40	2	Calcium cyclamate granules	130.00
4.00 mg	3	Dye yellow	1.33
0.16	4	Malic acid	51.67
0.50	5	Hydrolyzed cereal solids	165.00
–	6	Alcohol anhydrous	90.00
–	7	Water purified	10.00
15.00	8	Silicon dioxide colloidal	15.00
0.25	9	Flavor	81.66
0.20	10	Flavor	65.33

Manufacturing Directions

1. Pass items 1 to 4 and, if necessary, item 5 through a 686-mm mesh using a comminuting mill with impact forward.
2. Charge the materials from step 1 and item 5 in a suitable mixer and mix for 20 minutes.
3. Mix items 6 and 7 separately and add to step 2; mix for 5 minutes or until satisfactory mass is obtained.
4. Spread wet granules on paper-lined trays and dry at 40°C to 60°C to NMT 1.5% loss on drying.
5. Sift granules through an 840-μm aperture and grind through a 1.27-mm aperture.
6. Screen the flavors and, if necessary, item 8 through a 20 mesh.
7. Load half the granulation in a blender and add step 6 followed by remainder granules and blend for 20 to 30 minutes.
8. Fill in suitable sachet 3 g.

Prazosin and Polythiazide Capsules*

Each 1-mg capsule of contains drug equivalent to 1-mg free base. Inert ingredients in the formulations are hard gelatin capsules (which may contain FD&C blue No. 1, FD&C red No. 3, FD&C red No. 28, FD&C red No. 40, and other inert ingredients), magnesium stearate, sodium lauryl sulfate, starch, and sucrose.

Prednisolone Targeted-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
10.00	1	Prednisolone	10.00
100.00	2	Succinic acid	100.00
30.00	3	Eudragit E100 (5%)	30.00
100.00	4	Hydroxypropyl methylcellulose acetate succinate	100.00
QS	5	Ethanol	QS
QS	6	Purified water	QS
QS	7	Talc	QS

Manufacturing Directions

1. Add items 1 and 2 to a suitable mixer and blend well. Fill in a size 2 capsule the core capsule.
2. Spray-coat the core capsule with a 5% by weight solution of Eudragit E100 dissolved in ethanol, in a coating amount of 30 mg/capsule (48% by weight, based on the weight of the used empty hard capsule) as Eudragit E100 to obtain a capsule coated with a low pH-soluble polymer film.
3. The coated capsule is further spray-coated with a coating solution prepared by dissolving item 4 in a mixture of ethanol and water [5:3 (w/w)] to obtain a 5% by weight item 4 solution and adding thereto talc in an amount of 2.5% by weight, based on the total weight of the 5% item 4 solution, in a coating amount of 100 mg/capsule (159% by weight, based on the weight of the used empty hard capsule) as item 4 by means of an appropriate coater.
4. The formulation described above releases in the lower part of the digestive tract.

Procarbazine Hydrochloride Capsules*

Procarbazine hydrochloride, a hydrazine derivative antineoplastic agent, is available as capsules containing the equivalent of 50 mg of procarbazine as the hydrochloride. Each capsule also contains cornstarch, mannitol, and talc. Gelatin capsule shells contain parabens (methyl and propyl), potassium sorbate, titanium dioxide, FD&C yellow No. 6, and D&C yellow No. 10.

Prochlorperazine Sustained-Release Capsules

Spansule sustained-release capsules—each Compazine Spansule is so prepared that an initial dose is released promptly and the remaining medication is released gradually over a prolonged period. Inactive ingredients consist of ammonio methacrylate copolymer, D&C green No. 5, D&C yellow No. 10, FD&C blue No. 1, FD&C blue No. 1 aluminum lake, FD&C red No. 40, FD&C yellow No. 6, gelatin, hydroxypropyl methylcellulose, propylene glycol, silicon dioxide, simethicone emulsion, sodium lauryl sulfate, sorbic acid, sugar spheres, talc, triethyl citrate, and trace amounts of other inactive ingredients.

Propoxyphene Hydrochloride, Caffeine, and Aspirin Capsules*

Each capsule contains 65 mg (172.9 mmol) of propoxyphene hydrochloride, 389 mg (2159 mmol) of aspirin, and 32.4 mg (166.8 mmol) of caffeine. It also contains FD&C red No. 3, FD&C yellow No. 6, gelatin, glutamic acid hydrochloride, iron oxide, kaolin, silicone, titanium dioxide, and other inactive ingredients.

Propoxyphene Hydrochloride Capsules

Each Pulvule contains 65 mg (172.9 mmol) (No. 365) of propoxyphene hydrochloride. It also contains D&C red No. 33, FD&C yellow No. 6, gelatin, magnesium stearate, silicone, starch, titanium dioxide, and other inactive ingredients.

Propranolol Hydrochloride and Hydrochlorothiazide Capsules

Each capsule contains propranolol (80 mg) and hydrochlorothiazide (50 mg); alternately, the capsule may contain 120/50 or 160/50 mg, respectively. It contains the following inactive ingredients: calcium carbonate, ethylcellulose, gelatin capsules, hydroxypropyl methylcellulose, lactose, magnesium stearate, microcrystalline cellulose, sodium lauryl sulfate, sodium starch glycolate, titanium dioxide, and D&C yellow No. 10. In addition, 80/50-mg and 120/50-mg capsules contain D&C red No. 33; 120/50- and 160/50-mg capsules contain FD&C blue No. 1 and FD&C red No. 40.

Propranolol Hydrochloride Long-Acting Capsules*

It is available as 60-, 80-, 120-, and 160-mg capsules. The capsules contain the following inactive ingredients: cellulose, ethylcellulose, gelatin capsules, hydroxypropyl methylcellulose, and titanium dioxide. In addition, Inderal LA® 60-, 80-, and 120-mg capsules contain D&C red No. 28 and FD&C blue No. 1; Inderal LA 160-mg capsules contain FD&C blue No. 1. These capsules comply with USP Drug Release Test 1.

Propranolol Hydrochloride Multiple Bead Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
160.00	1	Propranolol hydrochloride [total]	160.00
		Powder Blend	
30.00	2	Propranolol hydrochloride powder	30.00
54.00	3	Lactose	54.00
15.00	4	Microcrystalline cellulose	15.00
1.00	5	Magnesium stearate	1.00

Propranolol Hydrochloride Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
160.00	1	Propranolol hydrochloride	160.00
128.92	2	Sucrose	128.92
42.97	3	Cornstarch	42.97
22.86	4	Shellac	22.86
35.25	5	Talc	35.25
–	6	Ethyl alcohol	91.44
–	7	Water purified	QS

Manufacturing Directions

1. Neutral pellets
   A. Weigh and mix in a stainless steel mixer suitable quantities of sucrose and cornstarch in the proportion of 3:1 w/w. Sift through a screen of suitable size to break up possible lumps.
   B. Transfer the mixture to a stainless steel coating pan and adjust rotary speed between 20 and 30 rpm to obtain a good tumbling action.
   C. By means of a suitable spray gun, spray over the powder a quantity of water equal to 15% w/w in very minute drops.
   D. Place the wet pellets over a thermostatic tray dryer and dry at 37°C for complete evaporation of water.
   E. Pass the dried pellets through sieves of suitable screens to ensure removal of dust and selection of cores of desired size.
2. Active pellets
   A. Dissolve shellac in ethyl alcohol. To 65% of this solution, add propranolol hydrochloride. (Reserve the remaining 35% of the solution for the film coating.)
   B. Transfer 171.89 kg of neutral pellets obtained from step I-E to a stainless steel coating pan and adjust the rotation speed between 20 and 30 rpm so as to obtain good tumbling action.
   C. Spray over the neutral pellets the result of step II-A.
   D. Keep the pan rotating to allow partial evaporation of the solvent.
   E. Complete evaporation of the solvent by drying the pellets in a thermostat at 35°C for 3 days.
3. Film-coated pellets
   A. Transfer the active pellets obtained from step II-E to a stainless steel coating pan and adjust the rotatory speed so as to obtain a good tumbling action.
   B. Spray the pellets as uniformly as possible with the alcoholic solution of shellac reserved from step II-A.
   C. Spread the wet pellets with talc to prevent agglutination.
   D. Keep the pan rotating to achieve solidification of the film coating and partial evaporation of the solvent.
   E. Complete evaporation of the solvent by drying the pellets in a thermostat at 35°C for 3 days.
4. Blending of pellets
   A. Transfer the film-coated pellets obtained from step III-E to a stainless steel pan and add a suitable quantity of neutral pellets obtained from step III-E to obtain the required dosage.
   B. Add 0.5% w/w talc to eliminate electrostatic charges and mix for 30 to 35 minutes.
5. Assembly
   A. Fill the blended pellets obtained from step IV-B into capsules of size 1 at the weight of 390 mg.

Propranolol Timed- and Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
80.00	1	Propranolol	80.00
4.14	2	Polyvinylpyrrolidone K-30	4.14
55.85	3	Nonpareil sugar beads 25–30 mesh	55.85
2.80	4	Opadry clear	2.80
2.33	5	Ethyl cellulose	2.33
0.23	6	Diethyl phthalate	0.23
–	7	Water purified	QS
–	8	Acetone	QS
9.75	9	Ethyl cellulose	9.75
8.57	10	Hydroxypropyl methylcellulose phthalate	8.57
3.10	11	Diethyl phthalate	3.10

Manufacturing Directions

1. Prepare a solution of item 2 in item 7 and add item 1 slowly; mix well. This is the drug solution.
2. In a Glatt fluid bed dryer, charge item 3 and coat with step 1 slowly and then dry to less than 2% moisture.
3. Apply item 4 coating to dried granules from step 2 to obtain 2% weight gain.
4. In a separate vessel, prepare a solution of items 5 and 6 in 98 parts of item 8 and 2 parts of item 7. Spray this inner coating on to step 3.
5. Prepare an acetone:water solution of items 9 to 11 and coat on step 4.
6. Dry and fill in capsules to yield 80, 120, and 160 mg of item 1. This product provides drug loading of 56% w/w based on core composition corresponding to 45.7% drug based on final time and sustained-release beads.

Proton Pump Inhibitor Powder for Reconstitution for Oral Use

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
20.00	1	Omeprazole (or another PPI)	20.00
20.00	2	Calcium acetate	175.00
	3	Calcium glycerophosphate	175.00
	4	Sodium bicarbonate	500.00
	5	Calcium hydroxide	50.00
	6	Glycerin	200.00

Note: This formula can be used for most proton pump inhibitor drugs.

Manufacturing Directions

1. Granulate active drug with items 2 to 6.
2. Dry sieve.
3. Pack in moisture-resistant container.

Proton Pump Inhibitor Powder for Reconstitution for Oral Use

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
10.00	1	Lansoprazole or other PPI equipotent	10.00
200.00	2	Calcium lactate	200.00
200.00	3	Calcium glycerophosphate	200.00
400.00	4	Sodium bicarbonate	400.00
12.00	5	Croscarmellose sodium	12.00
3.00	6	Pregelatinized starch	3.00

Note: This formula can be used for most proton pump inhibitor drugs.

Manufacturing Directions

1. Granulate active drug with items 2 to 6.
2. Dry sieve.
3. Pack in moisture-resistant container.

Pseudoephedrine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
24.00	1	Pseudoephedrine hydrochloride	24.00
15.00	2	Hydroxyethylcellulose, NF	15.00
60.00	3	Anhydrous lactose	60.00
1.00	4	Magnesium stearate	1.00

Manufacturing Directions

1. Blend all the ingredients in a twin-shell blender for 10 minutes.
2. Fill No. 0 capsules with fill weight of 500 mg using a tamping force of 200 N.

Pseudoephedrine Hydrochloride Capsules

1. Composition by weight: Pseudoephedrine HCl, USP 60 mg, yellow beeswax 10 to 20 mg, partially hydrogenated vegetable oil 15 to 25 mg, lecithin, NF 2 to 8 mg, colloidal silicon dioxide 2 to 8 mg, soybean oil, USP 150 to 250 mg.
2. Fill.

Pseudoephedrine and Guaifenesin Capsules

Each capsule contains pseudoephedrine hydrochloride 120 mg in a specially prepared base to provide prolonged action and guaifenesin 250 mg designed for immediate release to provide rapid action. Alternate dosing is 60 mg and 300 mg respectively. The capsules also contain as inactive ingredients calcium stearate, FD&C blue No. 1 (for higher strength identification), gelatin, pharmaceutical glaze, starch, sucrose, talc, and titanium dioxide.

Pseudoephedrine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
24.00	1	Pseudoephedrine hydrochloride	24.00
15.00	2	Hydroxyethylcellulose NF	15.00
60.00	3	Lactose anhydrous	60.00
1.00	4	Magnesium stearate	1.00

Manufacturing Directions

1. Blend all the ingredients in a twin-shell blender for 10 minutes.
2. Fill size 0 capsules with fill weight of 500 mg using tamping force of 200 N.

Psyllium and Dioctyl Sodium Sulfosuccinate Powder

Manufacturing Directions

1. Psyllium husk 5.1 g, dioctyl sodium sulfosuccinate 240 mg.
2. The psyllium husk is milled to a small particle size, no more than 4% on 100 mesh and between 25% and 50% through 200 mesh.
3. These psyllium particles are then agglomerated with maltodextrin and citric acid is sprayed on.
4. Dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, can be substituted for dioctyl sodium sulfosuccinate, or two or three of these can be combined.
5. Methylcellulose, polycarbophil, calcium polycarbophil, bran, malt soup extract, karaya, guar gum, or mixtures of these can be substituted for the psyllium.
6. The amounts of psyllium and/or dioctyl sulfosuccinate can be varied within the ranges specified herein.

Psyllium and Docusate Sodium Wafer

Formulation

Ascorbic acid 0.15%, natural and artificial flavors 1.54%, corn oil 14.80%, cornstarch 1.97%, fructose crystalline 6.82%, lecithin oil 0.99%, molasses granular light 0.39%, oat hull fiber 6.42%, psyllium husk 13.32%, sodium bicarbonate 0.20%, sucrose white granulated 17.40%, table oats 8.89%, water purified USP QS, wheat flour 19.21%, docusate sodium 0.63%, sorbitan tristearin 0.20%.

Manufacturing Directions

1. In an appropriate mixer, add corn oil and lecithin and mix for 1 minute using low speed.
   Note: Preheat (microwave) lecithin, if necessary.
2. Add psyllium, docusate (which has been coated with the sorbitan tristearin) and mix for 1 minute using low speed.
3. Into a separate bowl, add part of the sucrose, fructose, molasses, and half of the water.
4. Mix for 1 minute using low speed.
5. Add psyllium/oil/lecithin premix and oat fiber.
6. Mix for 1 minute Add rest of water, soda, flavors, ascorbic acid, and starch.
7. Mix for 1 minute at low speed.
8. Add flour to the mixer and mix for 1 minute at low speed.
9. Roll dough into sheets approximately 0.1 in thick.
10. Cut dough into rectangles (approximately 2.5-in length × 1.6-in width).
11. Place bars on baking trays and bake at 375°C for 10 to 12 minutes.
12. Ethylcellulose, polycarbophil, calcium polycarbophil, bran, malt soup extract, karaya, guar gum, or mixtures of these can be substituted for the psyllium. The amounts of psyllium and/or dioctyl sulfosuccinate can be varied within the ranges specified herein. Dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, can be substituted for dioctyl sodium sulfosuccinate, or two or three of these can be combined.

Psyllium Husk Granules

1. Raw, unmilled psyllium seed husk (2 g) is stirred with 0.2 N sodium hydroxide (400 mL) containing sodium borohydride (400 mg) in a nitrogen atmosphere at ambient temperature for 90 minutes.
2. The pH of the solution is from 10 to 11.
3. The solution is passed through a pasteurizer at a temperature of 100°C for a period of 50 seconds.
4. Once pasteurized, the mixture is centrifuged for 20 minutes at 23500 × g.
5. The supernatant is decanted from an insoluble fraction that settles out in the centrifuge bottle.
6. The insoluble fraction is mixed with fresh sodium hydroxide/sodium borohydride solution (100 mL) and recentrifuged for 15 minutes to increase yield of the soluble fraction.
7. The pH of the supernatant is adjusted to 5.5 by the addition of acetic acid at ambient temperature with stirring forming a gel.
8. The gel is desiccated with isopropanol added with high shear mixing.
9. The isopropanol solution is then decanted from the gel.
10. The solids content of the gel is 30%.
11. The gel material is passed through an extruder and extruded into individual particles with an average particle size of 500 microns.
12. The extruded particles enter a fluidized bed dryer fitted with a cyclonic airflow screen, such as a Conidur screen.
13. The air temperature is maintained at 80°C.
14. The gel temperature remains below 70°C throughout the drying process.
15. The particles are dried to a powder with 90% of the water being removed.
16. The yield of the gel-forming polysaccharide is 85%.
17. The final compositions comprise the following components by weight: gel-forming 50.0%, polysaccharide sorbitol neosorb p20 48.16%, magnesium stearate 0.5%, flavorant 0.4%, colorant 0.14%, citric acid 0.8%.
18. The granules can be coated using the coating formulation: Isopropanol 94.5% Eudragit RD100 5%, polyethylene glycol 0.5%.
19. The coated gel-forming polysaccharide particles are dried and combined with the excipients as described above.

Ranitidine Effervescent Granules*

Granules for oral administration are effervescent formulations of ranitidine; these must be dissolved in water before use. Each packet contains 168 mg of ranitidine HCl equivalent to 150 mg of ranitidine and the following inactive ingredients: aspartame, monosodium citrate anhydrous, povidone, and sodium bicarbonate.

Ribavirin Capsules

Capsules consist of a white powder in a white opaque gelatin capsule. Each capsule contains 200 mg of ribavirin and the following inactive ingredients: microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink, which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, *N*-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C blue No. 2 aluminum lake.

Rifabutin Capsules

The antimycobacterial agent rifabutin is a semisynthetic ansamycin antibiotic derived from rifamycin S. The capsules contain 150 mg of rifabutin, USP, per capsule, along with the following inactive ingredients: microcrystalline cellulose, magnesium stearate, red iron oxide, silica gel, sodium lauryl sulfate, titanium dioxide, and edible white ink.

Rifampicin Capsules

Rifampicin (rifampin) capsules contain 150 or 300 mg of rifampin per capsule. The 150- and 300-mg capsules also contain as inactive ingredients cornstarch, D&C red No. 28,

FD&C blue No. 1, FD&C red No. 40, gelatin, magnesium stearate, and titanium dioxide.

Rifampin and Isoniazid Capsules

This is a combination capsule containing 300 mg of rifampin and 150 mg of isoniazid. The capsules also contain as inactive ingredients colloidal silicon dioxide, FD&C blue No. 1, FD&C red No. 40, gelatin, magnesium stearate, sodium starch glycolate, and titanium dioxide.

Rivastigmine Tartrate Capsules*

It is supplied as capsules containing rivastigmine tartrate, equivalent to 1.5, 3, 4.5, and 6 mg of rivastigmine base for oral administration. Inactive ingredients are hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. Each hard gelatin capsule contains gelatin, titanium dioxide, and red and/or yellow iron oxides.

Salmeterol Xinafoate Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
2.00	1	Salmeterol xinafoate	2.00
97.00	2	Starch 1500 DC	97.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

Blend and fill 100 mg in each capsule.

Salmeterol Xinafoate Inhalation Powder*

It is a specially designed plastic device containing a double-foil blister strip of a powder formulation of salmeterol xinafoate intended for oral inhalation only. Each blister on the double-foil strip within the device contains 50 μg of salmeterol administered as the salmeterol xinafoate salt in 12.5 mg of formulation containing lactose. When a blister containing medication is opened by activating the device, the medication is dispersed into the air stream created when the patient inhales through the mouthpiece.

Salmeterol Xinafoate Inhalation Powder

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
0.05	1	Salmeterol xinafoate micronized	0.05
12.50	2	Lactose anhydrous	12.50

Saquinavir Mesylate Capsules*

It is available as light brown and green opaque hard gelatin capsules for oral administration in a 200-mg strength (as saquinavir free base). Each capsule also contains the inactive ingredients: lactose, microcrystalline cellulose, povidone K30, sodium starch glycolate, talc, and magnesium stearate. Each capsule shell contains gelatin and water with the following dye systems: red iron oxide, yellow iron oxide, black iron oxide, FD&C blue No. 2, and titanium dioxide. Another formulation contains inactives. Each capsule also contains the inactive ingredients: medium chain mono- and diglycerides, povidone, and DL-alpha-tocopherol. Each capsule shell contains gelatin and glycerol 85% with the following colorants: red iron oxide, yellow iron oxide, and titanium dioxide.

Selegiline Hydrochloride

Each aqua blue capsule contains 5 mg of selegiline hydrochloride. The inactive ingredients are citric acid, lactose, magnesium stearate, and microcrystalline cellulose.

Sevelamer Hydrochloride Capsules*

Each hard gelatin capsule of Renagel® contains 403 mg of sevelamer hydrochloride on an anhydrous basis. The inactive ingredients are colloidal silicon dioxide and stearic acid. The capsule and imprint contain titanium dioxide and indigo carmine ink.

Sibutramine Hydrochloride Capsules*

Each capsule contains 5, 10, or 15 mg of sibutramine hydrochloride monohydrate. It also contains as inactive ingredients lactose monohydrate, NF; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; and magnesium stearate, NF in a hard-gelatin capsule [which contains titanium dioxide, USP; gelatin; FD&C blue No. 2 (5- and 10-mg capsules only); D&C yellow No. 10 (5- and 15-mg capsules only), and other inactive ingredients].

Sibutramine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
5.00	1	Sibutramine hydrochloride	5.00
78.50	2	Lactose anhydrous	78.50
5.00	3	Polyvinylpyrrolidone	5.00
15.00	4	Cornstarch	15.00
1.50	5	Magnesium stearate	1.50
QS	6	Alcohol	QS

Manufacturing Directions

1. Mix items 1, 2, and 4 and granulate with alcoholic solution of item 3.
2. Dry, size, and blend with item 5.
3. Fill 105 mg; adjust for higher dose with item 2.

Simethicone Instant Granules (60 mg and 120 mg)

Formulation

Simethicone (Abil® 200, Goldschmidt), 10.0 g; cremophor RH 40 [1], 5.0 g; Kollidon VA 64, 3.0 g; ethanol, 40.0 g; sorbitol, crystalline 50.0 g; fructose, 50.0 g; Kollidon CL-M [1], 50.0 g; orange flavor (Dragoco), 0.5 g.

Manufacturing Directions

Introduce solution II into the mixture I.

1. Granulate the powder mixture III with the well-stirred mixture I/II; dry and pass through a 1-mm sieve.
2. Fill 1 or 2 g in sachets.

Stavudine Capsules*

The stavudine capsules are supplied for oral administration in strengths of 15, 20, 30, and 40 mg of stavudine. Each capsule also contains inactive ingredients microcrystalline cellulose, sodium starch glycolate, lactose, and magnesium stearate. The hard gelatin shell consists of gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and iron oxides.

Succimer Capsules*

Each opaque white capsule for oral administration contains beads coated with 100 mg of succimer and is imprinted in black with CHEMET 100®. The inactive ingredients in medicated beads are povidone, sodium starch glycolate, starch, and sucrose. The inactive ingredients in the capsule are gelatin, iron oxide, titanium dioxide, and other ingredients.

Sucralafate Granules

Bill of Materials			
Scale (mg/sachet) (2 g)	Item	Material Name	Qty/2 kg (g)
1000.00	1	Sucralafate	1000.00
100.00	2	Cornstarch	100.00
240.00	3	Povidone	240.00
QS	4	Lactose, QS to 2000	QS
—	5	Alcohol	QS

Manufacturing Directions

1. Charge items 1 and 2 in a fluid bed granulator (e.g., Glatt) and mix for 5 minutes at inlet temperature of 30°C.
2. Dissolve item 3 in a separate container in item 5 and spray into step 1 to granulate.
3. Dry granules at 50°C until the temperature reaches 30°C.
4. Sieve through No. 18.
5. Fill 1.9 to 2.1 g per sachet.

Sulfamethoxazole + Trimethoprim Dry Syrup (400 mg + 80 g/10 mL)

Formulation

Sulfamethoxazole, 4 g; trimethoprim, 0.8 g; sorbitol, crystalline [10], 30 g; sodium citrate, 5 g; sodium gluconate, 5 g; Kollidon CL-M [1], 10 g; vanillin, 0.1 g; saccharin sodium, 0.1 g; chocolate flavor, 0.1 g; sodium benzoate, 0.1 g.

Manufacturing Directions

Mix all components and sieve for administration. Fill 55 g of the mixture in a 100-mL flask.

Tacrine Hydrochloride Capsules

Each capsule contains tacrine as the hydrochloride. Inactive ingredients are hydrous lactose, magnesium stearate, and microcrystalline cellulose. The hard gelatin capsules contain gelatin, silicon dioxide, sodium lauryl sulfate, and the following dyes: 10 mg: D&C yellow No. 10, FD&C green No. 3, titanium dioxide; 20 mg; D&C yellow No. 10, FD&C blue No. 1, titanium dioxide; 30 mg; D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 40, titanium dioxide; 40 mg; D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, and titanium dioxide. Each 10-, 20-, 30-, and 40-mg capsule for oral administration contains 12.75, 25.50, 38.25, and 51.00 mg of tacrine hydrochloride respectively.

Tacrolimus Capsules*

Tacrolimus is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 0.5, 1, or 5 of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 0.5-mg capsule shell contains gelatin, titanium dioxide, and ferric oxide; the 1-mg capsule shell contains gelatin and titanium dioxide; and the 5-mg capsule shell contains gelatin, titanium dioxide, and ferric oxide.

Tacrolimus Capsules*

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
1.00	1	Tacrolimus	1.00
1.00	2	Hydroxypropyl methylcellulose 2910	1.00
QS	3	Ethanol	QS
58.00	4	Lactose	58.00

Manufacturing Directions

1. Item 1 is mixed with items 2 and 3. The mixture is kneaded and granulated to pass through sieves to collect particle size 180 to 250 mm; the other particle size is regranulated.
2. Dry granulation in step 1 is dried at room temperature.
3. In a suitable blending vessel, add item 4 and gradually add the step 2 granulation. Mix for 10 minutes and fill in size 0 capsules.

Talc, Crospovidone, and Starch Topical Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Croscarmellose sodium (crospovidone)	100.00
800.00	2	Cornstarch	800.00
100.00	3	Talc	100.00

Manufacturing Directions

Mix and fill in bottles.

Tamsulosin Hydrochloride Capsules*

Each capsule for oral administration contains tamsulosin HCl 0.4 mg and the following inactive ingredients: methacrylic acid copolymer; microcrystalline cellulose; triacetin; polysorbate 80; sodium lauryl sulfate; calcium stearate; talc; FD&C blue No. 2; titanium dioxide; ferric oxide; gelatin; and trace amounts of shellac, industrial methylated spirit 74 OP, *n*-butyl alcohol, isopropyl alcohol, propylene glycol, dimethylpolysiloxane, and black iron oxide (E172).

Tamsulosin Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
0.40	1	Tamsulosin hydrochloride	0.40
35.60	2	Crystalline cellulose	35.60
13.32	3	Eudragit L30D-55	13.32
4.00	4	Magnesium stearate	4.00

Manufacturing Directions

1. After sufficiently mixing item 1, crystalline cellulose, and magnesium stearate, a mixture of Eudragit L30D-55 and 40 mL of water is added to the aforementioned mixture, and the resultant mixture is kneaded and granulated by a centrifugal fluidized bed granulator.
2. The granules obtained were spheres having particle sizes of 0.1 to 1.5 mm, mainly 0.2 to 1.0 mm.

Temazepam Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
7.50	1	Temazepam micronized	7.50
7.50	2	Lactose anhydrous	7.50
232.50	3	Lactose anhydrous	232.50
2.50	4	Magnesium stearate	2.50

Manufacturing Directions

1. Item 1 is processed as follows: White crystalline temazepam having a purity of not less than 98% is fed into an Alpine 160 UPZ mill with a stainless steel pin at a rate of about 40 kg/h using a mill speed of about 11000 rpm to obtain temazepam particles having a specific surface area of 0.65 to 1.1 m^2/g area and 95% of the particles having a particle size diameter of less than 65 mm. The surface area measurement is made with the Quantector Gas Flow System and Quantasorb Surface Area Analyser at the temperature of liquid nitrogen (-196°C) using krypton as the absorbent and helium as the carrier gas. The particle size diameter is determined with the Malverne Particle Sizer at an obscuration value of 0.2 to 0.25 using a 0.1% Tween 80 solution in water saturated with temazepam in which 1 to 2 g of temazepam sample to be tested has been dispersed. After the feed rate and mill speed of the Alpine mill have been set, they are monitored at regular intervals to maintain the required particle size and surface area.
2. To prepare hard gelatin capsules containing 7.5 mg of the temazepam processed as in step 1, charge items 1 and 2 in a mill and pass through an 18-mesh screen.
3. Pass item 3 through 18-mesh screen and add to step 2.
4. Pass item 4 through 18-mesh screen and add to step 3 in a PK Mixer® without an intensity bar.
5. Mix for 30 minutes using tumbling action only.
6. The capsule mix is encapsulated in number 3 Lock hard gelatin capsules. Each capsule contains 250 mg of capsule mix and 7.5 mg of temazepam.

Temozolomide Capsules*

Each capsule contains 5, 20, 100, or 250 mg of temozolomide. The inactive ingredients for Temodar® capsules are lactose anhydrous, colloidal silicon dioxide, sodium starch glycolate, tartaric acid, and stearic acid. The gelatin capsule shells contain titanium dioxide. The capsules are imprinted with pharmaceutical ink.

Terazosin Capsules (1–10 mg) Hytrin*

Hytrin capsules are supplied in four dosage strengths, containing terazosin hydrochloride equivalent to 1, 2, 5, or 10 mg of terazosin. Hytrin inactive ingredients: 1-mg capsules: gelatin, glycerin, iron oxide, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin; 2-mg capsules: D&C yellow No. 10, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin; 5-mg capsules: D&C red No. 28, FD&C red No. 40, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin; 10-mg capsules: FD&C blue No. 1, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.

Terazosin Capsules

1. Capsules containing 5 mg of terazosin are prepared by blending the following ingredients in No. 3 gelatin capsules.
2. Terazosin HCL anhydrous 5.471; lactose monohydrate, NF 174.529; microcrystalline cellulose, NF 28.000; crospovidone, NF 14.000; magnesium stearate, NF 3.000; total capsule fill weight 225.000.

Terazosin Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
5.000	1	Terazosin hydrochloride anhydrous	5.471
174.529	2	Lactose monohydrate	174.529
28.000	3	Microcrystalline cellulose	28.000
14.000	4	Crospovidone	14.000
3.000	5	Magnesium stearate	3.000

Manufacturing Directions

1. Add and blend all items 1 to 5 in a suitable blender.
2. Fill using size 3 capsules; fill weight of 225.00 mg.

Terfenadine Oral Granules Directions

1. Micronized terfenadine (30 g) and 15 g of the block copolymer wetting agent (Pluronic polyol F-68) were mixed slowly in a "V-blender" for about 5 minutes.
2. Sorbitol instant (300 g) is added to the mixture and blended therewith for another 5 minutes to form a blend of all three components.
3. Microcrystalline cellulose (30 g; Avicel CL-611), PVP (50 g, KOLLIDON K-90), maltodextrin (200 g, MALTRIN QD M500), and 375 g of fine, granular fructose were added to the above blend and blending is continued for another 10 minutes to form a homogeneous, dry terfenadine composition that is a free-flowing powder.
4. The blended dry composition is thereafter packaged into 2 g sachets as unit doses to provide 60 mg of terfenadine.

Tetracycline Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
250.00	1	Tetracycline, USE tetracycline	275.00
46.00	2	Lactose monohydrate (dense)	46.00
2.00	3	Colloidal silicon dioxide (Aerosil 200)	2.00
2.00	4	Magnesium stearate	2.00
1.00	5	Empty hard gelatin capsule, size 1	1000.00

Manufacturing Directions

1. Check the temperature and relative humidity of the room before start of processing. Limits: RH 50% to 55%, temperature: 22°C to 27°C.
2. Pass the items 1, 2, and 3 through a 630-mm sieve using a sifter. Collect in stainless steel drum.
3. Pass item 4 through a 250-mm sieve using a sifter. Collect in polythene bag. Load the sieved powder to the drum (step 1) and mix for 5 minutes using drum mixer.
4. Load the empty capsule shells (size 1) in the hopper.
5. Run the machine and check the locking of shells.
6. Fill weight of one capsule = 325 mg + average weight of one empty shell.

Thalidomide Capsules

Thalidomide capsules are available in 50-mg capsules for oral administration. Active ingredient: thalidomide. Inactive ingredients: anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

Theophylline Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
150.00	1	Theophylline anhydrous (B. F. Goodrich)	150.00
26.60	2	Carbopol 934P (GAF Corporation)	26.60
172.10	3	PVP C-15	172.10
3.50	4	Talc	3.50
1.80	5	Zinc stearate	1.80

Manufacturing Directions

1. Carbopol 934P, PVP C-15 (mean molecular weight of about 8000) talc, and zinc stearate are combined in a mixer and mixed.
2. Theophylline anhydrous is added to this mixture and mixed well to achieve a uniform mixture.
3. The resulting particulate mixture, 354 mg, is filled into size 1 hard gelatin capsule shells.

Thiothixene Capsules*

Each capsule contains 1, 2, 5, or 10 mg of thiothixene and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium (type A), gelatin, magnesium stearate, microcrystalline cellulose, powdered cellulose, pregelatinized starch, sodium lauryl sulfate, titanium dioxide, and other inactive ingredients. The following coloring agents are employed: 1 mg—FD&C blue No. 1, D&C red No. 28, FD&C red No. 40, FD&C yellow No. 6; 2 mg—FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6, D&C yellow No. 10; 5 mg—FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6; 10 mg—FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6.

Tibolone Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
0.30	1	Tibolone (Org GD 14)	0.30
1.95	2	Hydroxypropyl cellulose	1.95
32.50	3	Cornstarch	32.50
0.32	4	Magnesium stearate	0.32
QS	5	Lactose	QS to 130.00
QS	6	Water purified	QS

Manufacturing Directions

1. Charge in a mixer items 3 and 5 and mix well.
2. Prepare a suspension of items 1 and 2 in item 6 and mix thoroughly; add to step 1 and granulate in a granulator by mixing for 2 to 3 minutes.
3. Dry the sieved wet material for 4 hours in a vacuum dryer at 40°C.
4. Screen the dried granules through a 710-mm sieve in the drum.
5. Load the empty capsule shells (size 1) in the hopper.
6. Run the machine and check the locking of shells.
7. Fill 130 mg in suitable capsules.

Tiotropium Inhalation Powder

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
21.70	1	Tiotropium bromide micronized	21.70
270.00	2	Endothelin antagonist 2	270.00
4708.30	3	Lactose	4708.30

Manufacturing Directions

1. Item 1 should first be prepared in an inhalable powder form by the following method:
   a. 150 kg of tiotropium bromide is placed in 25.7 kg of water in a suitable reaction vessel.
   b. The mixture is heated to 80°C to 90°C and stirred at constant temperature until a clear solution is formed.
   c. Activated charcoal (0.8 kg) moistened with water is suspended in 4.4 kg of water. This mixture is added to the solution containing the tiotropium bromide and the resulting mixture is rinsed with 4.3 kg of water.
   d. The mixture thus obtained is stirred for at least 15 minutes at 80°C to 90°C. Then it is filtered through a heated filter into an apparatus preheated to an external temperature of 70°C.
   e. The filter is rinsed with 8.6 kg of water. The contents of the apparatus are cooled at 3°C to 5°C for every 20 minutes to a temperature of 20°C to 25°C.
   f. The apparatus is cooled further to 10°C to 15° using cold water and crystallization is completed by stirring for at least another hour.
   g. The crystals are isolated using a suction filter dryer. The crystals are washed with cold water (10–15°C) and cold acetone (10–15°C).
   h. The crystals obtained are dried at 25°C in nitrogen current over a period of 2 hours. Yield: 13.4 μg of tiotropium bromide monohydrate (86% of theory).
2. Add and mix all items and mix well.
3. Fill 5 g per unit dose.

Tolmetin Sodium Capsules*

Capsules for oral administration contain tolmetin sodium as the dihydrate in an amount equivalent to 400 mg of tolmetin. Each capsule contains 36 mg (1.568 mEq) of sodium and the following inactive ingredients: gelatin, magnesium stearate, cornstarch, talc, FD&C red No. 3, FD&C yellow No. 6, and titanium dioxide.

Tolterodine Capsules*

Capsules contain 2 or 4 mg of tolterodine tartrate. The inactive ingredients are sucrose, starch, hydroxypropylmethylcellulose, ethylcellulose, medium-chain triglycerides, oleic acid, gelatin, and FD&C blue No. 2. The 2-mg capsules also contain yellow iron oxide. Both capsule strengths are imprinted with a pharmaceutical grade printing ink that contains shellac, titanium dioxide, propylene glycol, and simethicone.

Tolterodine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
2.00	1	Tolterodine	2.00
186.00	2	Lactose anhydrous	186.00
20.00	3	Cornstarch	20.00
15.00	4	Talc	15.00
2.00	5	Magnesium stearate	2.00

Note: For 1-mg strength, adjust with item 2.

Manufacturing Directions

1. Item 1 is accordingly mixed with items 2 and 3 and then milled.
2. The resulting mixture is then mixed with ingredients 4 and 5 and then filled into capsules of appropriate size.

Topiramate Capsules*

Topiramate capsules, sprinkle capsules, are available as 15- and 25-mg sprinkle capsules for oral administration as whole capsules or opened and sprinkled onto soft food. Sprinkle capsules contain topiramate-coated beads in a hard gelatin capsule. The inactive ingredients are sugar spheres (sucrose and starch), povidone, cellulose acetate, gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and black pharmaceutical ink.

Tretinoin Capsules

It is available in a 10-mg soft gelatin capsule for oral administration. Each capsule also contains beeswax, butylated hydroxyanisole, edetate disodium, hydrogenated soybean oil flakes, hydrogenated vegetable oils, and soybean oil. The gelatin capsule shell contains glycerin, yellow iron oxide, red iron oxide, titanium dioxide, methylparaben, and propylparaben.

Triamterene and Hydrochlorothiazide Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
23.01	1	Triamterene	23.01
15.34	2	Hydrochlorothiazide	15.34
2.50	3	Glycine	2.50
7.50	4	Polysorbate 80	7.50
QS	5	Water purified	QS
QS	6	Isopropyl alcohol	QS
52.15	7	Lactic acid	52.15

Manufacturing Directions

1. Add and dissolve item 3 in a suitable quantity of item 5.
2. Add items 1 and 2 and prepare a good wet mass.
3. Separately dissolve item 4 in item 6 and add to step 2 until granules are formed.
4. Dry granules in vacuum and mill.
5. Fill in size 4 capsules.

Triamterene Capsules*

Each capsule for oral use, with an opaque red cap and body, contains triamterene, 50 or 100 mg. The inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C red No. 33, FD&C yellow No. 6, gelatin, lactose, magnesium stearate, povidone, sodium lauryl sulfate, titanium dioxide, and trace amounts of other inactive ingredients.

Triclosan and Zinc Foot Deodorant Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
3.00	1	Triclosan (Irgasan® DP300)	3.00
2.00	2	Zinc undecylenate, USP	2.00
0.20	3	Menthol (crystals), USP	0.20
926.80	4	Talc (powder), USP	926.80
30.00	5	Magnesium stearate	30.00
30.00	6	Cornstarch, NF	30.00
8.00	7	Perfume	8.00

Manufacturing Directions

1. Pass the following ingredients through a 250-μm screen or similar: Irgasan DP300, zinc undecylenate, magnesium stearate, cornstarch, menthol, and approximately 10% of the total amount of talc.
2. Charge materials from first step into a suitable mixer.
3. Mix until uniform.
4. Discharge powder from second step into another suitable mixer.
5. Add and disperse perfume.
6. Mix until uniform.
7. Pass mixture from step above through a 250-μm screen or similar.
8. Charge mixture from step above into a V-mixer or similar and add balance of talc powder.
9. Mix for 30 minutes or until homogeneous.

Triclosan and Zinc Undecylenate Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tabs (g)
3.0	1	Triclosan-Irgasan DP300	3.0
2.0	2	Zinc undecylenate	2.0
0.2	3	Menthol	0.2
926.8	4	Talc	926.8
30.0	5	Magnesium stearate	30.0
30.0	6	Cornstarch	30.0
8.0	7	Perfume	8.0

Manufacturing Directions

1. Pass the following ingredients through a 250-mm aperture screen or similar screen: Triclosan-Irgasan DP300, zinc undecylenate, magnesium stearate, cornstarch, menthol, and approximately 10% of the total amount of talc.
2. Charge materials from first step into a suitable mixer. Mix until uniform.
3. Discharge powder from second step into another suitable mixer. Add and disperse perfume. Mix until uniform. Pass mixture from step above through a 250-mm aperture screen or similar screen. Charge mixture from step 2 into a V-mixer or a similar mixer and add balance of talc powder.
4. Mix for 30 minutes or until homogeneous.

Trientine Hydrochloride Capsules*

It is available as 250-mg capsules for oral administration. It contains gelatin, iron oxides, stearic acid, and titanium dioxide as inactive ingredients.

Trimebutine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
25%	1	Trimebutine	25%
50%	2	Calcium	50%
7.5%	3	Polycarbophil microcrystalline cellulose (Avicel 102)	7.5%
25%	4	Talc	25%

Manufacturing Directions

Mix and fill in No. 2 hard gelating capsule.

Trimethoprim and Sulfamethoxazole Oral Suspension*

Trimethoprim–sulfamethoxazole is a combination product available in double strength (DS) pediatric suspension for oral administration. Each teaspoonful (5 mL) of the pediatric suspension contains 40 mg trimethoprim and 200 mg sulfamethoxazole in a vehicle containing 0.3% alcohol, edetate disodium, glycerin, microcrystalline cellulose, parabens (methyl and propyl), polysorbate 80, saccharin sodium, simethicone, sorbitol, sucrose, FD&C yellow No. 6, FD&C red No. 40, flavors, and water.

Trimipramine Maleate Capsules*

Each capsule contains trimipramine maleate equivalent to 25, 50, or 100 mg of trimipramine as the base. The inactive ingredients present are FD&C blue 1, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25-mg dosage strength also contains D&C yellow No. 10 and FD&C yellow No. 6; the 50-mg dosage strength also contains D&C red No. 28, FD&C red No. 40, and FD&C yellow No. 6.

Troleandomycin Capsules

Inert ingredients in the formulation are hard gelatin capsules (which may contain inert ingredients), lactose, magnesium stearate, sodium lauryl sulfate, and starch.

Typhoid Vaccine Live Oral Capsules

The vaccine strain is grown in fermenters under controlled conditions in a medium containing a digest of yeast extract, an acid digest of casein, dextrose, and galactose. The bacteria are collected by centrifugation, mixed with a stabilizer containing sucrose, ascorbic and amino acids, and lyophilized. The lyophilized bacteria are mixed with lactose and magnesium stearate and filled into gelatin capsules, which are coated with an organic solution to render them resistant to dissolution in stomach acid. The enteric-coated, salmon/white capsules are then packaged in four-capsule blisters for distribution. The contents of each enteric-coated capsule are

Viable *Staphylococcus typhi* Ty21[a]	2–6 H 109 colony-forming units[a]
Nonviable *S. typhi* Ty21[a]	5–50 H 109 bacterial cells
Sucrose	26–130 mg
Ascorbic acid	1–5 mg
Amino acid mixture	1.4–7.0 mg
Lactose	100–180 mg
Magnesium stearate	3.6–4.4 mg

[a]Vaccine potency (viable cell counts per capsule) is determined by inoculation of agar plates with appropriate dilutions of the vaccine suspended in physiological saline.

Valsartan and Hydrochlorothiazide Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
80.00	1	Valsartan	80.00
12.50	2	Hydrochlorothiazide	12.50
1.50	3	Colloidal anhydrous silica Aerosil	1.50
31.50	4	Microcrystalline cellulose Avicel	31.50
20.00	5	Polyvinylpyrrolidone crospovidone	20.00
4.50	6	Magnesium stearate	4.50

Manufacturing Directions

1. The components, except for a portion of the magnesium stearate, are blended in a container mixer.
2. The blended material is sieved and preblended for an additional time period in a container mixer. The blended material is compacted using a roller compactor by applying a compaction force of 25 to 65 kN and a roller speed of 1.3 to 7.5 rpm.
3. The compacted material is sieved again and the remaining portion of the magnesium stearate is added and finally blended in a container mixer.
4. Then 150 mg of the homogeneous mixture is filled in capsules or compressed for tablets and subsequent coating.

Valsartan Capsules*

It is available as capsules for oral administration, containing either 80 or 160 mg of valsartan. The inactive ingredients contained in the capsules are cellulose compounds, crospovidone, gelatin, iron oxides, magnesium stearate, povidone, sodium lauryl sulfate, and titanium dioxide.

Valsartan Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
80.00	1	Valsartan	80.00
1.50	2	Colloidal anhydrous silica Aerosil	1.50
31.50	3	Microcrystalline cellulose Avicel	31.50
20.00	4	Polyvinylpyrrolidone crospovidone	20.00
4.50	5	Magnesium stearate	4.50

Manufacturing Directions

1. The components, except for a portion of the magnesium stearate, are blended in a container mixer.
2. The blended material is sieved and preblended for an additional period of time in a container mixer. The blended material is compacted using a roller compactor by applying a compaction force of 25 to 65 kN and a roller speed of 1.3 to 7.5 rpm.
3. The compacted material is sieved again and the remaining portion of the magnesium stearate is added and finally blended in a container mixer.
4. Then 138.50 mg of the homogeneous mixture is filled in capsules or compressed for tablets and subsequent coating.

Vancomycin Hydrochloride Capsules*

Each capsule contains vancomycin hydrochloride equivalent to 125 mg (0.08 mmol) or 250 mg (0.17 mmol) vancomycin. The Pulvules also contain FD&C blue No. 2, gelatin, iron oxide, polyethylene glycol, titanium dioxide, and other inactive ingredients.

Venlafaxine Capsules

37.5 mg venlafaxine capsule comprises nonpareil seeds 17.26%, venlafaxine HCl 44.24%, sodium alginate 17.91%, talc 5.6%, Kollicaot SR30 D (copolymer of polyvinyl acetate), 12.03%, and purified water in required quantity.

Ingredients	mg/cap
Nonpareil Seeds	16.546 Drug coating
Venlafaxine HCl	42.400
Sodium Alginate	11.660
Talc	1.930
Titanium Dioxide	1.250
Purified Water	QS
*Subtotal	73.786 Seal coating
Sodium Alginate	5.510
Talc	0.892
Titanium Dioxide	0.392
Purified Water	QS
*Subtotal	80.580 Functional coating
Kollicoat SR30D	11.535
Propylene Glycol	1.154
Talc	2.551
Purified Water	QS
*Total	95.82
*Does not remain in formulation.	

1. Load the drug on NPS using solution containing Venlafaxine HCl, sodium alginate, talc & titanium dioxide by fluid bed coating technique.
2. Seal coat the drug-coated pellets using solution containing sodium alginate, talc, and titanium dioxide by fluid bed coating technique
3. Functional coat the seal-coated pellets using solution containing Kollicoat SR 30D, propylene glycol, and talc by fluid bed coating technique.

Verapamil Hydrochloride Capsules*

It is available for oral administration as a 360-mg hard gelatin capsule (lavender cap/yellow body), a 240-mg hard gelatin capsule (dark blue cap/yellow body), a 180-mg hard gelatin capsule (light gray cap/yellow body), and a 120-mg hard gelatin capsule (yellow cap/yellow body). These pellet-filled capsules provide a sustained release of the drug in the gastrointestinal tract. In addition to verapamil HCl, the capsule contains the following inactive ingredients: fumaric acid, talc, sugar spheres, povidone, shellac, gelatin, FD&C red No. 40, yellow iron oxide, titanium dioxide, methylparaben, propylparaben, silicon dioxide, and sodium lauryl sulfate. In addition, the 240-mg and 360-mg capsules contain FD&C blue No. 1 and D&C red No. 28; and the 180-mg capsule contains black iron oxide.

Verapamil Hydrochloride Capsules

Manufacturing Directions

1. Verapamil hydrochloride (30 kg), malic acid (10 kg), and talc (2.4 kg) are blended and passed through a No. 100 mesh screen using a conventional milling machine.
2. A polymer suspension is prepared containing 5% hydroxypropyl methylcellulose in methanol/methylene chloride 60/40.
3. Sugar/Starch seeds (0.4–0.5 mm, 9 kg) are placed in a standard coating pan and rotation commenced.
4. The seeds are wetted with sufficient polymer suspension to dampen them thoroughly and then an amount of the powder blend is dusted on until no more adhered. This step is repeated until the entire powder blend has been applied.
5. The coated seeds are allowed to dry after each application of polymer suspension.
6. When all of the powder has been applied, the coated seeds are dried at 40°C to 60°C until all of the solvent has been driven off.
7. A membrane suspension is prepared from the following components: two parts by volume 5% hydroxypropyl methylcellulose in methanol/methylene chloride 60/40, eight parts by volume 5% ethylcellulose in methanol/methylene chloride 60/40, and five parts by weight talc.
8. The coated seeds, which are prepared previously and which define the active core of the pellets being prepared, are placed in a coating pan and rotation commenced. The membrane suspension is applied to the coated seeds in separate coats, each coat corresponding to 10 mL of the membrane suspension per kg of coated seeds. After each coat had been applied, the pellets are air dried in the coating pan.
9. After the final coat has been applied, the pellets are dried at 40°C to 60°C to evaporate all traces of solvent. Rapid-release pellets as used in the controlled absorption pharmaceutical formulation of the invention are prepared by forming active cores without the subsequent application of a membrane thereto.

Verapamil Hydrochloride Sustained-Release Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
120.00	1	Verapamil hydrochloride	120.00
20.00	2	Sucrose and cornstarch neutral microgranules	20.00
11.30	3	Shellac, bleached, wax-free	11.30
0.75	4	Eudragit L100	0.75
3.60	5	Eudragit L30D	3.60
1.23	6	Eudrafit NE30D	1.23
0.37	7	Diethyl phthalate	0.37
1.60	8	Talc	1.60
–	9	Alcohol	QS
–	10	Acetone	QS
–	11	Water purified	QS

Note: For 240-mg strength, scale to twice the formula.

Manufacturing Directions

1. The neutral microgranules (item 2) are placed in a coating pan and pan started.
2. Prepare a 20% solution of item 3 in a mixture of acetone and alcohol.
3. Set temperature of step 1 to 25°C ± 5°C. Apply shellac solution alternating with item 1 powder until the entire active ingredient is incorporated.
4. Sieve microgranules through a 0.85-mm aperture. Dry microgranules at 30°C to 40°C for 8 hours.
5. Sieve dried microgranules and dry again at 30°C to 40°C for 8 hours.
6. Prepare a 15% alcoholic solution of Eudragit L100 and apply with talc; dry and apply until all solution is incorporated.
7. Sieve microgranules using a 1.18-mm aperture sieve.
8. Prepare an aqueous dispersion of item 5 (L30D) and item 7. Apply part of suspension to microgranules together with part of item 8. Allow to dry. Repeat operation until desired dissolution rate is obtained.
9. Sieve microgranules using 1.18-mm sieve and then dry at 30°C to 40°C for 12 hours.
10. Prepare aqueous solution of NE30D and item 7, apply in parts with remaining talc, and then dry. Repeat until desired dissolution rate is obtained.
11. Sieve using a 1.18-mm sieve. Dry at 30°C to 40°C for 12 hours.
12. Fill appropriate quantity based on assay. Use approximately 158.85 mg for 120-mg strength and 317.70 mg for 240-mg strength.

Vincamine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
30.00	1	Vincamine	30.00
17.50	2	Lactose	17.50
166.80	3	Sucrose and cornstarch microgranules, size 20	166.80
3.30	4	Polyvinyl pyrrolidone	3.30
1.30	5	Shellac	1.30
3.60	6	Eudragit L	3.60
7.50	7	Talc	7.50
–	8	Alcohol	QS

Manufacturing Directions

1. Charge item 3 in a coating pan and run the pan.
2. Prepare solution of item 4 in item 8.
3. Add and mix items 1 and 2 in a separate container.
4. Heat step 1 to 25°C ± 5°C; apply solution in Step2 and alternate with powder mixture in step 3 until all of step 3 is incorporated.
5. Sieve granules through a 1.18-mm sieve in step 4 and dry at 30°C to 40°C for 8 hours.
6. Prepare an alcoholic solution of item 5 in item 8 and apply to step 5 until all incorporated.
7. Sieve microgranules through a 1.18-mm sieve and dry at 30°C to 40°C for 8 hours.
8. Prepare a solution of item 6 in item 8 and apply in steps until all solution is incorporated.
9. Sieve microgranules through a 1.18-mm sieve and dry at 30°C to 40°C for 8 hours.
10. Fill appropriate quantity in capsules, approximately 230 mg.

Vinpocetine Multiple Bead Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
160.00	1	Vinpocetine	160.00
	Powder Blend		
5.00	1	Vinpocetine	5.00
0.10	2	Sodium lauryl sulfate	0.10
3.0	3	Sodium starch glycolate	3.00
6.00	4	Glutamic acid	6.00
7.00	5	Cornstarch	7.00
62.00	6	Lactose	62.00
13.00	7	Microcrystalline cellulose	13.00
1.00	8	Magnesium stearate	1.00

Vitamin B Complex, Amino Acids, and Magnesium Effervescent Granules (Sugar-Free)

Bill of Materials			
Scale (mg/Tab)	Item	Material Name	Qty/1000 Tabs (g)
2.00	1	Thiamin hydrochloride	2.00
2.00	2	Pyridoxine hydrochloride	2.00
5.00	3	Cyanocobalamin dry powder 0.1%	5.00
20.00	4	L-Glutamine	20.00
10.00	5	Inositol	10.00
10.00	6	Potassium L-aspartate	10.00
500.00	7	DL-Carnitine hydrochloride	500.00
350.00	8	Magnesium L-aspartate	350.00
600.00	9	Citric acid, anhydrous	600.00
500.00	10	Sodium bicarbonate	500.00
QS	11	Flavors	QS
50.00	12	Kollidon VA 64	50.00
–	13	Isopropanol	80.00

Manufacturing Directions

1. Mix items 1 to 6, add the mixture of items 7 to 12, granulate mixture of these two combinations with item 13, pass through a 0.8-mm sieve, dry well, and mix.
2. Fill 2.1 g of the granules in sachets.

Vitamin B Complex + Amino Acid + Magnesium Effervescent Granules (Sugar-free)

(1 RDA of vitamins + 500 mg carnitine + 20 mg glutamine)

Formulation

Thiamin hydrochloride, 2 g; pyridoxine hydrochloride, 2 g; cyanocobalamin dry powder 0.1%, 5 g; L-glutamine, 20 g; inositol, 10 g; potassium L-aspartate, 10 g; DL-carnitine hydrochloride, 500 g; magnesium L-aspartate, 350 g; citric acid, anhydrous, 600 g; sodium bicarbonate, 500 g; flavors, QS; Kollidon VA 64 50 g; isopropanol, 80 g.

Manufacturing Directions

1. Mix the components I, add the mixture II, granulate mixture I+II with the liquid III, pass through a 0.8-mm sieve, dry well, and mix with III.
2. Fill 2.1 g of the granules in sachets.

Vitamin B Complex and Vitamin C Instant Granules

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
3.60	1	Thiamine hydrochloride	3.60
5.70	2	Riboflavin phosphate sodium	5.70
45.00	3	Nicotinamide	45.00
4.50	4	Pyridoxine hydrochloride	4.50
15.0	5	Cyanocobalamin (gelatin-coated, 0.1%)	15.00
150.0	6	Ascorbic acid (powder)	150.00
723.00	7	Sucrose	723.00
51.00	8	Kollidon 30	51.00
QS	9	Ethanol	180.00 mL

Manufacturing Directions

1. Mix items 1 to 7, granulate with solution of items 8 and 9, dry, and pass through a 0.8-mm sieve.
2. Fill 1 g of the granules in sachets (or 10 g in 100 mL flakes as dry syrup) to produce yellow homogeneous granules dispersible in cold water.
3. Approximately 1 g of the granules (=1 sachet) corresponds to two daily vitamin B and vitamin C requirements of adults.
4. Because of the high loss of riboflavin phosphate sodium, it should be substituted by riboflavin.

Vitamin C and Calcium Carbonate Effervescent Powder

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tabs (g)
300.00	1	Calcium, USE calcium carbonate	315.00
450.00	2	Sodium tartaric acid, powder bicarbonate	450.00
600.00	3	Kollidon 30	600.00
35.00	4	Kollidon 30	35.00
200.00	5	Isopropanol	200.00
400.00	6	Sucrose crystalline	400.00
500.00	7	Ascorbic acid, crystalline, with excess	550.00
120.00	8	Kollidon CL	120.00
60.00	9	Polyethylene glycol 6000, powder	60.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with solution of items 4 and 5, mix with item 6, and dry.
2. Add items 7 to 9 and press with a high compression force at maximum 30% of relative atmospheric humidity.
3. Package 2500 mg in aluminum-lined sachet.

Zanamivir Powder*

It is for administration to the respiratory tract by oral inhalation only. Each disc contains four regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose. The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the Diskhaler®. The drug is also administered as aqueous solution (10%) with 0.04% benzalkonium chloride and 0.40% phenylethyl alcohol. In an aqueous cosolvent system, it contains 10% active drug, 0.04% benzalkonium chloride, 10% PEG 400, and 30% propylene glycol (balance purified water). In an aerosol formulation, there is 7.5% active drug, 25.6% propellant 11, and 66.5% propellant 12.

Zanamivir Powder

Bill of Materials			
Scale (mg/disk)	Item	Material Name	Qty/1000 Disks (g)
5.00	1	Zanamivir	5.00
20.00	2	Lactose anhydrous	20.00

Zidovudine Capsules

Each capsule contains 100 mg of zidovudine and the inactive ingredients cornstarch, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 100-mg empty hard gelatin capsule, printed with edible black ink, consists of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical shellac, soya lecithin, and titanium dioxide. The blue band around the capsule consists of gelatin and FD&C blue No. 2.

Zidovudine Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Zidovudine (3′-azido-3′-deoxythymidine)	100.00
200.00	2	Lactose	200.00
50.00	3	Cornstarch	50.00
5.00	4	Polyvinylpyrrolidone	5.00
4.00	5	Magnesium stearate	4.00

Manufacturing Directions

1. Sieve items 1 to 4 through 80-mesh sieve and blend.
2. Pass item 5 through a 100-mesh sieve and add to step 1 and blend for 2 minutes.
3. Fill 359 mg in capsules.

Zinc Oxide and Cornstarch Powder

Cornstarch baby powder combines zinc oxide (10%) with topical starch (cornstarch) for topical application. Also contains fragrance and tribasic calcium phosphate.

Ziprasidone Hydrochloride Capsules*

Capsules are supplied for oral administration in 20-, 40-, 60-, and 80-mg doses. Capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.

Ziprasidone Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
20.00	1	Ziprasidone, USE ziprasidone hydrochloride	22.65
66.10	2	Lactose monohydrate	66.10
10.00	3	Pregelatinized cornstarch	10.00
0.75	4	Magnesium stearate	0.75

Manufacturing Directions

1. Pass items 1 to 3 through 80-mesh screen and blend.
2. Pass item 4 through 100-mesh screen and add and blend for 2 minutes.
3. Fill in size 4 capsules (100 mg). For higher strengths, scale up the quantity and size of capsule. The lactose monohydrate weight is adjusted according to small potency changes in the ziprasidone hydrochloride monohydrate to maintain a constant capsule weight.

Zonisamide Capsules*

Each capsule contains the labeled amount of zonisamide plus the following inactive ingredients: microcrystalline cellulose, hydrogenated vegetable oil, sodium lauryl sulfate, gelatin, and colorants.

Zonisamide Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Caps (g)
100.00	1	Zonisamide	100.00
35.00	2	Lactose anhydrous	35.00
17.00	3	Cornstarch	17.00
40.00	4	Crystalline cellulose	40.00
6.00	5	Hydroxypropyl cellulose	6.00
1.00	6	Light anhydrous silicic acid	1.00
1.00	7	Magnesium stearate	1.00
QS	8	Water purified	QS

Manufacturing Directions

1. Among the preceding components, zonisamide, lactose, cornstarch, and crystalline cellulose are blended and thereto is added hydroxypropyl cellulose being dissolved in water. The mixture is kneaded, dried, and granulated.
2. To these granules are added magnesium stearate and light anhydrous silicic acid and the mixture is filled (200 mg) in each capsule.
3. A 20% powder formulation contains zonisamide, 200 g; lactose, 719 g; hydroxypropyl cellulose, 20 g; light anhydrous silicic acid, 1 g. Total, 940 g.
4. Using a high-shear granulator, all the preceding components for powder formulation are blended, sprayed with an ethanolic solution (200 g) containing ethylcellulose (40 g) and hydroxypropyl cellulose (20 g) for granulation, and are then made into granules. These are dried and regulated in size to give 20% powders.

COMMERCIAL PHARMACEUTICAL FORMULATIONS

14 L-Crystalline amino acid formula—700 mg/cap-L-lysine HCL, L-isoleucine, L-glutamine, L-tyrosine, L-threonine, L-alanine, L-leucine, L-histidine, L-arginine HCL, L-aspartic acid, L-valine, L-methionine, L-cystine, L-glutamic acid, glycine, L-phenylalanine, N-acetyl-L-tyrosine, L-serine, L-proline plus ornithine alpha-ketoglutarate, and dipeptides; L-alanyl-L-glutamine and L-glycyl-L-glutamine. 20 L-Crystalline amino acid formula helps reverse negative nitrogen balance. 677 mg. L-Crystalline amino acids including neurotransmitter precursors, sulfur, and branched chain amino acids plus alpha-lipoic acid: L-lysine HCL, L-isoleucine, L-glutamine, L-tyrosine, L-threonine, L-alanine, L-leucine, L-histidine, L-arginine HCL, L-aspartic Acid, L-valine, ornithine alpha-ketoglutarate, L-methionine, L-cystine, L-glutamic acid, glycine, L-phenylalanine, N-acetyl-L-tyrosine, L-serine, L-proline, alpha-lipoic acid.

- Adipex-P capsules contain the inactive ingredients cornstarch, gelatin, lactose monohydrate, magnesium stearate, titanium dioxide, black iron oxide, FD&C blue No. 1, FD&C red No. 40, and D&C red No. 33.
- Aggrenox® (aspirin/extended-release dipyridamole) is a combination antiplatelet agent intended for oral administration. Each hard gelatin capsule contains 200 mg dipyridamole in an extended-release form and 25 mg aspirin as an immediate-release sugar-coated tablet. In addition, each capsule contains the following inactive ingredients: acacia, aluminum stearate, colloidal silicon dioxide, cornstarch, dimethicone, hypromellose, hypromellose phthalate, lactose monohydrate, methacrylic acid copolymer, microcrystalline cellulose, povidone, stearic acid, sucrose, talc, tartaric acid, titanium dioxide, and triacetin. Each capsule shell contains gelatin, red iron oxide and yellow iron oxide, titanium dioxide, and water.
- Amitiza™ (lubiprostone) is available for oral administration in an imprinted, oval, orange soft gelatin capsule containing 24 μg lubiprostone and the following inactive ingredients: medium-chain triglycerides, gelatin, sorbitol, FD&C red No. 40, D&C yellow No. 10, and purified water.
- Amnesteem contains isotretinoin, a retinoid, and is available in 10-, 20-, and 40-mg soft gelatin capsules for oral administration. Each capsule contains yellow wax, butylated hydroxyanisole, edetate disodium, hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain glycerin with the following dye systems: 10 mg—red iron oxide paste and black ink; 20 mg—red iron oxide paste, yellow iron oxide paste, titanium dioxide, and black ink; 40 mg—red iron oxide paste, yellow iron oxide paste, titanium dioxide, and black ink.
- Benefiber® is a 100% natural fiber that can be mixed with almost anything. Ingredients: partially hydrolyzed guar gum (a 100% natural fiber). Guar gum is derived from the seed of the cluster bean.
- Biaxin for suspension, clarithromycin suspension (clarithromycin for oral suspension, USP), contains 125 or 250 mg of clarithromycin. Each bottle of Biaxin granules contains 1250 mg (50-mL size), 2500 mg (50- and 100-mL sizes), or 5000 mg (100-mL size) of clarithromycin and the following inactive ingredients: carbomer, castor oil, citric acid, hypromellose phthalate, maltodextrin, potassium sorbate, povidone, silicon dioxide, sucrose, xanthan gum, titanium dioxide, and fruit punch flavor.
- Brevibloc (esmolol hydrochloride) premixed injection is a clear, colorless to light yellow, sterile, nonpyrogenic isoosmotic solution of esmolol hydrochloride in sodium chloride. 2500-mg, 250-mL single use premixed bag—Each milliliter contains 10 mg esmolol hydrochloride, 5.9 mg sodium chloride, USP, and water for injection, USP, buffered with 2.8 mg sodium acetate trihydrate, USP, and 0.546 mg glacial acetic acid, USP. Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 5.0 (4.5–5.5). The calculated osmolarity is 312 mOsmol/L. The 250-mL bag is a nonlatex, non-PVC IntraVia bag with dual PVC ports. The IntraVia bag is manufactured from a specially designed multilayer plastic (PL 2408). Solutions in contact with the plastic container leach out certain chemical compounds from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials. 2000-mg, 100-mL single use premixed bag double strength—Each milliliter contains 20 mg esmolol hydrochloride, 4.1 mg sodium chloride, USP, and water for injection, USP, buffered with 2.8 mg sodium acetate trihydrate, USP, and 0.546 mg glacial acetic acid, USP. Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 5.0 (4.5–5.5). The calculated osmolarity is 312 mOsmol/L. The 100-mL bag is a nonlatex, non-PVC IntraVia bag with dual PVC ports. The IntraVia bag is manufactured from a specially designed multilayer plastic (PL 2408). Brevibloc injection is a clear, colorless to light yellow, sterile, nonpyrogenic isoosmotic solution of esmolol hydrochloride in sodium chloride. 100-mg, 10-mL single dose vial—Each milliliter contains 10 mg esmolol hydrochloride, 5.9 mg sodium chloride, USP, and water for injection, USP, buffered with 2.8 mg sodium acetate trihydrate, USP, and 0.546 mg glacial acetic acid, USP. Sodium hydroxide and/or hydrochloric acid added, as necessary to adjust pH to 5.0 (4.5–5.5). 100-mg, 5-mL double-strength single-dose vial—Each milliliter contains 20 mg esmolol hydrochloride, 4.1 mg sodium chloride, USP, and water for injection, USP, buffered with 2.8 mg sodium acetate trihydrate, USP, and 0.546 mg glacial acetic acid, USP. Sodium hydroxide and/or hydrochloric acid added, as necessary to adjust pH to 5.0 (4.5–5.5). Brevibloc Concentrate is a clear, colorless to light yellow, sterile nonpyrogenic concentrate. 2500-mg, 10-mL Ampul—Each milliliter contains 250 mg esmolol hydrochloride in 25% propylene glycol, USP, 25% alcohol, USP, and water for injection, USP, buffered with 17.0 mg sodium acetate trihydrate, USP, and 0.00715 mL glacial acetic acid, USP. Sodium hydroxide and/or hydrochloric acid added, as necessary, to adjust pH to 3.5 to 5.5.
- Buphenyl® (sodium phenylbutyrate) powder for oral, nasogastric, or gastrostomy tube administration contains sodium phenylbutyrate. Each gram of Buphenyl powder contains 0.94 g of sodium phenylbutyrate and the inactive ingredients calcium stearate and colloidal silicon dioxide.
- Ceftin for oral suspension when reconstituted with water provides the equivalent of 125 or 250 mg of cefuroxime (as cefuroxime axetil) per 5 mL of suspension. Ceftin for oral suspension contains the inactive ingredients acesulfame potassium, aspartame, povidone K30, stearic acid, sucrose, tutti-frutti flavoring, and xanthan gum.
- Cevimeline (30 mg) The pH of a 1% solution ranges from 4.6 to 5.6. Inactive ingredients include lactose monohydrate, hydroxypropyl cellulose, and magnesium stearate.
- Chemet (succimer) opaque white capsule for oral administration contains beads coated with 100 mg of succimer and is imprinted black with CHEMET 100. Inactive ingredients in medicated beads are povidone, sodium starch glycolate, starch, and sucrose. Inactive ingredients in

capsule are gelatin, iron oxide, titanium dioxide, and other ingredients.

- Colace® (docusate sodium) active ingredient: Colace capsules 100 mg contains 100 mg of docusate sodium. Inactive ingredients: D&C red No. 33, FD&C red No. 40, FD&C yellow No. 6, gelatin, glycerin, methylparaben, polyethylene glycol 400, propylene glycol, propylparaben, sorbitol, titanium dioxide. Colace capsules 50 mg contains 50 mg of docusate sodium.
- Colyte® with flavor packs is a colon lavage preparation provided as water-soluble components for solution. In solution this preparation with one flavor pack added delivers the following in grams per liter. Polyethylene glycol 3350 60.00, sodium chloride 1.46, potassium chloride 0.745, sodium bicarbonate 1.68, sodium sulfate 5.68, flavor ingredients 0.805. When dissolved in sufficient water to make 4 L, the final solution contains 125 mEq/L sodium, 10 mEq/L potassium, 20 mEq/L bicarbonate, 80 mEq/L sulfate, 35 mEq/L chloride, and 18 mEq/L polyethylene glycol 3350. The reconstituted solution is isoosmotic and has a mild salty taste. This preparation can be used without the flavor packs and is administered orally or via nasogastric tube. Each orange flavor pack (3.22 g) contains hypromellose, natural and artificial orange powder, saccharin sodium, colloidal silicon dioxide. Each citrus berry flavor pack (3.22 g) contains hypromellose, artificial citrus berry powder, saccharin sodium, colloidal silicon dioxide. Each lemon lime flavor pack (3.22 g) contains hypromellose, natural and artificial lemon lime powder, Prosweet® powder natural, saccharin sodium, colloidal silicon dioxide. Each cherry flavor pack (3.22 g) contains hypromellose, artificial cherry powder, saccharin sodium, colloidal silicon dioxide. Each pineapple flavor pack (3.22 g) contains hypromellose, artificial pineapple flavor powder, Magna Sweet™, saccharin sodium, colloidal silicon dioxide.
- Creon® 20 capsules are orally administered and contain 497 mg of delayed-release Minimicrospheres® of pancrelipase, which is of porcine pancreatic origin. Each Creon 20 capsule contains lipase 20,000 USP units, protease 75,000 USP units, and amylase 66,400 USP units. Inactive ingredients include dibutyl phthalate, dimethicone, hydroxypropylmethylcellulose phthalate, light mineral oil, and polyethylene glycol. The capsule shells contain gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The capsule imprinting ink contains dimethicone, 2-ethoxyethanol, shellac, soya lecithin, and titanium dioxide. Creon® 10 capsules are orally administered and contain 249 mg of delayed-release Minimicrospheres of pancrelipase, which is of porcine pancreatic origin. Each Creon 10 capsule contains lipase 10,000 USP units, protease 37,500 USP units, and amylase 33,200 USP units. Inactive ingredients include dibutyl phthalate, dimethicone, hydroxypropylmethylcellulose phthalate, light mineral oil, and polyethylene glycol. The capsule shells contain black iron oxide, gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The capsule imprinting ink contains dimethicone, 2-ethoxyethanol, shellac, soya lecithin, and titanium dioxide. Creon® 5 capsules are orally administered and contain 124 mg of delayed-release Minimicrospheres of pancrelipase, which is of porcine pancreatic origin. Each Creon 5 capsule contains lipase 5,000 USP units, protease 18,750 USP units, and amylase 16,600 USP units. Inactive ingredients include dibutyl phthalate, dimethicone, hydroxypropylmethylcellulose phthalate, light mineral oil, and polyethylene glycol. The capsule shells contain gelatin, red iron oxide, titanium dioxide, yellow iron oxide, and FD & C blue No. 2. The capsule imprinting ink contains dimethicone, 2-ethoxyethanol, shellac, soya lecithin, and titanium dioxide.
- Crixivan* (indinavir sulfate) capsules are formulated as a sulfate salt and are available for oral administration in strengths of 100, 200, 333, and 400 mg of indinavir (corresponding to 125, 250, 416.3, and 500 mg indinavir sulfate, respectively). Each capsule also contains the inactive ingredients anhydrous lactose and magnesium stearate. The capsule shell has the following inactive ingredients and dyes: gelatin, titanium dioxide, silicon dioxide, and sodium lauryl sulfate.
- Cuprimine, penicillamine, for oral administration contain either 125 or 250 mg of penicillamine. Each capsule contains the following inactive ingredients: D&C yellow No. 10, gelatin, lactose, magnesium stearate, and titanium dioxide. The 125-mg capsule also contains iron oxide.
- Cymbalta® (duloxetine hydrochloride) capsule contains enteric-coated pellets of 22.4, 33.7, or 67.3 mg of duloxetine hydrochloride equivalent to 20, 30, or 60 mg of duloxetine, respectively. These enteric-coated pellets are designed to prevent degradation of the drug in the acidic environment of the stomach. Inactive ingredients include FD&C blue No. 2, gelatin, hypromellose, hydroxypropylmethylcellulose acetate succinate, sodium lauryl sulfate, sucrose, sugar spheres, talc, titanium dioxide, and triethyl citrate. The 20- and 60-mg capsules also contain iron oxide yellow.
- Dalmane is available as capsules containing 15-or 30-mg flurazepam hydrochloride. Each 15-mg capsule also contains cornstarch, lactose, magnesium stearate, and talc; gelatin capsule shells contain the following dye systems: D&C red No. 28, FD&C red No. 40, FD&C yellow No. 6, and D&C yellow No. 10. Each 30-mg capsule also contains cornstarch, lactose, and magnesium stearate; gelatin capsule shells contain the following dye systems: FD&C blue No. 1, FD&C yellow No. 6, D&C yellow No. 10, and either FD&C red No. 3 or FD&C red No. 40. Flurazepam hydrochloride is chemically 7-chloro-1-[2-(diethylamino)ethyl]-5-(o -fluorophenyl)-1, 3-dihydro-2 H -1, 4-benzodiazepin-2-one dihydrochloride.
- Dantrium (dantrolene sodium) is supplied in capsules of 25 mg, 50 mg, and 100 mg. Inactive ingredients: Each capsule contains edible black ink, FD&C yellow No. 6, gelatin, lactose, magnesium stearate, starch, synthetic iron oxide red, synthetic iron oxide yellow, talc, and titanium dioxide.
- DDS®-Acidophilus is the source of a special strain of *Lactobacillus acidophilus* free of dairy products, corn, soy, and preservatives. Each capsule or tablet contains 1 billion viable DDS-1 *L. acidophilus* at the time of manufacturing. 1 g of powder contains two billion viable DDS-1 *L. acidophilus*.
- Demser* (Metyrosine) capsule contains 250 mg metyrosine. Inactive ingredients are colloidal silicon dioxide, gelatin, hydroxypropyl cellulose, magnesium stearate, titanium dioxide, and FD&C blue 2.
- Depakene (valproic acid) is a carboxylic acid designated as 2-propylpentanoic acid. Depakene capsules and syrup are antiepileptics for oral administration. Each soft elastic capsule contains 250 mg valproic acid. The syrup contains the equivalent of 250 mg valproic acid per 5 mL as the sodium salt. Inactive ingredients 250-mg capsules: corn oil, FD&C yellow No. 6, gelatin, glycerin, iron oxide, methylparaben, propylparaben, and titanium dioxide.
- Detrol LA capsules contain tolterodine tartrate. Detrol LA for oral administration contains 2 or 4 mg of tolterodine tartrate. Inactive ingredients are sucrose, starch, hypromellose, ethylcellulose, medium-chain triglycerides, oleic acid,

gelatin, and FD&C blue No. 2. The 2-mg capsules also contain yellow iron oxide. Both capsule strengths are imprinted with a pharmaceutical grade printing ink that contains shellac glaze, titanium dioxide, propylene glycol, and simethicone.

- Dexedrine (dextroamphetamine sulfate) Spansule sustained- release capsule is so prepared that an initial dose is released promptly and the remaining medication is released gradually over a prolonged period. Each capsule, with brown cap and clear body, contains dextroamphetamine sulfate. The 5-mg capsule is imprinted 5 mg and 3512 on the brown cap and is imprinted 5 mg and SB on the clear body. The 10-mg capsule is imprinted 10 mg and 3513 on the brown cap and is imprinted 10 mg and SB on the clear body. The 15-mg capsule is imprinted 15 mg and 3514 on the brown cap and is imprinted 15 mg and SB on the clear body. A narrow bar appears above and below 15 mg and 3514. Product reformulation in 1996 has caused a minor change in the color of the time-released pellets within each capsule. Inactive ingredients now consist of cetyl alcohol, D&C yellow No. 10, dibutyl sebacate, ethylcellulose, FD&C blue No. 1, FD&C blue No. 1 aluminum lake, FD&C red No. 40, FD&C yellow No. 6, gelatin, hypromellose, propylene glycol, povidone, silicon dioxide, sodium lauryl sulfate, sugar spheres, and trace amounts of other inactive ingredients.
- Divalproex sodium is a stable coordination compound comprised of sodium valproate and valproic acid in a 1:1 molar relationship and formed during the partial neutralization of valproic acid with 0.5 equivalent of sodium hydroxide. Divalproex sodium occurs as a white powder with a characteristic odor. Depakote Sprinkle Capsules are for oral administration. Depakote Sprinkle Capsules contain specially coated particles of divalproex sodium equivalent to 125 mg of valproic acid in a hard gelatin capsule. Inactive ingredients 125-mg Depakote Sprinkle Capsules: cellulosic polymers, D&C red No. 28, FD&C blue No. 1, gelatin, iron oxide, magnesium stearate, silica gel, titanium dioxide, and triethyl citrate.
- Dyazide capsule for oral use, with opaque red cap and opaque white body, contains hydrochlorothiazide 25 mg and triamterene 37.5 mg. Inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C red No. 33, FD&C yellow No. 6, gelatin, glycine, lactose, magnesium stearate, microcrystalline cellulose, povidone, polysorbate 80, sodium starch glycolate, titanium dioxide, and trace amounts of other inactive ingredients. Dyazide capsules meet Drug Release Test 3 as published in the USP 23 monograph for triamterene and hydrochlorothiazide capsules.
- Edecrin, ethacrynic acid, is supplied as 25-mg tablets for oral use. The tablets contain the following Inactive ingredients: colloidal silicon dioxide, lactose, magnesium stearate, starch and talc. Intravenous sodium Edecrin* (ethacrynate sodium) is a sterile freeze-dried powder and is supplied in a vial containing ethacrynate sodium equivalent to ethacrynic acid 50 mg. Inactive ingredient: Mannitol 62.5 mg.
- EES (erythromycin ethylsuccinate) granules are intended for reconstitution with water. Each 5-mL teaspoonful of reconstituted cherry-flavored suspension contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin. The pleasant-tasting, fruit-flavored liquids are supplied ready for oral administration. Inactive: EES granules: citric acid, FD&C red No. 3, magnesium aluminum silicate, sodium carboxymethylcellulose, sodium citrate, sucrose, and artificial flavor.
- Effexor XR is an extended-release capsule for oral administration. Effexor XR is formulated as an extended-release capsule for once-a-day oral administration. Drug release is controlled by diffusion through the coating membrane on the spheroids and is not pH dependent. Capsules contain venlafaxine hydrochloride equivalent to 37.5-mg, 75-mg, or 150-mg venlafaxine. Inactive ingredients consist of cellulose, ethylcellulose, gelatin, hypromellose, iron oxide, and titanium dioxide.
- Eldepryl (selegiline hydrochloride) contains 5 mg selegiline hydrochloride. Inactive ingredients are anhydrous citric acid, lactose, magnesium stearate, and microcrystalline cellulose.
- EMCYT (estramustine phosphate sodium) capsules are white and opaque, each containing estramustine phosphate sodium as the disodium salt monohydrate equivalent to 140 mg estramustine phosphate for oral administration. Each capsule also contains magnesium stearate, silicon dioxide, sodium lauryl sulfate, and talc. Gelatin capsule shells contain the pigment titanium dioxide.
- EMEND* (aprepitant) capsule contains either 80 or 125 mg of aprepitant and the following inactive ingredients: sucrose, microcrystalline cellulose, hydroxypropyl cellulose, and sodium lauryl sulfate. The capsule shell excipients are gelatin, titanium dioxide, and may contain sodium lauryl sulfate and silicon dioxide. The 125-mg capsule also contains red ferric oxide and yellow ferric oxide.
- Encora™ is a prescription vitamin and mineral nutritional supplement with essential fatty acids consisting of two capsules and two tablets on each blister card designated for AM and PM oral administration as follows. The AM tablet is an oval-shaped, light pink film-coated tablet containing the following ingredients: calcium (calcium carbonate) 400 mg, vitamin D_3 (cholecalciferol) 200 IU, vitamin C (as Ester-C®) 25 mg, folic acid USP 2 mg, vitamin B_6 (pyridoxine hydrochloride, USP 25 mg. The PM tablet is an oval-shaped, purple film-coated tablet containing the following ingredients: calcium (calcium carbonate) 600 mg, vitamin D_3 (cholecalciferol) 600 IU, vitamin C (as Ester-C) 25 mg, folic acid USP 0.5 mg, vitamin B_6 (pyridoxine hydrochloride, USP) 12.5 mg. The AM and PM capsules are a pink soft gelatin capsule containing the following ingredients: essential fatty acids (omega-3) 650 mg, DHA and EPA 550 mg, alpha-linolenic acid (ALA)100 mg, linoleic acid (LA) 10 mg, vitamin E (DL-alpha-tocopheryl acetate) 50 IU. Ester-C is a patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate. Eicosapentaenoic acid (EPA) to docosahexaenoic acid (DHA) ratio is approximately 2.7:1. Inactive ingredients: Tablets: acacia, butylated hydroxyanisole, butylated hydroxytoluene, colloidal silicon dioxide, cornstarch, croscarmellose sodium, D&C red No. 27 aluminum lake, hydrolyzed gelatin, lecithin, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, sodium lauryl sulfate, stearic acid, sucrose, talc, titanium dioxide, and vegetable oil. The AM tablet also contains FD&C blue No. 2 aluminum lake. The PM tablet also contains FD&C blue No. 1 aluminum lake. Capsules: D&C red No. 33, ethyl vanillin, FD&C red No. 40, gelatin, glycerine, soybean oil, and titanium dioxide.
- Entocort® EC capsules contains 3 mg of micronized budesonide with the following inactive ingredients: ethylcellulose, acetyltributyl citrate, methacrylic acid copolymer type C, triethyl citrate, antifoam M, polysorbate 80, talc, and sugar spheres. The capsule shells have

the following inactive ingredients: gelatin, iron oxide, and titanium dioxide.

- EryPed 200 and EryPed Drops (erythromycin ethylsuccinate for oral suspension) when reconstituted with water forms a suspension containing erythromycin ethylsuccinate equivalent to 200 mg erythromycin per 5 mL (teaspoonful) or 100 mg/2.5 mL (dropperful) with an appealing fruit flavor. EryPed 400 when reconstituted with water forms a suspension containing erythromycin ethylsuccinate equivalent to 400 mg of erythromycin per 5 mL (teaspoonful) with an appealing banana flavor. Inactives: EryPed 200, EryPed 400, and EryPed. Drops: Caramel, polysorbate, sodium citrate, sucrose, xanthan gum, and artificial flavors.
- Erythromycin delayed-release capsules contain enteric-coated pellets of erythromycin base for oral administration. Each erythromycin delayed-release capsule contains 250 mg of erythromycin base. Inactive ingredients: cellulosic polymers, citrate ester, D&C red No. 30, D&C yellow No. 10, magnesium stearate, and povidone. The capsule shell contains FD&C blue No. 1, FD&C red No. 3, gelatin, and titanium dioxide.
- Eskalith contains lithium carbonate, a white, light alkaline powder. Eskalith capsules with opaque gray cap and opaque yellow body are imprinted with the product name ESKALITH and SB and contain lithium carbonate 300 mg. Inactive ingredients consist of benzyl alcohol, cetylpyridinium chloride, D&C yellow No. 10, FD&C green No. 3, FD&C red No. 40, FD&C yellow No. 6, gelatin, lactose, magnesium stearate, povidone, sodium lauryl sulfate, titanium dioxide, and trace amounts of other inactive ingredients.
- Eulexin capsules contain flutamide and cornstarch, lactose, magnesium stearate, povidone, and sodium lauryl sulfate. Gelatin capsule shells may also contain benzyl alcohol, butylparaben, colloidal silicon dioxide, edetate calcium disodium, methylparaben, propylparaben, and sodium propionate, and the following dye systems: FD&C blue No. 1, FD&C red No. 3, FD&C yellow No. 6, titanium dioxide, black ink, and other inactive ingredients.
- Exelon® (rivastigmine tartrate) capsules contain rivastigmine tartrate, equivalent to 1.5, 3, 4.5, and 6 mg of rivastigmine base for oral administration. Inactive ingredients are hydroxypropyl methylcellulose, magnesium stearate, microcrystalline cellulose, and silicon dioxide. Each hard gelatin capsule contains gelatin, titanium dioxide, and red and/or yellow iron oxides.
- Exubera® consists of blisters containing human insulin inhalation powder, which are administered using the Exubera inhaler. Each unit dose blister of Exubera contains a 1-or 3-mg dose of insulin in a homogeneous powder formulation containing sodium citrate (dihydrate), mannitol, glycine, and sodium hydroxide.
- Ferrochel® soft gelatin capsule for oral administration contains iron (as Ferrochel ferrous bis-glycinate chelate elemental iron) 70 mg; vitamin C as Ester-C patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate; ascorbic acid (as calcium ascorbate) 150 mg; threonic acid (as calcium threonate) 2 mg; vitamin B_{12} (cyanocobalamin) 10 μg; desiccated stomach substance100 mg. Inactive ingredients: soybean oil, gelatin, glycerine, yellow beeswax, lecithin (unbleached), titanium dioxide, methyl-/propylparaben blend, ethyl vanillin, FD&C red No. 40, FD&C yellow No. 6, FD&C blue No. 1.
- Focalin™ XR (dexmethylphenidate hydrochloride) extended-release capsules are an extended-release formulation of dexmethylphenidate with a bimodal release profile. Focalin XR uses the proprietary SODAS® (spheroidal oral drug absorption system) technology. Each bead-filled Focalin XR capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of dexmethylphenidate and a second delayed release of dexmethylphenidate. Focalin XR 5-, 10-, and 20-mg capsules provide in a single dose the same amount of dexmethylphenidate as dosages of 2.5, 5, or 10 mg of Focalin™ tablets given bid. Inactive ingredients: ammonio methacrylate copolymer, FD&C blue No. 2 (5-mg strength), FDA/E172 yellow iron oxide (10-mg strength), gelatin, ink tan SW-8010, methacrylic acid copolymer, polyethylene glycol, sugar spheres, talc, titanium dioxide, and triethyl citrate.
- Foradil® Aerolizer® consists of a capsule dosage form containing a dry powder formulation of Foradil (formoterol fumarate) intended for oral inhalation only with the Aerolizer inhaler. Each clear, hard gelatin capsule contains a dry powder blend of 12 μg of formoterol fumarate and 25 mg of lactose as a carrier.
- Geodon® is available as Geodon capsules (ziprasidone hydrochloride) for oral administration and as Geodon for injection (ziprasidone mesylate) for intramuscular injection.
- Geodon capsules contain a monohydrochloride, monohydrate salt of ziprasidone. Geodon capsules are supplied for oral administration in 20 mg (blue/white), 40 mg (blue/blue), 60 mg (white/white), and 80 mg (blue/white) capsules. Geodon capsules contain ziprasidone hydrochloride monohydrate, lactose, pregelatinized starch, and magnesium stearate.
- Hep-Forte capsule contains vitamin A (palmitate) 1, 200 IU, vitamin E (d-alpha tocopherol) 10 IU, vitamin C (ascorbic acid) 10 mg, folic acid 0.06 mg, vitamin B_1 (thiamine mononitrate) 1 mg, vitamin B_2 (riboflavin) 1 mg, niacinamide 10 mg, vitamin B_6 (pyridoxine HCl) 0.5 mg, vitamin B_{12} (cobalamin) 1 μg, biotin 3.3 μg, pantothenic acid 2 mg, choline bitartrate 21 mg, zinc (zinc sulfate) 2 mg, desiccated liver 194.4 mg, liver concentrate 64.8 mg, liver fraction number 2 64.8 mg, yeast (dried) 64.8 mg, DL-methionine 10 mg, inositol 10 mg. Other ingredients: microcrystalline cellulose, stearic acid, croscarmellose sodium, silicon dioxide, magnesium stearate, titanium dioxide coating.
- Hexalen (altretamine) capsules contain 50 mg of altretamine for oral administration. Inert ingredients include lactose, anhydrous and calcium stearate. Altretamine is a white crystalline powder melting at 172°C ± 1°C.
- Hytrin (terazosin hydrochloride) is supplied in four dosage strengths containing terazosin hydrochloride equivalent to 1 mg, 2 mg, 5 mg, or 10 mg of terazosin. Inactive ingredients: 1-mg capsules: gelatin, glycerin, iron oxide, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin. 2-mg capsules: D&C yellow No. 10, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin. 5-mg capsules: D&C red No. 28, FD&C red No. 40, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin. 10-mg capsules: FD&C blue No. 1, gelatin, glycerin, methylparaben, mineral oil, polyethylene glycol, povidone, propylparaben, titanium dioxide, and vanillin.

- Imodium® (loperamide hydrochloride) is available in 2-mg capsules. The inactive ingredients are lactose, cornstarch, talc, and magnesium stearate. Imodium capsules contain FD&C yellow No. 6.
- Indocin for oral administration contain either 25 or 50 mg of indomethacin and the following inactive ingredients: colloidal silicon dioxide, FD&C blue 1, FD&C red 3, gelatin, lactose, lecithin, magnesium stearate, and titanium dioxide.
- Inspra for oral administration contains 25 or 50 mg of eplerenone and the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, hypromellose, sodium lauryl sulfate, talc, magnesium stearate, titanium dioxide, polyethylene glycol, polysorbate 80, and iron oxide yellow and iron oxide red.
- Kadian® capsules 20, 30, 50, 60 and 100 mg contain identical polymer-coated sustained-release pellets of morphine sulfate for oral administration. Each Kadian sustained-release capsule contains either 20, 30, 50, 60, or 100 mg of morphine sulfate USP and the following inactive ingredients common to all strengths: hypromellose, ethylcellulose, methacrylic acid copolymer, polyethylene glycol, diethyl phthalate, talc, cornstarch, and sucrose. The 20-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C yellow No. 10, titanium dioxide, and black ink SW-9009. The 30-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, FD&C red No. 3, FD&C blue No. 1, titanium dioxide and black ink S-1–8114 or S-1–8115. The 50-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C red No. 28, FD&C red No. 40, FD&C blue No. 1, titanium dioxide, and black ink SW-9009. The 60-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C red No. 28, FD&C red No. 40, FD&C blue No. 1, titanium dioxide, and black ink S-1–8114 or S-1–8115. The 100-mg capsule shell contains gelatin, silicon dioxide, sodium lauryl sulfate, D&C yellow No. 10, FD&C blue No. 1, titanium dioxide, and black ink SW-9009.
- K-LOR (potassium chloride for oral solution, USP) packet of 20 mEq powder contains potassium 20 mEq and chloride 20 mEq provided by potassium chloride 1.5 g. Inactive ingredients: FD&C yellow No. 6, maltodextrin (contains corn derivative), malic acid, saccharin, silica gel, and natural flavoring.
- Kristalose™ (lactulose) is a synthetic disaccharide in the form of crystals for reconstitution prior to use for oral administration. Each 10 g of lactulose contains less than 0.3 g galactose and lactose as a total sum. The pH range is 3 to 7. Lactulose is a colonic acidifier, which promotes laxation.
- Lanoxicaps (digoxin) is a stable solution of digoxin enclosed within a soft gelatin capsule for oral use. Each capsule contains the labeled amount of digoxin USP dissolved in a solvent comprised of polyethylene glycol 400 USP, 8 percent ethyl alcohol, propylene glycol USP, and purified water USP. Inactive ingredients in the capsule shell include D&C yellow No. 10 (0.1-mg and 0.2-mg capsules), FD&C blue No. 1 (0.2-mg capsule), gelatin, glycerin, methylparaben and propylparaben (added as preservatives), purified water, and sorbitol. Capsules are printed with edible ink.
- Lescol® (fluvastatin sodium) is supplied as extended-release tablets containing fluvastatin sodium, equivalent to 80 mg of fluvastatin, for oral administration. Active ingredient: fluvastatin sodium. Inactive ingredients in capsules: gelatin, magnesium stearate, microcrystalline cellulose, pregelatinized starch (corn), red iron oxide, sodium lauryl sulfate, talc, titanium dioxide, yellow iron oxide, and other ingredients. Capsules may also include benzyl alcohol, black iron oxide, butylparaben, carboxymethylcellulose sodium, edetate calcium disodium, methylparaben, propylparaben, silicon dioxide, and sodium propionate. Inactive ingredients in extended-release tablets: microcrystalline cellulose, hydroxypropyl cellulose, hydroxypropylmethylcellulose, potassium bicarbonate, povidone, magnesium stearate, iron oxide yellow, titanium dioxide, and polyethylene glycol 8000.
- Lotrel is a combination of amlodipine besylate and benazepril hydrochloride. The capsules are formulated in four different strengths for oral administration with a combination of amlodipine besylate equivalent to 2.5, 5, or 10 mg of amlodipine, with 10 or 20 mg of benazepril hydrochloride providing for the following available combinations: 2.5/10 mg, 5/10 mg, 5/20 mg, and 10/20 mg. The inactive ingredients of the capsules are calcium phosphate, cellulose compounds, colloidal silicon dioxide, crospovidone, gelatin, hydrogenated castor oil, iron oxides, lactose, magnesium stearate, polysorbate 80, silicon dioxide, sodium lauryl sulfate, sodium starch (potato) glycolate, starch (corn), talc, and titanium dioxide.
- Lyrica (pregabalin) capsules are supplied as imprinted hard shell capsules containing 25, 50, 75, 100, 150, 200, 225, and 300 mg of pregabalin, along with lactose monohydrate, cornstarch, and talc as inactive ingredients. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid that may or may not be present in the capsule shells. The imprinting ink contains shellac, black iron oxide, propylene glycol, and potassium hydroxide.
- Marinol® capsule, dronabinol, is supplied as round, soft gelatin capsules containing either 2.5 mg, 5 mg, or 10 mg dronabinol. Each Marinol capsule is formulated with the following inactive ingredients: FD&C blue No. 1 (5 mg), FD&C red No. 40 (5 mg), FD&C yellow No. 6 (5 mg and 10 mg), gelatin, glycerin, methylparaben, propylparaben, sesame oil, and titanium dioxide.
- Matulane (procarbazine hydrochloride) is available as capsules containing the equivalent of 50 mg procarbazine as the hydrochloride. Each capsule also contains cornstarch, mannitol, and talc. Gelatin capsule shells contain parabens (methyl and propyl), potassium sorbate, titanium dioxide, FD&C yellow No. 6, and D&C yellow No. 10.
- Maxair Autohaler (pirbuterol acetate) is a pressurized metered-dose aerosol unit for oral inhalation. It provides a fine-particle suspension of pirbuterol acetate in the propellant mixture of trichloromonofluoromethane and dichlorodifluoromethane with sorbitan trioleate. Each actuation delivers 253 μg of pirbuterol (as pirbuterol acetate) from the valve and 200 μg of pirbuterol (as pirbuterol acetate) from the mouthpiece. The unit is breath-actuated such that the medication is delivered automatically during inspiration without the need for the patient to coordinate actuation with inspiration. Each 14.0 g canister provides 400 inhalations and each 2.8 g canister provides 80 inhalations.
- Meridia® (sibutramine hydrochloride monohydrate) capsule contains 5 mg, 10 mg, and 15 mg of sibutramine hydrochloride monohydrate. It also contains as inactive ingredients: lactose monohydrate, NF; microcrystalline cellulose, NF; colloidal silicon dioxide, NF; and magnesium stearate, NF in a hard-gelatin capsule [which contains

titanium dioxide, USP; gelatin; FD&C blue No. 2 (5- and 10-mg capsules only); D&C yellow No. 10 (5- and 15-mg capsules only), and other inactive ingredients].

- Metadate CD is a central nervous system (CNS) stimulant. The extended-release capsules comprise both immediate-release (IR) and extended-release (ER) beads such that 30% of the dose is provided by the IR component and 70% of the dose is provided by the ER component. Metadate CD is available in three capsule strengths containing 10 mg (3 mg IR; 7 mg ER), 20 mg (6 mg IR; 14 mg ER), or 30 mg (9 mg IR; 21 mg ER) of methylphenidate hydrochloride for oral administration. Metadate CD also contains the following inert ingredients: sugar spheres, povidone, hydroxypropylmethylcellulose and polyethylene glycol, ethylcellulose aqueous dispersion, dibutyl sebacate, gelatin, titanium dioxide, FD&C blue No. 2, FDA/E172 yellow iron oxide (10-mg capsules), FDA/E172 red iron oxide (30-mg capsules).
- Metamucil contains psyllium husk (from the plant *Plantago ovata*). Each dose of Metamucil powder and Metamucil fiber wafers contains approximately 3.4 g of psyllium husk (or 2.4 g of soluble fiber). A listing of ingredients and nutrition information is available in the listing of Metamucil fiber laxative in the Nonprescription Drug section. Metamucil smooth texture sugar-free regular flavor and Metamucil capsules contain no sugar and no artificial sweeteners. Metamucil smooth texture sugar-free orange flavor contains aspartame (phenylalanine content of 25 mg per dose). Metamucil powdered products are gluten-free.
- Nalfon® (fenoprofen calcium capsules, USP) contain fenoprofen calcium as the dihydrate in an amount equivalent to 200 mg (0.826 mmol) or 300 mg (1.24 mmol) of fenoprofen. The capsules also contain cellulose, gelatin, iron oxides, silicone, titanium dioxide, and other inactive ingredients. The 300-mg capsules also contain D&C yellow No. 10 and FD&C yellow No. 6.
- Neurontin® (gabapentin) capsules are supplied as imprinted hard shell capsules containing 100 mg, 300 mg, and 400 mg of gabapentin. The inactive ingredients for the capsules are lactose, cornstarch, and talc. The 100-mg capsule shell contains gelatin and titanium dioxide. The 300-mg capsule shell contains gelatin, titanium dioxide, and yellow iron oxide. The 400-mg capsule shell contains gelatin, red iron oxide, titanium dioxide, and yellow iron oxide. The imprinting ink contains FD&C blue No. 2 and titanium dioxide.
- Nexium® (esomeprazole magnesium) delayed-release capsules contain 20 or 40 mg of esomeprazole (present as 22.3 or 44.5 mg esomeprazole magnesium trihydrate) in the form of enteric-coated pellets with the following inactive ingredients: glyceryl monostearate 40–50, hydroxypropyl cellulose, hypromellose, magnesium stearate, methacrylic acid copolymer type C, polysorbate 80, sugar spheres, talc, and triethyl citrate. The capsule shells have the following inactive ingredients: gelatin, FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, titanium dioxide, shellac, ethyl alcohol, isopropyl alcohol, *N*-butyl alcohol, propylene glycol, sodium hydroxide, polyvinyl pyrrolidone, and D&C yellow No. 10.
- Nimotop® (nimodipine) capsules are formulated as soft gelatin capsules for oral administration. Each liquid-filled capsule contains 30 mg of nimodipine in a vehicle of glycerin, peppermint oil, purified water, and polyethylene glycol 400. The soft gelatin capsule shell contains gelatin, glycerin, purified water, and titanium dioxide.
- Norvasc® is the besylate salt of amlodipine. Norvasc (amlodipine besylate) tablets are formulated as white tablets equivalent to 2.5, 5, and 10 mg of amlodipine for oral administration. In addition to the active ingredient, amlodipine besylate, each tablet contains the following inactive ingredients: microcrystalline cellulose, dibasic calcium phosphate anhydrous, sodium starch glycolate, and magnesium stearate.
- Norvir (ritonavir) soft gelatin capsules are available for oral administration in a strength of 100 mg ritonavir with the following inactive ingredients: butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxyl 35 castor oil, and titanium dioxide.
- Omnicef® (cefdinir) capsules contain 300 mg cefdinir and the following inactive ingredients: carboxymethylcellulose calcium, NF; polyoxyl 40 stearate, NF; and magnesium stearate, NF. The capsule shells contain FD&C blue No. 1; FD&C red No. 40; D&C red No. 28; titanium dioxide, NF; gelatin, NF; silicon dioxide, NF; and sodium lauryl sulfate, NF.
- OxyIR® oxycodone is 14-hydroxydihydrocodeinone, a white odorless crystalline powder which is derived from the opium alkaloid thebaine. OxyIR oral capsules: Each 5 mg of OxyIR capsules contains oxycodone hydrochloride. 5 mg: Inactive ingredients: FD&C blue No. 2, FD&C yellow No. 6, gelatin, hypromellose, maize starch, polyethylene glycol, polysorbate 80, red iron oxide, silicon dioxide, sodium laurel sulfate, sucrose, titanium dioxide, and yellow iron oxide.
- Pentasa (mesalamine) for oral administration is a controlled-release formulation of mesalamine. Each 250-mg capsule contains 250 mg of mesalamine and acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains D&C yellow No. 10, FD&C blue No. 1, FD&C green No. 3, gelatin, titanium dioxide, and other ingredients. Each 500-mg capsule contains 500 mg of mesalamine. It also contains the following inactive ingredients: acetylated monoglyceride, castor oil, colloidal silicon dioxide, ethylcellulose, hydroxypropyl methylcellulose, starch, stearic acid, sugar, talc, and white wax. The capsule shell contains FD&C blue No. 1, gelatin, titanium dioxide, and other ingredients.
- Phenytek® (phenytoin sodium) capsule (extended phenytoin sodium capsule, USP) for oral administration contains 200 or 300 mg of phenytoin sodium. Each capsule also contains the following inactive ingredients: black iron oxide, colloidal silicon dioxide, D&C yellow no. 10 aluminum lake, FD&C blue No. 1, FD&C blue no. 1 aluminum lake, FD&C blue no. 2 aluminum lake, FD&C red no. 40 aluminum lake, gelatin, hydroxyethyl cellulose, magnesium oxide, magnesium stearate, microcrystalline cellulose, pharmaceutical glaze, povidone, propylene glycol, silicon dioxide, sodium lauryl sulfate and titanium dioxide. Phenytek capsules, 200 mg and 300 mg, meet USP Dissolution Test 3.
- PhosLo Gelcaps (calcium acetate) contains 667 mg calcium acetate, USP [anhydrous; Ca (CH 3 COO) 2; MW = 158.17 g] equal to 169 mg (8.45 mEq) calcium, and 10 mg of the inert binder, polyethylene glycol 8000 NF. The gelatin cap and body have the following inactive ingredients: FD&C blue No. 1, D&C red No. 28, titanium dioxide, USP, and gelatin, USP.
- Precare. Each powder-filled capsule for oral administration contains Ferrochel* (elemental iron) 80 mg, polysaccharide

iron (elemental iron) 70 mg, vitamin C as Ester-C, ascorbic acid (as calcium ascorbate) 60 mg, threonic acid (as calcium threonate) 0.8 mg, folic acid, USP 1 mg, vitamin B_{12} (cyanocobalamin) 25 μg. Ferrochel (ferrous bisglycinate chelate) is a registered trademark of Albion International, Inc., Clearfield, Utah, and is protected under U. S. Patent Nos. 4, 599, 152 and 4, 830, 716. Ester-C is a patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate. Ester-C is a licensed trademark of Zila Nutraceuticals, Inc. Inactive ingredients: Magnesium stearate, silicon dioxide, gelatin, titanium dioxide, FD&C red No. 40, D&C red No. 28, FD&C blue No. 1, pharmaceutical glaze.

- Prelief powder: Each one-fourth teaspoon usage of powder is comparable to two tablets. The powder dissolves rapidly in food or nonalcoholic beverages. Tablets are recommended for taking with alcoholic beverages.
- Prevacid® (lansoprazole) delayed-release capsules contain the active ingredient, lansoprazole, in the form of enteric-coated granules and are available in two dosage strengths: 15 mg and 30 mg of lansoprazole per capsule. Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole, hydroxypropyl cellulose, low substituted hydroxypropylcellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C red No. 28, FD&C blue No. 1, FD&C green No. 3*, and FD&C red No. 40.
- Prevacid NapraPAC™ 375 is a combination package containing Naprosyn 375-mg tablets and Prevacid 15-mg capsules. Prevacid NapraPAC™ 500 is a combination package containing Naprosyn 500-mg tablets and Prevacid 15-mg capsules. Naprosyn tablets contain 250 mg, 375 mg, or 500 mg of naproxen (active ingredient) and croscarmellose sodium, iron oxides, povidone, and magnesium stearate (inactive ingredients). Prevacid capsules contain enteric-coated granules consisting of active ingredient, lansoprazole (15 mg), and inactive ingredients, hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C red No. 28, FD&C blue No. 1, FD&C green No. 3, and FD&C red No. 40 (inactive ingredients).
- Prevpac consists of a daily administration pack containing two Prevacid 30-mg capsules, four amoxicillin 500-mg capsules, USP, and two clarithromycin 500-mg tablets, USP, for oral administration. Prevacid (lansoprazole) delayed-release capsules. Each delayed-release capsule contains enteric-coated granules consisting of lansoprazole (30 mg), hydroxypropyl cellulose, low substituted hydroxypropyl cellulose, colloidal silicon dioxide, magnesium carbonate, methacrylic acid copolymer, starch, talc, sugar sphere, sucrose, polyethylene glycol, polysorbate 80, and titanium dioxide. Components of the gelatin capsule include gelatin, titanium dioxide, D&C red No. 28, FD&C blue No. 1, and FD&C red No. 40. The yellow opaque capsules contain amoxicillin trihydrate equivalent to 500 mg of amoxicillin. Inactive ingredients: Capsule shells—yellow ferric oxide, titanium dioxide, gelatin, black ferric oxide. Capsule contents—cellulose microcrystalline and magnesium stearate.
- PrimaCare® is a prescription prenatal/postnatal multivitamin/mineral capsule and tablet combination with essential fatty acids that consists of two dosage forms on each blister card designated as AM and PM, as follows: The AM dose is a dye-free, white soft gelatin capsule containing the following ingredients: essential fatty acids (as OmegaNate™): omega-3 fatty acids 300 mg, linoleic acid 30 mg, linolenic acid 30 mg, vitamin D_3 (cholecalciferol), 170 IU vitamin E (DL-alpha-tocopheryl acetate) 30 IU, calcium (calcium carbonate) 150 mg. The PM dose is a dye-free, oval shaped pink film-coated tablet containing the following ingredients: biotin 35 μg; folic acid, USP 1 mg; vitamin B_1 (thiamine mononitrate, USP) 3 mg; vitamin B_2 (riboflavin, USP) 3.4 mg; vitamin B_3 (niacinamide) 20 mg; vitamin B_6 (pyridoxine HCl, USP) 50 mg; vitamin B_{12} (cyanocobalamin) 12 μg; vitamin C (as Ester-C) 100 mg; vitamin D_3 (cholecalciferol) 230 IU; vitamin K 90 μg; pantothenic acid 7 mg; calcium (as CalciPure™ calcium carbonate) 250 mg; chromium 45 μg; copper (cupric oxide) 1.3 mg; iron (as MicroMask® ferrous fumarate) 30 mg; molybdenum 50 μg; selenium 75 μg; zinc (zinc oxide, USP) 11 mg.*Ester-C is a patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate. Ester-C is a licensed trademark of Zila Nutraceuticals, Inc. Inactive ingredients: Capsule: Natural wax, natural oils, and other ingredients. Dye free. Tablet: Cellulose polymers, flow agents, natural wax, natural oils, flavor, and other ingredients. Dye free.
- PrimaCare ONE is a prescription prenatal/postnatal multivitamin/mineral capsule with essential fatty acids. Each purple soft gelatin capsule contains omega-3 fatty acids 300 mg, linoleic acid 30 mg, linolenic acid 30 mg. Folic acid, USP 1 mg; vitamin B_6 (as pyridoxine HCl) 25 mg; vitamin C (as Ester-C)* 25 mg; vitamin D_3 (from cholecalciferol) 170 IU; vitamin E (from DL-alpha-tocopheryl acetate) 30 IU; calcium 150 mg; iron (as carbonyl iron) 27 mg. Inactive ingredients: Gelatin, vegetable shortening, glycerin, soybean oil, yellow beeswax, lecithin, titanium dioxide, methylparaben, ethylvanillin, D&C red No. 33, propylparaben, FD&C blue No. 1.
- Prograf capsules (tacrolimus capsules) contain the equivalent of 0.5 mg, 1 mg, or 5 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 0.5-mg capsule shell contains gelatin, titanium dioxide, and ferric oxide; the 1-mg capsule shell contains gelatin and titanium dioxide; and the 5-mg capsule shell contains gelatin, titanium dioxide, and ferric oxide.
- Prometrium® (progesterone, USP) capsules contain micronized progesterone for oral administration. Prometrium capsules are available in multiple strengths to afford dosage flexibility for optimum management. Prometrium capsules contain 100 or 200 mg micronized progesterone. The inactive ingredients for Prometrium capsules 100 mg include peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C yellow No. 10, and FD&C red No. 40. The inactive ingredients for Prometrium capsules 200 mg include peanut oil NF, gelatin NF, glycerin USP, lecithin NF, titanium dioxide USP, D&C yellow No. 10, and FD&C yellow No. 6.
- Prozac® (fluoxetine hydrochloride) Weekly™ capsules, a delayed-release formulation, contain enteric-coated pellets of fluoxetine hydrochloride equivalent to 90 mg (291 μmol) of fluoxetine. The capsules also contain D&C yellow No. 10, FD&C blue No. 2, gelatin, hypromellose, hydroxypropyl methylcellulose acetate succinate, sodium lauryl

sulfate, sucrose, sugar spheres, talc, titanium dioxide, triethyl citrate, and other inactive ingredients.

- Rebetol contains ribavirin. Each capsule consists of a white powder in a white, opaque gelatin capsule. Each capsule contains 200 mg ribavirin and the inactive ingredients microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, and magnesium stearate. The capsule shell consists of gelatin, sodium lauryl sulfate, silicon dioxide, and titanium dioxide. The capsule is printed with edible blue pharmaceutical ink which is made of shellac, anhydrous ethyl alcohol, isopropyl alcohol, *N*-butyl alcohol, propylene glycol, ammonium hydroxide, and FD&C blue No. 2 aluminum lake.
- ReishiMax® GLp is a proprietary, standardized extract of Reishi (Ganoderma lucidum) mushroom. ReishiMax supports healthy immune system function by stimulating cell-mediated immunity. Each capsule contains 495 mg of standardized Reishi mushroom extract and 5 mg of Reishi cracked spores standardized to 6% triterpenes and 13.5% polysaccharides.
- Relenza is zanamivir. Rotadisk® contains four regularly spaced double-foil blisters with each blister containing a powder mixture of 5 mg of zanamivir and 20 mg of lactose (which contains milk proteins). The contents of each blister are inhaled using a specially designed breath-activated plastic device for inhaling powder called the Diskhaler. After a Relenza Rotadisk is loaded into the Diskhaler, a blister that contains medication is pierced and the zanamivir is dispersed into the air stream created when the patient inhales through the mouthpiece. The amount of drug delivered to the respiratory tract will depend on patient factors such as inspiratory flow. Under standardized in vitro testing, Relenza Rotadisk delivers 4 mg of zanamivir from the Diskhaler device when tested at a pressure drop of 3 kPa (corresponding to a flow rate of about 62–65 L/minutes) for 3 seconds.
- Retrovir (zidovudine) capsules are for oral administration. Each capsule contains 100 mg of zidovudine and the inactive ingredients cornstarch, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 100-mg empty hard gelatin capsule, printed with edible black ink, consists of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical shellac, soya lecithin, and titanium dioxide. The blue band around the capsule consists of gelatin and FD&C blue No. 2.
- Ritalin LA® (methylphenidate hydrochloride) extended-release capsules are an extended-release formulation of methylphenidate with a bimodal release profile. Ritalin LA uses the proprietary SODAS™ (Spheroidal Oral Drug Absorption System) technology. Each bead-filled Ritalin LA capsule contains half the dose as immediate-release beads and half as enteric-coated, delayed-release beads, thus providing an immediate release of methylphenidate and a second delayed release of methylphenidate. Ritalin LA 10-, 20-, 30-, and 40-mg capsules provide in a single dose the same amount of methylphenidate as dosages of 5, 10, 15, or 20 mg of Ritalin® tablets given bid. Inactive ingredients: ammonio methacrylate copolymer, black iron oxide (10- and 40-mg capsules only), gelatin, methacrylic acid copolymer, polyethylene glycol, red iron oxide (10- and 40-mg capsules only), sugar spheres, talc, titanium dioxide, triethyl citrate, and yellow iron oxide (10-, 30-, and 40-mg capsules only).
- Robitussin capsule. Active ingredients (in each capsule): guaifenesin, USP 200 mg, pseudoephedrine HCl USP 30 mg. Inactive ingredients: FD&C green no. 3, gelatin, glycerin, mannitol, pharmaceutical glaze, polyethylene glycol, povidone, propylene glycol, sorbitan, sorbitol, titanium dioxide, water. Active ingredients (in each capsule): acetaminophen, USP 250 mg; dextromethorphan HBr, USP 10 mg; guaifenesin, USP 100 mg; pseudoephedrine HCl, USP 30 mg. Inactive ingredients: D&C yellow no. 10, FD&C red no. 40, fractionated coconut oil, gelatin, glycerin, mannitol, pharmaceutical ink, polyethylene glycol, povidone, propylene glycol, purified water, sorbitol, sorbitol anhydrides. Active ingredients (in each capsule): dextromethorphan HBr, USP 10 mg; guaifenesin, USP 200 mg; pseudoephedrine HCl, USP 30 mg. Inactive ingredients (Capsules): FD&C blue no. 1, FD&C red no. 40, gelatin, glycerin, mannitol, pharmaceutical glaze, polyethylene glycol, povidone, propylene glycol, sorbitan, sorbitol, titanium dioxide, water.
- Senokot™ brand wheat bran, made with 100% natural bran, provides 4.6 g of wheat bran per serving. Ingredients: Orange flavor: fructose, wheat bran, sucrose, gum arabic, citric acid, locust bean gum, natural orange flavor, beta-carotene, xanthan gum. Calories 70, sodium 5 mg, total carbohydrates 16 g, dietary fiber 3 g, soluble fiber 1 g, insoluble fiber 2 g, sugars 12 g, iron 0.6 mg.
- Serevent Diskus (salmeterol xinafoate inhalation powder) is a specially designed plastic inhalation delivery system containing a double-foil blister strip of a powder formulation of salmeterol xinafoate intended for oral inhalation only. The Diskus®, which is the delivery component, is an integral part of the drug product. Each blister on the double-foil strip within the unit contains 50 μg of salmeterol administered as the salmeterol xinafoate salt in 12.5 mg of formulation containing lactose (which contains milk proteins). After a blister-containing medication is opened by activating the Diskus, the medication is dispersed into the air stream created by the patient inhaling through the mouthpiece. Under standardized in vitro test conditions, Serevent Diskus delivers 47 μg when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function [mean forced expiratory volume in 1 second (FEV 1) 20–30% of predicted], mean peak inspiratory flow (PIF) through a Diskus was 82.4 L/min (range 46.1–115.3 L/min). The actual amount of drug delivered to the lung will depend on patient factors, such as inspiratory flow profile.
- Seromycin® (cycloserine capsules, USP) capsule contains cycloserine, 250 mg (2.45 mmol); D&C yellow No. 10; FD&C blue No. 1; FD&C red No. 3; FD&C yellow No. 6; gelatin; iron oxide; talc; titanium dioxide; and other inactive ingredients.
- Soriatane (acitretin), a retinoid, is available in 10-mg and 25-mg gelatin capsules for oral administration. Each capsule contains acitretin, microcrystalline cellulose, sodium ascorbate, gelatin, black monogramming ink, and maltodextrin (a mixture of polysaccharides). Gelatin capsule shells contain gelatin, iron oxide (yellow, black, and red), and titanium dioxide. They may also contain benzyl alcohol, carboxymethylcellulose sodium, edetate calcium disodium.
- Sutent® (atomoxetine HCl) capsule contains atomoxetine HCl equivalent to 10, 18, 25, 40, or 60 mg of atomoxetine. The capsules also contain pregelatinized starch and dimethicone. The capsule shells contain gelatin, sodium lauryl sulfate, and other inactive ingredients. The capsule shells also contain one or more of the following: FD&C blue No. 2, synthetic yellow iron oxide,

titanium dioxide. The capsules are imprinted with edible black ink.

- Suprax (cefixime) for oral suspension is a semisynthetic cephalosporin antibiotic for oral administration. After reconstitution each teaspoonful (5 mL) of suspension contains 100 mg of cefixime as the trihydrate. In addition, the suspension contains the following inactive ingredients: strawberry flavor, sodium benzoate, sucrose, colloidal silicon dioxide, and xanthan gum.
- Surmontil (trimipramine maleate) capsules contain trimipramine maleate equivalent to 25 mg, 50 mg, or 100 mg of trimipramine as the base. The inactive ingredients present are black ink, FD&C blue 1, gelatin, lactose, magnesium stearate, and titanium dioxide. The 25-mg dosage strength also contains benzyl alcohol, D&C yellow 10, edetate calcium disodium, FD&C yellow 6, parabens (butyl, propyl, and methyl), sodium lauryl sulfate, and sodium propionate; the 50-mg dosage strength also contains benzyl alcohol, D&C red 28, edetate calcium disodium, FD&C red 40, FD&C yellow 6, parabens (butyl, propyl, and methyl), sodium lauryl sulfate, and sodium propionate.
- Sutent® (sunitinib malate) capsules are supplied as printed hard shell capsules containing sunitinib malate equivalent to 12.5, 25, or 50 mg of sunitinib together with mannitol, croscarmellose sodium, povidone (K-25), and magnesium stearate as inactive ingredients. The orange gelatin capsule shells contain titanium dioxide and red iron oxide. The caramel gelatin capsule shells also contain yellow iron oxide and black iron oxide. The printing ink contains shellac, propylene glycol, sodium hydroxide, povidone, and titanium dioxide.
- Symbyax® (olanzapine and fluoxetine HCl capsules) combines two psychotropic agents, olanzapine (the active ingredient in Zyprexa® and Zyprexa Zydis®) and fluoxetine hydrochloride (the active ingredient in Prozac, Prozac Weekly™, and Sarafem®). Symbyax capsules are available for oral administration in the following strength combinations: 6 mg/25 mg, 6 mg/50 mg, 12 mg/25 mg, 12 mg/50 mg. Each capsule also contains pregelatinized starch, gelatin, dimethicone, titanium dioxide, sodium lauryl sulfate, edible black ink, red iron oxide, yellow iron oxide, and/or black iron oxide.
- Targretin® (bexarotene) capsule also contains the following inactive ingredients: polyethylene glycol 400, NF; polysorbate 20, NF; povidone, USP; and butylated hydroxyanisole, NF. The capsule shell contains gelatin, NF; sorbitol special-glycerin blend; and titanium dioxide, USP.
- Tegreen® is a standardized decaffeinated polyphenol extract of the fresh green tea leaves with proven free radical scavenging and antioxidant properties. Each 250-mg capsule contains a 20:1 extract of green tea leaves (*Camellia sinensis*) standardized to a minimum 97% pure polyphenols including 162 mg catechins, of which 95 mg is EGCg, 37 mg is ECG, and 15 mg is EGC.
- Tessalon Perle contains benzonatate, USP 100 mg. Each Tessalon capsule contains benzonatate, USP 200 mg. Tessalon capsules also contain D&C yellow 10, gelatin, glycerin, methylparaben, and propylparaben.
- Thalomid® (thalidomide) is available in 50-mg, 100-mg and 200-mg capsules for oral administration. Active ingredient: thalidomide. Inactive ingredients: pregelatinized starch and magnesium stearate. The 50-mg capsule shell contains gelatin, titanium dioxide, and black ink. The 100-mg capsule shell contains black iron oxide, yellow iron oxide, titanium dioxide, gelatin, and black ink. The 200-mg capsule shell contains FD&C blue No. 2, titanium dioxide, gelatin, and white ink.
- Thiothixene capsule contains 1 mg, 2 mg, 5, or 10 mg of thiothixene and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium (type A), gelatin, magnesium stearate, microcrystalline cellulose, powdered cellulose, pregelatinized starch, sodium lauryl sulfate, titanium dioxide, and other inactive ingredients. The following coloring agents are employed: 1 mg—FD&C blue No. 1, D&C red No. 28, FD&C red No. 40, FD&C yellow No. 6; 2 mg—FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6, D&C yellow No. 10; 5 mg—FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6; 10 mg—FD&C blue No. 1, FD&C red No. 40, FD&C yellow No. 6.
- Tiazac® (diltiazem hydrochloride) capsules contain diltiazem hydrochloride in extended-release beads at doses of 120, 180, 240, 300, 360 and 420 mg. Tiazac also contains microcrystalline cellulose NF, sucrose stearate, Eudragit, povidone USP, talc USP, magnesium stearate NF, hypromellose USP, titanium dioxide USP, polysorbate NF, simethicone USP, gelatin NF, FD&C blue No. 1, FD&C red No. 40, D&C red No. 28, FD&C green No. 3, black iron oxide USP, and other solids.
- Toprol-XL, metoprolol succinate tablets, comprises a multiple unit system containing metoprolol succinate in a multitude of controlled-release pellets. Each pellet acts as a separate drug delivery unit and is designed to deliver metoprolol continuously over the dosage interval. The tablets contain 23.75, 47.5, 95 and 190 mg of metoprolol succinate equivalent to 25, 50, 100 and 200 mg of metoprolol tartrate, USP, respectively.
- TriLyte™ is a white powder for reconstitution containing 420 g polyethylene glycol 3350, 5.72 g sodium bicarbonate, 11.2 g sodium chloride, 1.48 g potassium chloride. Flavor packs, each containing 3.22 g of flavoring ingredients, are attached to the 4-L bottle. When dissolved in water to a volume of 4 L, TriLyte™ with flavor packs (PEG-3350, sodium chloride, sodium bicarbonate, and potassium chloride for oral solution) is an isosmotic solution, for oral administration, having a pleasant mineral water taste. One flavor pack can be added before reconstitution to flavor the solution. TriLyte™ with flavor packs is administered orally or via nasogastric tube as a gastrointestinal lavage.
- Verelan® PM (verapamil hydrochloride) is available for oral administration as a 100-mg hard gelatin capsule (white opaque cap/amethyst body), a 200-mg hard gelatin capsule (amethyst opaque cap/amethyst body), and as a 300-mg hard gelatin capsule (lavender opaque cap/amethyst body). Verapamil is administered as a racemic mixture of the R and S enantiomers. In addition to verapamil HCl, the Verelan PM capsule contains the following inactive ingredients: D&C red No. 28, FD&C blue No. 1, FD&C red No. 40, fumaric acid, gelatin, povidone, shellac, silicon dioxide, sodium lauryl sulfate, starch, sugar spheres, talc, and titanium dioxide.
- VFEND for oral suspension is a white to off-white powder providing a white to off-white orange-flavored suspension when reconstituted. Bottles containing 45 g powder for oral suspension are intended for reconstitution with water to produce a suspension containing 40 mg/mL voriconazole. The inactive ingredients include colloidal silicon dioxide, titanium dioxide, xanthan gum, sodium citrate dihydrate, sodium benzoate, anhydrous citric acid, natural orange flavor, and sucrose.

- Viracept oral powder is available for oral administration in a 50 mg/g strength (as nelfinavir free base) in bottles. The oral powder also contains the following inactive ingredients: microcrystalline cellulose, maltodextrin, dibasic potassium phosphate, crospovidone, hypromellose, aspartame, sucrose palmitate, and natural and artificial flavor.
- Zavesca® (miglustat capsules, 100 mg) is supplied in hard gelatin capsules each containing 100 mg miglustat for oral administration. Each Zavesca 100-mg capsule also contains sodium starch glycolate, povidone (K30), and magnesium stearate. Ingredients in the capsule shell include gelatin and titanium dioxide, and the shells are printed with edible ink consisting of black iron oxide, shellac, soya lecithin, and antifoam.
- Zemplar (Paricalcitol, USP) is available as soft gelatin capsules for oral administration containing 1 μg, 2 μg, or 4 μg of paricalcitol. Each capsule also contains medium-chain triglycerides, alcohol, and butylated hydroxytoluene. The medium-chain triglycerides are fractionated from coconut oil or palm kernel oil. The capsule shell is composed of gelatin, glycerin, titanium dioxide, iron oxide red (2 μg capsules only), iron oxide yellow (2 μg and 4 μg capsules), iron oxide black (1 μg capsules only), and water.
- Zithromax® (azithromycin capsules, azithromycin tablets and azithromycin for oral suspension) contain the active ingredient azithromycin. Zithromax capsules contain azithromycin dihydrate equivalent to 250 mg of azithromycin. The capsules are supplied in red opaque hard-gelatin capsules (containing FD&C red No. 40). They also contain the following inactive ingredients: anhydrous lactose, cornstarch, magnesium stearate, and sodium lauryl sulfate.
- Zithromax for oral suspension is supplied in a single dose packet containing azithromycin dihydrate equivalent to 1 g azithromycin. It also contains the following inactive ingredients: colloidal silicon dioxide, sodium phosphate tribasic, anhydrous; spray-dried artificial banana flavor, spray-dried artificial cherry flavor, and sucrose.
- Zonegran® (zonisamide) capsules containing 25, 50, or 100 mg zonisamide. Each capsule contains the labeled amount of zonisamide plus the following inactive ingredients: microcrystalline cellulose, hydrogenated vegetable oil, sodium lauryl sulfate, gelatin, and colorants.

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Pharmaceutical Science

about the book...

Providing methodologies that can serve as a reference point for new formulations, the second volume covers uncompressed solids, which include formulations of powders, capsules, powders ready for reconstitution, and other similar products.

Highlights from ***Uncompressed Solid Products, Volume Two*** include:

- the fundamental issues of good manufacturing practices
- formulations for more than 400 pharmaceutical products, including currently approved products and innovative products such as small proteins, instantly liquifiable powders, and nanoparticles
- access to US FDA guidelines, as well as all major guidelines around the world
- identification and inclusion of the most often approved capsules and powders in the US

about the author...

SARFARAZ K. NIAZI is Consultant, Pharmaceutical Scientist, Inc., Deerfield, Illinois, USA. Dr. Niazi has over 35 years of worldwide experience in managing multidisciplinary research; he has been teaching and conducting research in the field of pharmaceutical and biotechnology sciences and has published over 100 research articles, dozens of books, both technical and literary including several textbooks. He is a recipient of several research recognition awards. He is a licensed practitioner of patent law before the US Patent and Trademark Office and serves the global pharmaceutical and biotechnology industry in the transition of research ideas into useful technology. Dr. Niazi holds several major US and worldwide patents for his inventions and writes in the fields of philosophy, sociology, rhetoric, and poetry; he is the author of the first book on clinical pharmacokinetics and the largest work on pharmaceutical manufacturing formulations and also on the manufacturing of therapeutic proteins. He has extensive experience in global management of research in healthcare systems.

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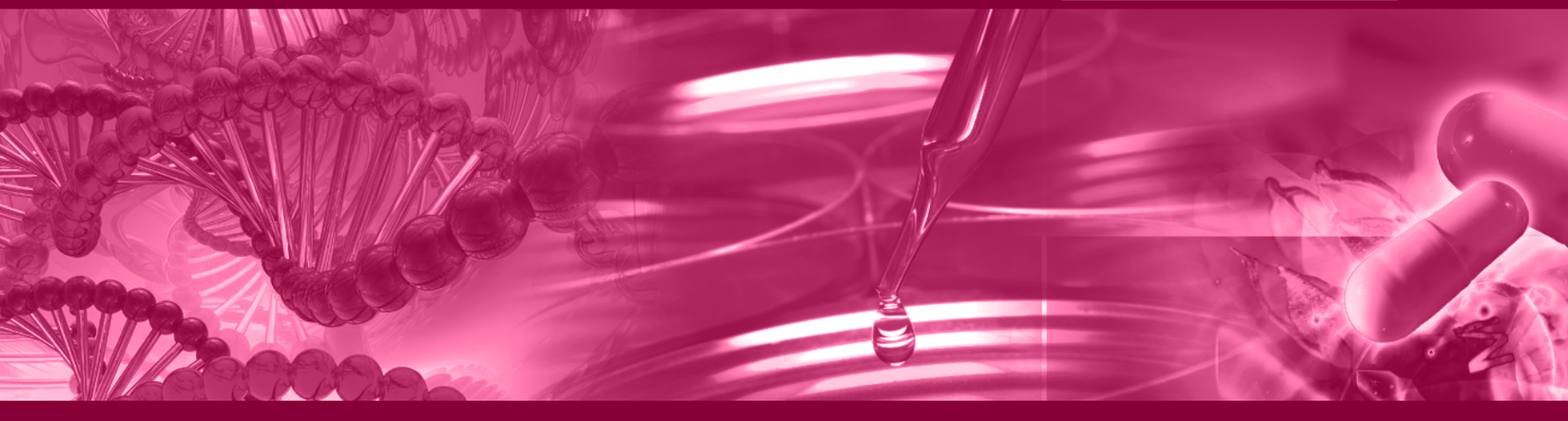

VOLUME THREE

Second Edition

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Handbook of Pharmaceutical Manufacturing Formulations Second Edition

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to August P. Lemberger

Preface to the Series—Second Edition

The science and the art of pharmaceutical formulation keeps evolving as new materials, methods, and machines become readily available to produce more reliable, stable, and release-controlled formulations. At the same time, globalization of sourcing of raw and finished pharmaceuticals brings challenges to regulatory authorities and results in more frequent revisions to the current good manufacturing practices, regulatory approval dossier requirements, and the growing need for cost optimization. Since the publication of the first edition of this book, a lot has changed in all of these areas of importance to pharmaceutical manufacturers. The second edition builds on the dynamic nature of the science and art of formulations and provides an evermore useful handbook that should be highly welcomed by the industry, the regulatory authorities, as well as the teaching institutions.

The first edition of this book was a great success as it brought under one umbrella the myriad of choices available to formulators. The readers were very responsive and communicated with me frequently pointing out to the weaknesses as well as the strengths of the book. The second edition totally revised attempts to achieve these by making major changes to the text, some of which include:

1. Complete, revised errors corrected and subject matter reorganized for easy reference. Whereas this series has six volumes differentiated on the basis of the type of dosage form and a separate inclusion of the U.S. OTC products, ideally the entire collection is needed to benefit from the myriad of topics relating to formulations, regulatory compliance, and dossier preparation.
2. Total number of pages is increased from 1684 to 2726.
3. Total number of formulations is expanded by about 30% with many newly approved formulations.
4. Novel formulations are now provided for a variety of drugs; these data are collected from the massive intellectual property data and suggest toward the future trend of formulations. While some of these formulations may not have been approved in the United States or Europe, these do provide additional choices, particularly for the NDA preparation. As always, it is the responsibility of the manufacturer to assure that the intellectual property rights are not violated.
5. A significant change in this edition is the inclusion of commercial products; while most of this information is culled out from the open source such as the FOIA (http://www.fda.gov/foi/default.htm), I have made attempts to reconstruct the critical portions of it based on what I call the generally acceptable standards. The drug companies are advised to assure that any intellectual property rights are not violated and this applies to all information contained in this book. The freedom of information act (FOIA) is an extremely useful conduit for reliable information and manufacturers are strongly urged to make use of this information. Whereas this information is provided free of charge, the process of obtaining the information may be cumbersome, in which case, commercial sources of these databases can prove useful, particularly for the non-U.S. companies.
6. Also included are the new Good Manufacturing Guidelines (2007) with amendments (2008) for the United States and similar updates for European Union and WHO; it is strongly urged that the companies discontinue using all old documents as there are significant changes in the revised form, and many of them are likely to reduce the cost of GMP compliance.
7. Details on design of clean rooms is a new entry that will be of great use to sterile product manufacturers; whereas the design and flow of personnel and material flow is of critical nature, regulatory agencies view these differently and the manufacturer is advised always to comply with most stringent requirements.
8. Addition of a self-auditing template in each volume of the series. While the cGMP compliance is a complex issue and the requirements diversified across the globe, the basic compliance remains universal. I have chosen the European Union guidelines (as these are more in tune with the ICH) to prepare a self-audit module that I recommend that every manufacturer adopt as a routine to assure GMP compliance. In most instances reading the template by those responsible for compliance with keep them sensitive to the needs of GMP.
9. OTC products cross-referenced in other volumes where appropriate. This was necessary since the regulatory authorities worldwide define this class of drug differently. It is important to iterate that regardless of the prescription or the OTC status of a product, the requirements for compliance with the cGMP apply equally.
10. OTC monograph status is a new section added to the OTC volume and this should allow manufacturers to chose appropriate formulations that may not require a filing with the regulatory agencies; it is important to iterate that an approved OTC monograph includes details of formulation including the types and quantities of active drug and excipients, labeling, and presentation. To qualify the exemption, the manufacturer must comply with the monograph in its entirety. However, subtle modifications that are merely cosmetic in nature and where there is an evidence that the modification will not affect the safety and efficacy of the products can be made but require prior approval of the regulatory agencies and generally these approvals are granted.
11. Expanded discussion on critical factors in the manufacturing of formulations provided; from basic shortcuts to smart modifications now extend to all dosage forms. Pharmaceutical compounding is one of the oldest professions and whereas the art of formulations has been

relegated to more objective parameters, the art nevertheless remains. An experienced formulator, like an artist, would know what goes with what and why; he avoids the pitfalls and stays with conservative choices. These sections of the book present advice that is time tested, although it may appear random at times; this is intended for experienced formulators.

12. Expanded details on critical steps in the manufacturing processes provided but to keep the size of the book manageable, and these are included for prototype formulations. The reader is advised to browse through similar formulations to gain more insight. Where multiple formulations are provided for the same drug, it intended to show the variety of possibilities in formulating a drug and whereas it pertains to a single drug, the basic formulation practices can be extended to many drugs of same class or even of diversified classes. Readers have often requested that more details be provided in the Manufacturing Direction sections. Whereas sufficient details are provided, this is restricted to prototype formulations to keep the size of the book manageable and to reduce redundancy.
13. Addition of a listing of approved excipients and the level allowed by regulatory authorities. This new section allows formulators a clear choice on which excipients to choose; the excipients are reported in each volume pertaining to the formulation type covered. The listing is drawn from the FDA-approved entities. For the developers of an ANDA, it is critical that the level of excipients be kept within the range generally approved to avoid large expense in justifying any unapproved level. The only category for which the listing is not provided separately is the OTC volume since it contains many dosage forms and the reader is referred to dosage form–specific title of the series. The choice of excipients forms keeps increasing with many new choices that can provide many special release characteristics to the dosage forms. Choosing correct excipients is thus a tedious exercise and requires sophisticated multivariate statistical analysis. Whereas the formulator may choose any number of novel or classical components, it is important to know the levels of excipients that are generally allowed in various formulations to reduce the cost of redundant exercises; I have therefore included, as an appendix to each volume, a list of all excipients that are currently approved by the U.S. FDA along their appropriate levels. I suggest that a formulator consult this table before deciding on which level of excipient to use; it does not mean that the excipient cannot be used outside this range but it obviates the need for a validation and lengthy justification studies in the submission of NDAs.
14. Expanded section on bioequivalence submission was required to highlight the recent changes in these requirements. New entries include a comprehensive listing of bioequivalence protocols in abbreviated form as approved by the U.S. FDA; these descriptions are provided in each volume where pertinent. To receive approval for an ANDA, an applicant must generally demonstrate, among other things, equivalence of the active ingredient, dosage form, strength, route of administration and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. Bioequivalent drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 U.S.C. 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320. The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-specific BE studies, the U.S. FDA will be issuing product-specific BE recommendations (www.fda.gov/cder/ogd/index.htm). To make this vital information available, an appendix to each volume includes a summary of all currently approved products by the U.S. FDA where a recommendation on conducting bioequivalence studies is made available by the U.S. FDA. When filing an NDA or an ANDA, the filer is faced with the choice of defending the methods used to justify the bioavailability or bioequivalence data. The U.S. FDA now allows application for waiver of bioequivalence requirement; a new chapter on this topic has been added along with details of the dissolution tests, where applicable, approved for various dosage forms.
15. Dissolution testing requirements are included for all dosage forms where this testing is required by the FDA. Surrogate testing to prove efficacy and compliance is getting more acceptance at regulatory agencies; in my experience, a well-designed dissolution test is the best measure of continuous compliance. Coupled with chapters on waivers of bioequivalence testing, this information on dissolution testing should be great value to all manufacturers; it is recommended that manufacturers develop their own in-house specifications, more stringent than those allowed in these listings and the USP.
16. Best-selling products (top 200 prescription products) are identified with an asterisk and a brand name where applicable; in all instances, composition of these products is provided and formulation of generic equivalents. Despite the vast expansion of pharmaceutical sales and shifting of categories of blockbuster drugs, basic drugs affecting gastrointestinal tract, vascular system, and brain remain most widely prescribed.
17. Updated list of approved coloring agents in the United States, Canada, European Union, and Japan is included to allow manufactures to design products for worldwide distribution.
18. Tablet-coating formulations that meet worldwide requirements of color selection are included in the Volume 1 (compressed solids) and Volume 5 (OTC) because these represent the products often coated.
19. Guidelines on preparing regulatory filings are now dispersed throughout the series depending on where these guidelines are more crucial. However, the reader would, as before, need access to all volumes to benefit from the advice and guidelines provided.

As always, comments and criticism from the readers are welcomed and these can be sent to me at Niazi@pharmsci.com or Niazi@niazi.com. I would try to respond to any inquiries requiring clarification of the information enclosed in these volumes.

I would like to express deep gratitude to Sherri R. Niziolek and Michelle Schmitt-DeBonis at Informa, the publisher of

this work, for seeing an immediate value to the readers in publishing the second edition of this book and allowing me enough time to prepare this work. The diligent editing and composing staff at Informa, particularly Joseph Stubenrauch, Baljinder Kaur and others are highly appreciated. Regardless, all errors and omissions remain altogether mine.

In the first edition, I had dedicated each volume to one of my mentors; the second edition continues the dedication to these great teachers.

Sarfaraz K. Niazi, Ph.D.
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Preface to the Series—First Edition

No industry in the world is more highly regulated than the pharmaceutical industry because of the potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity to final regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. It is anticipated that the industry will spend about $20 billion on research and development in 2004. Because patent protection on a number of drugs is expiring, the generic drug market is becoming one of the fastest growing segments of the pharmaceutical industry with every major multinational company having a significant presence in this field.

Many stages of new drug development are inherently constrained by time, but the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the first major attempt to consolidate the available knowledge about formulations into a comprehensive and, by nature, rather voluminous presentation.

The book is divided into six volumes based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and over-the-counter (OTC) products. Although they may easily fall into one of the other five categories, OTC products are considered separately to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of the product, and of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of pharmaceutical products into these six categories. Each volume includes a description of regulatory filing techniques for the formulations described. Also included are regulatory guidelines on complying with current good manufacturing practices (cGMPs) specific to the dosage form and advice is offered on how to scale up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and reduce the time required to file by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a fixed paradigm when it comes to selecting formulations: "Not invented here" perhaps is kept in the back of the minds of many seasoned formulations scientists when they prefer certain platforms for development. It is expected that with a quick review of the formulation possibilities that are made available in this book such scientists would benefit from the experience of others. For teachers of formulation sciences, this series offers a wealth of information. Whether it is selection of a preservative system or the choice of a disintegrant, the series offers many choices to study and consider.

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Preface to the Volume—First Edition

Liquid products, for the purpose of inclusion in this volume, include nonsterile drugs administered by any route in the form of solutions (monomeric and multimeric), suspensions (powder and liquid), drops, extracts, elixirs, tinctures, paints, sprays, colloidons, emulsions, aerosols, and other fluid preparations. Sterile liquid products are presented in another volume. Whereas liquid drugs do not share the compression problems of solid dosage forms, the filling problems of powder dosage forms, and the consistency problems of semisolid dosage forms, they do have their own set of considerations in the formulation and manufacturing stages. The considerations of prime importance for liquid drugs include solubility of active drugs, preservation, taste masking, viscosity, flavoring, appearance, and stability (chemical, physical, and microbiological), raw materials, equipment, the compounding procedures (often the order of mixing), and finally the packaging (to allow a stable product to reach patients). Suspensions present a special situation in which even the powder for reconstitution needs to be formulated such that it can be stable after reconstitution; therefore, limited examples are included here.

Chapter 1 in section I (Regulatory and Manufacturing Guidance) describes the practical details in complying with the current good manufacturing practice (cGMP) requirements in liquid manufacturing. This chapter does not address the specific cGMP parameters but deals with the practical aspects as may arise during a U.S. Food and Drug Administration (FDA) inspection. This includes what an FDA inspector would be looking into when auditing a liquid manufacturing facility.

Chapter 2 describes the stability testing of new drugs and dosage forms. Drawn from the most current international conference on harmonization (ICH) guidelines, this chapter describes in detail the protocols used for stability testing not only for new drugs but also for new dosage forms. The chapter is placed in this volume because stability studies are of greater concern in liquid dosage forms; however, keeping in mind the overall perspective of the series of this title, this chapter would apply to all dosage forms. Again, emphasis is placed on the practical aspects, and the reader is referred to official guidelines for the development of complete testing protocols. It is noteworthy that the ICH guidelines divide the world into four zones; the discussion given in this chapter mainly refers to the U.S. and European regions, and again the formulator is referred to the original guideline for full guidance. Stability studies constitute one of the most expensive phases of product development because of their essential time investment. As a result, formulators often prepare a matrix of formulations to condense the development phase, particularly where there are known issues in compatibility, drug interactions, and packaging interactions. The FDA is always very helpful in this phase of study protocols, particularly where a generic drug is involved. It is also a good idea to benchmark the product against the innovator product. However, one should understand clearly that the FDA is not bound to accept stability data even though it might match that of the innovator product. The reason for this may lie in the improvements made since the innovator product was approved. For example, if a better packaging material that imparts greater safety and shelf life is available, the FDA would like this to be used (not for the purpose of shelf life, but for the safety factors). In recent years, the FDA has placed greater emphasis on the control of active pharmaceutical ingredient (API), particularly if it is sourced from a new manufacturer with a fresh DMF. Obviously, this is one way how the innovator controls the proliferation of generic equivalents. The original patents that pertain to synthesis or manufacturing of the active raw material may have been superseded by improved processes that are not likely to be a part of a later patent application (to protect the trade secret because of double-patenting issues). The innovator often goes on to revise the specifications of the active pharmaceutical ingredient to the detriment of the generic manufacturer. However, my experience tells me that such changes are not necessarily binding on the generic manufacturer, and as long as cGMP compliance in the API is demonstrated and the impurities do not exceed the reference standard (if one is available), there is no need to be concerned about this aspect. However, manufacturers are advised to seek a conference with the FDA should this be a serious concern. At times, the manufacturer changes the finished product specification as the patents expire or reformulates the product under a new patent. A good example of this practice was the reformulation of calcitriol injection by Abbott as its patent came to expiry. The new specifications include a tighter level of heavy metals, but a generic manufacturer should have no problem if the original specifications are met because the product was approvable with those specifications.

Chapter 3 describes the container closure systems; again, this discussion would apply to all dosage forms. It is noteworthy that the regulatory agencies consider containers and packaging systems, all those components that come in contact with the product, protect the product from environment, or are instrumental in the delivery of the product as part of the product definition. Whereas the industry is much attuned to studies of the effects of the API and dosage formulation components, the study of container or closure systems is often left to the end of the study trials. This is an imprudent practice, as it might result in loss of valuable time. The packaging industry generally undergoes faster changes than do the chemical or pharmaceutical industries. New materials, better tolerances, more environmentally friendly materials, and now, with the use of mechanical devices in many dosage forms, appropriate dosing systems emerge routinely. As a rule of thumb, the closure system for a product should be the first criterion selected before development of the dosage form. Switching between a glass and a plastic bottle at a later stage can be a very expensive exercise. Because many of these considerations are drawn by marketing teams, who may change their product positioning, the formulation team must be

appropriately represented in marketing decision conferences. Once a decision has been made about the presentation of a product, the product development team should prepare several alternatives, based on the ease of formulation and the cost of the finished product involved. It should be emphasized at all stages of development that packaging scale-ups require just as much work as does a formulation scale-up or changes. As a result, the FDA provides the scale-up and postapproval change (SUPAC) guidelines for packaging components. Changes in the dimensions of a bottle may expose a large surface of liquid to the gaseous phase in the bottle and thus require a new stability testing exercise. This chapter forms an important reminder to formulators on the need to give consideration to every aspect of the container closure system as part of routine development.

Chapter 4 introduces the area of Preapproval Inspections, a process initiated by the FDA in the wake of the grand scandals in the generic pharmaceutical industry a few years ago. The FDA guidelines now allow "profiling" of companies and list the requirements of Preapproval Inspections when an application has been filed. Whereas the emphasis in this chapter is on "preapproval," the advice provided here applies to all regulatory inspections. A regulatory inspection can be an arduous exercise if the company has not prepared for it continuously. Preparedness for inspection is not something that can be achieved through a last-minute crash program. This chapter goes into considerable detail on how to create a cGMP culture, how to examine the documentary needs, assignment of responsibility, preparation of validation plan, and above all, the art of presenting the data to the FDA. Also discussed are the analyses of the outcome of inspection. Advice is provided on how to respond to Form 483 issued by the FDA, and the manufacturer is warned of the consequences of failing an inspection. Insight is also provided for foreign manufacturers, for whom a different set of rules may be applied because of the physical constraints of inspection. The inspection guidelines provided apply to both the manufacturers of API as well as to the finished products.

Chapter 5 includes highlights of topics of importance in the formulation of liquid products. However, this chapter is not an all-inclusive guide to formulation. Only highlights of points of concern are presented here, and the formulator is referred to several excellent treatises available on the subject.

Section II contains formulations of liquid products and lists a wide range of products that fall under this classification, as interpreted in the volume. There are three levels at which these formulations are described. First, the Bill of Materials is accompanied by detailed manufacturing directions; second, the manufacturing directions are abbreviated because they are already described in another product of similar nature; and third, only the composition is provided as supplied by the manufacturer. With the wide range of formulations included in this volume, it should be a simple matter for an experienced formulator to convert these formulations into quantitative Bills of Materials and then to benchmark it against similar formulations to come up with a working formula. The problems incumbent in the formulation of liquid products are highlighted in chapter 5, but these are generic problems, and the formulator should be aware of any specific situations or problems that may arise from time to time. I would like to hear from the formulators about these problems so that they could be included in future editions of this book. Again, the emphasis in this series is on a practical resolution of problems; the theoretical teachings are left to other, more comprehensive works on this topic. The key application of the data provided herein is to allow the formulator to select the ingredients that are reportedly compatible, avoiding need for long-term studies to establish compatibilities.

I am grateful to CRC Press for taking this lead in publishing what is possibility the largest such work in the field of pharmaceutical products. It has been a distinct privilege to know Mr. Stephen Zollo, senior editor at CRC Press. Stephen has done more than any editor can do to encourage an author into completing this work on a timely basis. The editorial assistance provided by CRC Press staff was indeed exemplary, particularly the help given by Erika Dery, Amy Rodriguez, and others. Although much care has gone into correcting errors, any errors remaining are altogether mine. I shall appreciate the readers bringing these to my attention for correction in future editions of this volume (niazi@pharmsci.com).

This volume is dedicated to one of the great educators and a leader in the pharmaceutical profession, August P. Lemberger, who is truly a Wisconsin man. At the University of Wisconsin in Madison, he was an undergraduate and graduate student. He was then a professor, and twice Dean of the School of Pharmacy (1943–44, 1946–52, 1953–69, 1980–91). During the period between 1969 and 1980, he assumed the responsibility of deanship at the University of Illinois, where I was a graduate student. In 1972, he offered me my first teaching job, as an instructor of pharmacy at the University of Illinois, while I was still in graduate school. I was one of the greatest beneficiaries of his kindness and attention. Gus has an unusual ability to put everyone at ease, respect everyone around him, and in the end, come out as a group leader. Whatever little I have accomplished in my life is mostly because of Gus. Many awards, recognitions, and salutations were offered to Gus during his celebrated career. His research contributions included stability studies, suspension, emulsion stabilization, and later in his career, the various aspects of pharmaceutical education. I wish him many years of happy retirement and shuttling back and forth between his homes in Arizona and Wisconsin. Thanks, Gus.

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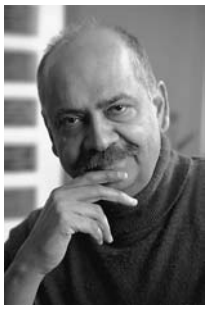
About the Author



Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 35 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents in the field of drug and dosage form delivery systems; he is also licensed to practice law before the U.S. Patent and Trademark Office. Having formulated hundreds of products from the most popular consumer entries to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science and art of formulating and regulatory filings of investigational new drugs (INDs) and new drug applications (NDAs). Dr. Niazi advises the pharmaceutical industry internationally on issues related to formulations, cGMP compliance, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (http://www.pharmsci.com). He can be contacted at Niazi@pharmsci.com.

Contents

Part I

Regulatory and Manufacturing Guidance

1

Manufacturing Practice Considerations in Liquid Formulations

I. INTRODUCTION

The manufacture and control of oral solutions and oral suspensions presents some unusual problems not common to other dosage forms. Although bioequivalency concerns are minimal (except for products in which dissolution is a rate-limiting or absorption-determining step, as in phenytoin suspension), other issues have frequently led to recalls of liquid products. These include microbiological, potency, and stability problems. In addition, because the population using these oral dosage forms includes newborns, pediatrics, and geriatrics, who may not be able to take oral solid dosage forms and who may have compromised drug metabolic or other clearance function, defective dosage forms can pose a greater risk if the absorption profiles are significantly altered from the profiles used in the development of drug safety profiles.

II. FACILITIES

The designs of the facilities are largely dependent on the type of products manufactured and the potential for cross-contamination and microbiological contamination. For example, the facilities used for the manufacture of over-the-counter oral products might not require the isolation that a steroid or sulfa product would require. However, the concern for contamination remains, and it is important to isolate processes that generate dust (such as those processes occurring before the addition of solvents). The HVAC (heating, ventilation, and air-conditioning) system should be validated just as required for processing of potent drugs. Should a manufacturer rely mainly on recirculation rather than filtration or fresh air intake, efficiency of air filtration must be validated by surface and air sampling. It is advisable not to take any shortcuts in the design of HVAC systems, as it is often very difficult to properly validate a system that is prone to breakdown; in such instances a fully validated protocol would need stress testing—something that may be more expensive than establishing proper HVAC systems in the first place. However, it is also unnecessary to overdo it in designing the facilities, as once the drug is present in a solution form, cross-contamination to other products becomes a lesser problem. It is, nevertheless, important to protect the drug from other powder sources (such as by maintaining appropriate pressure differentials in various cubicles).

III. EQUIPMENT

Equipment should be of sanitary design. This includes sanitary pumps, valves, flow meters, and other equipment that can be easily sanitized. Ball valves, the packing in pumps, and pockets in flow meters have been identified as sources of contamination. Contamination is an extremely important consideration, particularly for those sourcing manufacturing equipment from less developed countries; manufacturers of equipment often offer two grades of equipment: sanitary equipment, and equipment not qualified as sanitary and offered at substantial savings. All manufacturers intending to ship any product subject to U.S. Food and Drug Administration (FDA) inspection must insist on certification that the equipment is of sanitary design.

To facilitate cleaning and sanitization, manufacturing and filling lines should be identified and detailed in drawings and standard operating procedures. Long delivery lines between manufacturing areas and filling areas can be a source of contamination. Special attention should be paid to developing standard operating procedures that clearly establish validated limits for this purpose.

Equipment used for batching and mixing of oral solutions and suspensions is relatively basic. These products are generally formulated on a weight basis, with the batching tank on load cells so that a final volume can be made by weight; if you have not done so already, consider converting your systems to weight basis. Volumetric means, such as using a dipstick or a line on a tank, are not generally as accurate and should be avoided where possible. When volumetric means are chosen, make sure they are properly validated at different temperature conditions and other factors that might render this practice faulty. In most cases, manufacturers assay samples of the bulk solution or suspension before filling. A much greater variability is found with those batches that have been manufactured volumetrically rather than those that have been manufactured by weight. Again, the rule of thumb is to avoid any additional validation if possible.

The design of the batching tank with regard to the location of the bottom discharge valve often presents problems. Ideally, the bottom discharge valve is flush with the bottom of the tank. In some cases, valves—including undesirable ball valves—are several inches to a foot below the bottom of the tank. This is not acceptable. It is possible that in this situation the drug or preservative may not completely dissolve and may get trapped in the "dead leg" below the tank, with initial samples turning out subpotent. For the manufacture of suspensions, valves should be flush.

Transfer lines are generally hard piped and are easily cleaned and sanitized. In situations where manufacturers use flexible hoses to transfer product, it is not unusual to see these hoses lying on the floor, thus significantly increasing the potential for contamination. Such contamination can occur through operators picking up or handling hoses, and possibly even through operators placing them in transfer or batching tanks after the hoses had been lying on the floor. It is a good practice to store hoses in a way that allows them to drain, rather than coiling them, which may allow moisture to collect and be a potential source of microbial contamination.

Another common problem occurs when manifold or common connections are used, especially in water supply, premix, or raw material supply tanks. Such common connections can be a major source of contamination.

IV. RAW MATERIALS

The physical characteristics, particularly the particle size of the drug substance, are very important for suspensions. As with topical products in which the drug is suspended, particles are usually very fine to micronize (to <25 microns). For syrup, elixir, or solution dosage forms in which there is nothing suspended, particle size and physical characteristics of raw materials are not that important. However, they can affect the rate of dissolution of such raw materials in the manufacturing process. Raw materials of a finer particle size may dissolve faster than those of a larger particle size when the product is compounded.

Examples of a few oral suspensions in which a specific and well-defined particle-size specification for the drug substance is important include phenytoin suspension, carbamazepine suspension, trimethoprim and sulfamethoxazole suspension, and hydrocortisone suspension. It is therefore a good idea to indicate particle size in the raw material specification, even though it is meant for dissolving in the processing, to better validate the manufacturing process while avoiding scale-up problems.

V. COMPOUNDING

In addition to a determination of the final volume (on weight or volume basis) as previously discussed, there are microbiological concerns, and these are well covered in other chapters in this book.

For oral suspensions there is the additional concern of uniformity, particularly because of the potential for segregation during manufacture and storage of the bulk suspension, during transfer to the filling line, and during filling. It is necessary to establish procedures and time limits for such operations to address the potential for segregation or settling as well as other unexpected effects that may be caused by extended holding or stirring.

For oral solutions and suspensions, the amount and control of temperature is important from a microbiological as well as a potency aspect. For those products in which temperature is identified as a critical part of the operation, the batch records must demonstrate compliance using control charts. There are some processes in manufacturing in which heat is used during compounding to control the microbiological levels in the product. For such products, the addition of purified water to make up to final volume, the batch, and the temperatures during processing should be properly documented.

In addition to drug substances, some additives such as the most commonly used preservatives, parabens are difficult to dissolve, and require heat (often to 80°C). The control and verification of their dissolution during the compounding stage should be established in the method validation. From a potency aspect, the storage of product at high temperatures may increase the level of degradants. Storage limitations (time and temperature) should be justified.

There are also some oral liquids that are sensitive to oxygen and that have been known to undergo degradation. This is particularly true of the phenothiazine class of drugs, such as perphenazine and chlorpromazine. The manufacture of such products might require the removal of oxygen, as by nitrogen purging. In addition, such products might also require storage in sealed tanks, rather than in those with loose lids. Manufacturing directions provided in this book are particularly detailed about the purging steps, and these should be closely observed.

VI. MICROBIOLOGICAL QUALITY

Microbiological contamination can present significant health hazards in some oral liquids. For example, some oral liquids, such as nystatin suspension, are used in infants and immunocompromised patients, and microbiological contamination with organisms (such as Gram-negative organisms) is not acceptable. There are other oral liquid preparations such as antacids in which *Pseudomonas* sp. contamination is also objectionable. For other oral liquids such as cough preparations, contamination with *Pseudomonas* sp. might not present the same health hazard. However, the presence of a specific *Pseudomonas* sp. may also indicate other plant or raw material contamination and often points to defects in the water systems and environmental breaches; extensive investigations are often required to trace the source of contamination. Obviously, the contamination of any preparation with Gram-negative organisms is not desirable.

In addition to the specific contaminant being objectionable, such contamination would be indicative of a deficient process as well as an inadequate preservative system. For example, the presence of a *Pseudomonas putida* contaminant could also indicate that *P. aeruginosa*, a similar source organism, is also present.

Because FDA laboratories typically use more sensitive test methods than industry, samples of oral liquids in which manufacturers report microbiological counts well within limits may be found unacceptable by the federal laboratories. This result requires upgrading the sensitivity of testing procedures.

VII. ORAL SUSPENSIONS

Liquid products in which the drug is suspended (not in solution) present some unique manufacturing and control problems. Depending on the viscosity, many suspensions require continuous or periodic agitation during the filling process. If delivery lines are used between the bulk storage tank and the filling equipment, some segregation may occur, particularly if the product is not viscous. Procedures must therefore be established for filling and diagrams established for line setup prior to the filling equipment.

Good manufacturing practice would warrant testing bottles from the beginning, middle, and end of a batch to ensure that segregation has not occurred. Such samples should not be combined for the purpose of analysis. In-process testing for suspensions might also include an assay of a sample from the bulk tank. More important at this stage, however, may be testing for viscosity.

VIII. PRODUCT SPECIFICATIONS

Important specifications for the manufacture of all solutions include assay and microbial limits. Additional important specifications for suspensions include particle size of the suspended drug, viscosity, pH, and in some cases, dissolution. Viscosity can be important, from a processing aspect, to minimize segregation. In addition, viscosity has also been shown to be associated with bioequivalency. pH may also have some meaning regarding effectiveness of preservative systems and may even have an effect on the amount of drug in solution. With regard to dissolution, there are at least three products that have dissolution specifications. These

products include phenytoin suspension, carbamazepine suspension, and sulfamethoxazole and trimethoprim suspension. Particle size is also important, and at this point it would seem that any suspension should have some type of particle-size specification. As with other dosage forms, the underlying data to support specifications should be established.

IX. PROCESS VALIDATION

As with other products, the amount of data needed to support the manufacturing process will vary from product to product. Development (data) should have identified critical phases of the operation, including the predetermined specifications that should be monitored during process validation.

For example, for solutions, the key aspects that should be addressed during validation include ensuring that the drug substance and preservatives are dissolved. Parameters such as heat and time should be measured. In-process assay of the bulk solution during or after compounding according to predetermined limits is also an important aspect of process validation. For solutions that are sensitive to oxygen or light, dissolved oxygen levels would also be an important test. Again, the development data and the protocol should provide limits.

As discussed, the manufacture of suspensions presents additional problems, particularly in the area of uniformity. The development data should address the key compounding and filling steps that ensure uniformity. The protocol should provide for the key in-process and finished product tests, along with their specifications. For oral solutions, bioequivalency studies may not always be needed. However, oral suspensions, with the possible exception of some of the over-the-counter antacids, usually require a bioequivalency or clinical study to demonstrate their effectiveness. Comparison of product batches with the biobatch is an important part of the validation process. Make sure there are properly written protocol and process validation reports and, if appropriate, data for comparing full-scale batches with biobatch available during FDA inspection.

X. STABILITY

One area that has presented a number of problems is ensuring the stability of oral liquid products throughout their expiry period. The presence of water or other solvents enhances all reaction rates: Because fluids can contain a certain amount of oxygen, the oxidation reactions are also enhanced, as in the case of vitamins and the phenothiazine class of drugs. Good practice for these classes of drug products should include quantitation of both the active and primary degradant. There should be well-established specifications for the primary degradant, including methods of quantitation of both the active drug and degradant.

Because interactions of products with closure systems are possible, liquids and suspensions undergoing stability studies should be stored on their side or inverted to determine whether contact of the drug product with the closure system affects product integrity.

Other problems associated with inadequate closure systems are moisture losses that can cause the remaining contents to become superpotent and microbiological contamination.

XI. PACKAGING

Problems in the packaging of oral liquids have included potency (fill) of unit dose products and accurate calibration of measuring devices such as droppers, which are often provided. For unit dose solution products the label claim quantity within the limits described should be delivered.

Another problem in the packaging of oral liquids is lack of cleanliness of the containers before filling. Fibers and even insects often appear as debris in containers, particularly in the plastic containers used for many of these products. Many manufacturers receive containers shrink wrapped in plastic to minimize contamination from fiberboard cartons, and many manufacturers use compressed air to clean the containers. Vapors, such as oil vapors, from the compressed air have occasionally been found to present problems, and it is a good practice to use compressed gas from oil-free compressors.

2

Oral Solutions and Suspensions

I. INTRODUCTION

The manufacture and control of oral solutions and oral suspensions present unique problems to the industry. While bioequivalency concerns are minimal (except for antibiotic suspensions, for example), other issues have led to recalls, including microbiological, potency, and stability problems. Additionally, because the population using these oral dosage forms includes newborn, pediatric, and geriatric patients who may not be able to take oral solid dosage forms and may be compromised, defective dosage forms can pose an even greater risk than for other patients.

II. FACILITIES

The design of production facilities is largely dependent on the type of products manufactured and the potential for cross-contamination and microbiological contamination. For example, facilities used for the manufacture of over-the-counter (OTC) oral products might not require the isolation that a steroid or sulfa product would require. The manufacturer must establish policies of isolation of processes to minimize contamination. It should be further established whether or not particular drug substances and powdered excipients generate dust, given the method of manufacture used. System design and efficiency of dust removal system must be considered. A firm's HVAC system requires particular attention, especially where potent or highly sensitizing drugs are processed. Some manufacturers recirculate air without adequate filtration. Where air is recirculated, a firm's data must demonstrate the efficiency of air filtration through surface and/or air sampling.

III. EQUIPMENT

Equipment should be of a sanitary design and should include sanitary pumps, valves, flow meters, and other equipment that can be easily sanitized. Ball valves, packing in pumps, and pockets in flow meters have been identified as sources of contamination. In order to facilitate cleaning and sanitization, manufacturing and filling lines should be identified and detailed in drawings and standard operating procedures. In some cases, long delivery lines between manufacturing areas and filling areas have been a source of contamination. The standard operating procedures of many manufacturers have been found to be deficient, particularly with regard to time limitations between batches and for cleaning. Equipment used for batching and mixing of oral solutions and suspensions is relatively basic. Generally, these products are formulated on a weight basis with the batching tank on load cells so that a final quantity sufficient (QS) can be made by weight. Volumetric means, such as using a dipstick or line on a tank, have been found to be inaccurate. In most cases, manufacturers will assay samples of the bulk solution or suspension prior to filling. A much greater variability has been found with batches that have been manufactured volumetrically rather than by weight.

The design of the batching tank with regard to the location of the bottom discharge valve also presents problems. Ideally, the bottom discharge valve should be flush with the bottom of the tank. In some cases, valves (including undesirable ball valves) are several inches below the bottom of the tank; in others, the drug or preservative is not completely dissolved and lies in the dead leg below the tank, with initial samples being found to be subpotent. For the manufacture of suspensions, valves should be flush.

With regard to transfer lines, they are generally hard piped and easily cleaned and sanitized. In some cases, manufacturers have used flexible hoses to transfer product, but it is not unusual to find flexible hoses on the floor, thus significantly increasing the potential for contamination. Such contamination can occur when operators pick up or handle the hoses, possibly even placing them in transfer or batching tanks after picking them up from the floor. It is also a good practice to store hoses in a way that allows them to drain rather than coiling them, which may allow moisture to collect and be a potential source of microbial contamination.

Another common problem occurs when a manifold or common connection is used, especially in water supply, premix, or raw material supply tanks. Such common connections have been shown to be a source of contamination.

IV. RAW MATERIALS

Physical characteristics, particularly the particle size of the drug substance, are very important for suspensions. As with topical products in which the drug is suspended, particles are usually very fine to micronize (less than 25 μm). For syrups, elixirs, or solution dosage forms in which nothing is suspended, the particle size and physical characteristics of the raw materials are not that important; however, they can affect the rate of dissolution of such raw materials during the manufacturing process. Raw materials of a finer particle size may dissolve faster than those of a larger particle size when the product is compounded.

V. COMPOUNDING

In addition to a determination of the final volume (QS) as previously discussed, microbiological concerns also exist. For oral suspensions, an additional concern is uniformity, particularly because of the potential for segregation during the manufacture and storage of the bulk suspension, during transfer to the filling line, and during filling. A manufacturer's data should support storage times and transfer operations. Procedures and time limits for such operations

should be established to address the potential for segregation or settling, as well as other unexpected effects that may be caused by extended holding or stirring.

For oral solutions and suspensions, the amount and control of temperature are important from a microbiological as well as a potency aspect. For those products in which temperature is identified as a critical part of the operation, the manufacturer should maintain documentation of temperature, such as by control charts.

Some manufacturers rely on heat during compounding to control the microbiological levels in product. For such products, the addition of purified water to a final QS, the batch, and the temperatures during processing should be documented and available for review.

In addition to drug substances, some additives, such as paraben, are difficult to dissolve and require heat. The control and monitoring of their dissolution during the compounding stage should be documented. From a potency aspect, the storage of product at high temperatures may increase the level of degradants. Storage limitations (time and temperature) should be justified by manufacturers and are likely to be evaluated during an inspection.

Some oral liquids are sensitive to oxygen and have been known to undergo degradation. This is particularly true of the phenothiazine class of drugs, such as perphenazine and chlorpromazine. The manufacture of such products might require the removal of oxygen such as by nitrogen purging. Additionally, such products might also require storage in sealed tanks, rather than in tanks with loose lids. In the OTC category, the entire line of vitamins is subject to degradation if they are not properly protected against oxidation, particularly those products that contain minerals (which might contain highly active trace elements that catalyze degradation of vitamins).

VI. MICROBIOLOGICAL QUALITY

Microbiological contamination of some oral liquids can present significant health hazards. For example, some oral liquids, such as nystatin suspension, are used for infants and immunocompromised patients, and microbiological contamination with organisms such as Gram-negative organisms is objectionable. For other oral liquid preparations, such as antacids, *Pseudomonas* sp. contamination is also objectionable; however, for some oral liquids, such as cough preparations, contamination with *Pseudomonas* sp. might not present the same health hazard. Obviously, the contamination of any preparation with Gram-negative organisms is not desirable.

In addition to the specific contaminant being objectionable, such contamination would be indicative of a deficient process as well as an inadequate preservative system. The presence of a specific *Pseudomonas* sp. may also indicate that other plant or raw material contaminants could survive the process. For example, the fact that a *Pseudomonas putida* contaminant is present could also indicate that *Pseudomonas aeruginosa*, a similar source organism, could also be present.

VII. ORAL SUSPENSION UNIFORMITY

Liquid products in which the drug is suspended (and not in solution) present manufacturer control problems. Depending upon the viscosity, many suspensions require continuous or periodic agitation during the filling process. If delivery lines are used between the bulk storage tank and the filling equipment, some segregation may occur, particularly if the product is not viscous. Inspectors will review a manufacturer's procedures for filling and diagrams for line setup prior to the filling equipment. Good manufacturing practice would warrant testing bottles from the beginning, middle, and end to assure that segregation has not occurred. Such samples should not be composited or pooled. In-process testing for suspensions might also include an assay of a sample from the bulk tank. More important, however, may be testing for viscosity.

VIII. PRODUCT SPECIFICATIONS

Important specifications for the manufacture of all solutions include assay and microbial limits. Additional important specifications for suspensions include particle size of the suspended drug, viscosity, pH, and in some cases, dissolution. Maintaining an appropriate viscosity is important from a processing perspective to minimize segregation. Additionally, viscosity has also been shown to be associated with bioequivalency. The pH may also have some meaning regarding effectiveness of preservative systems and may even have an effect on the amount of drug in solution. With regard to dissolution, at least several products have dissolution specifications listed in their U.S. Pharmacopeia (USP) monographs. Particle size is also important, and at this point it would seem that any suspension should have some type of particle-size specification.

IX. PROCESS VALIDATION

As with other products, the amount of data required to support the manufacturing process will vary from product to product. Development (data) should identify critical phases of the operation, including the predetermined specifications that should be monitored during process validation. For example, for solutions the key aspects that should be addressed during validation include assurance that the drug substance and preservatives are dissolved. Parameters such as heat and time should be measured. In-process assay of the bulk solution during and/or after compounding according to predetermined limits is also an important aspect of process validation. For solutions that are sensitive to oxygen and/or light, dissolved oxygen levels would also be an important test. Again, the development data and the protocol should provide limits. The manufacture of suspensions presents additional problems, particularly in the area of uniformity. Again, development data should address the key compounding and filling steps that ensure uniformity. The protocol should provide for the key in-process and finished product tests, along with their specifications. For oral solutions, bioequivalency studies may not always be needed; however, oral suspensions, with the possible exception of some antacids and OTC products, usually require a bioequivalency or clinical study to demonstrate effectiveness. As with oral solid dosage forms, comparison to the biobatch is an important part of validating the process.

X. STABILITY

One area that has presented a number of problems includes maintaining the stability of oral liquid products throughout

their expiry period. Vitamins with fluoride oral liquid products have had a number of recalls because of vitamin degradation. Drugs in the phenothiazine class, such as perphenazine, chlorpromazine, and promethazine, have also shown evidence of instability. Good practice for this class of drug products would include quantitation of both the active and primary degradant. Dosage form manufacturers should know and have specifications for the primary degradant. These manufacturers' data and validation data for methods used to quantitate both the active drug and degradant are likely to be reviewed during an inspection. Because interactions of products with closure systems are possible, liquids and suspensions undergoing stability studies should be stored on their side or inverted in order to determine whether contact of the drug product with the closure system affects product integrity. Moisture losses that can cause the remaining contents to become superpotent and microbiological contamination are other problems associated with inadequate closure systems.

XI. PACKAGING

Problems in the packaging of oral liquids have included potency (fill) of unit dose products and accurate calibration of measuring devices such as droppers that are often provided. The USP does not provide for dose uniformity testing for oral solutions. Thus, unit-dose solution products should deliver label claims within the limits described in the USP. Inspectors will review a manufacturer's data to ensure uniformity of fill and test procedures to ascertain that unit-dose samples are being tested. Another problem in the packaging of oral liquids is a lack of cleanliness of containers prior to filling. Fibers and even insects have been identified as debris in containers, particularly plastic containers used for these products. Many manufacturers receive containers shrink wrapped in plastic to minimize contamination from fiberboard cartons. Some manufacturers may utilize compressed air to clean containers, in which case vapors (such as oil vapors) from the compressed air have occasionally been found to present problems.

3

The FDA Drug Product Surveillance Program

I. BACKGROUND

A primary mission of the Food and Drug Administration (FDA) is to conduct comprehensive regulatory coverage of all aspects of production and distribution of drugs and drug products to assure that such products meet the 501(a)(2)(B) requirements of the Food, Drugs, and Cosmetics Act. The FDA has developed two basic strategies:

1. Evaluating through factory inspections, including the collection and analysis of associated samples, the conditions and practices under which drugs and drug products are manufactured, packed, tested, and held
2. Monitoring the quality of drugs and drug products through surveillance activities such as sampling and analyzing products in distribution

This compliance program is designed to provide guidance for implementing the first strategy. Products from production and distribution facilities covered under this program are consistently of acceptable quality if the firm is operating in a state of control. The Drug Product Surveillance Program (CP 7356.008) provides guidance for the latter strategy.

II. IMPLEMENTATION

A. Objectives

The goal of this program's activities is to minimize consumer's exposure to adulterated drug products. Under this program, inspections and investigations, sample collections and analyses, and regulatory or administrative follow-up are made:

- To determine whether inspected firms are operating in compliance with applicable current Good Manufacturing Practices (cGMPs) requirements and, if not, to provide the evidence for actions to prevent adulterated products from entering the market; and, as appropriate, to remove adulterated products from the market and to take action against persons responsible as appropriate
- To provide cGMP assessment, which may be used in efficient determination of acceptability of the firm in the preapproval review of a facility for new drug applications
- To provide input to firms during inspections to improve their compliance with regulations
- To continue the FDA's unique expertise in drug manufacturing in determining the adequacy of cGMP requirements, FDA cGMP regulatory policy, and guidance documents.

B. Strategy

1. Biennial Inspection of Manufacturing Sites

Drugs and drug products are manufactured using many physical operations to bring together components, containers, and closures into a product that is released for distribution. Activities found in drug firms can be organized into systems that are sets of operations and related activities. Control of all systems helps to ensure that the firm will produce drugs that are safe, have the identity and strength, and meet the quality and purity characteristics as intended.

Biennial inspections (every 2 years) of manufacturing sites, which include repackaging, contract labs, etc., help to

- reduce the risk that adulterated products are reaching the marketplace,
- increase communication between the industry and the Agency,
- provide for timely evaluation of new manufacturing operations in the firm, and
- provide for regular feedback from the Agency to individual firms on the continuing status of the firm's GMP compliance

This program applies to all drug manufacturing operations. Currently, not enough FDA resources are available to audit every aspect of cGMP in every manufacturing facility during every inspection visit. Profile classes generalize inspection coverage from a small number of specific products to all the products in that class. This program establishes a systems approach to further generalize inspection coverage from a small number of profile classes to an overall evaluation of the firm. Reporting coverage for every profile class as defined in Field Accomplishment and Compliance Tracking System (FACTS), in each biennial inspection, provides the most broadly resource-efficient approach. Biennial updating of all profile classes will allow for cGMP acceptability determinations to be made without delays resulting from revisiting the firm. This will speed the review process, in response to compressed time frames for application decisions and in response to provisions of the FDA Modernization Act of 1997 (FDAMA). This will allow for Preapproval Inspections/ Investigations Program inspections and Postapproval Audit Inspections to focus on the specific issues related to a given application or the firm's ability to keep applications current.

The inspection is defined as audit coverage of two or more systems, with mandatory coverage of the Quality System (see the system definitions in section II.B.3.). Inspection options include different numbers of systems to be covered depending on the purpose of the inspection. Inspecting the minimum number of systems, or more systems as deemed necessary by the regional District of the FDA, will provide the basis for an overall cGMP decision.

2. Inspection of Systems

Inspections of drug manufacturers should be made and reported using the system definitions and organization in this compliance program. Focusing on systems instead of on profile classes will increase efficiency in conducting inspections because the systems are often applicable to multiple profile

classes. One biennial inspection visit will result in a determination of acceptability/nonacceptability for all profile classes. Inspection coverage should be representative of all the profile classes manufactured by the firm. The efficiency will be realized, because multiple visits to a firm will not be needed to cover all profile classes; delays in approval decisions will be avoided because up-to-date profile class information will be available at all times.

Coverage of a system should be sufficiently detailed, with specific examples selected, so that the system inspection outcome reflects the state of control in that system for every profile class. If a particular system is adequate, it should be adequate for all profile classes manufactured by the firm. For example, the way a firm handles "materials" (i.e., receipt, sampling, testing, acceptance, etc.) should be the same for all profile classes. The investigator should not have to inspect the Material System for each profile class. Likewise, the Production System includes general requirements such as standard operating procedure (SOP) use, charge-in of components, equipment identification, and in-process sampling and testing, which can be evaluated through selection of example products in various profile classes. Under each system, there may be something unique for a particular profile class (e.g., under the Materials System, the production of Water for Injection USP (*US Pharmacopeia*) for use in manufacturing. Selecting unique functions within a system will be at the discretion of the lead investigator). Any given inspection need not cover every system (see section III).

Complete inspection of one system may necessitate further follow-up of some items within the activities of another/other system(s) to fully document the findings. However, this coverage neither constitute nor require complete coverage of these other systems.

3. A Scheme of Systems for the Manufacture of Drugs and Drug Products

A general scheme of systems for auditing the manufacture of drugs and drug products consists of the following:

1. *Quality System*—This system assures overall compliance with cGMPs and internal procedures and specifications. The system includes the quality control unit and all its review and approval duties (e.g., change control, reprocessing, batch release, annual record review, validation protocols, and reports). It includes all product defect evaluations and evaluation of returned and salvaged drug products. (See the cGMP regulation, 21 CFR 211 subparts B, E, F, G, I, J, and K.)
2. *Facilities and Equipment System*—This system includes the measures and activities that provide an appropriate physical environment and the resources used in the production of the drugs or drug products. It includes the following:
   a. Buildings and facilities along with maintenance
   b. Equipment qualifications (installation and operation); equipment calibration and preventative maintenance; and cleaning and validation of cleaning processes as appropriate process performance qualification will be evaluated as part of the inspection of the overall process validation that is done within the system where the process is employed
   c. Utilities not intended for incorporation into the product such as heating, ventilating, and air conditioning (HVAC), compressed gases, steam, and water systems. (See the cGMP regulation, 21 CFR 211 subparts B, C, D, and J.)
3. *Materials System*—This system includes measures and activities to control finished products, components, including water or gases that are incorporated into the product, containers, and closures. It includes validation of computerized inventory control processes, drug storage, distribution controls, and records. (See the cGMP regulation, 21 CFR 211 subparts B, E, H, and J.)
4. *Production System*—This system includes measures and activities to control the manufacture of drugs and drug products including batch compounding, dosage form production, in-process sampling and testing, and process validation. It also includes establishing, following, and documenting performance of approved manufacturing procedures. (See the cGMP regulation, 21 CFR 211 subparts B, F, and J.)
5. *Packaging and Labeling System*—This system includes measures and activities that control the packaging and labeling of drugs and drug products. It includes written procedures, label examination and usage, label storage and issuance, packaging and labeling operations controls, and validation of these operations. (See the cGMP regulation, 21 CFR 211 subparts B, G, and J.)
6. *Laboratory Control System*—This system includes measures and activities related to laboratory procedures, testing, analytical methods development and validation or verification, and the stability program. (See the cGMP regulation, 21 CFR 211 subparts B, I, J, and K.)

The overall theme in devising this scheme of systems was the subchapter structure of the cGMP regulation. Every effort was made to group whole subchapters together in a rational set of six systems that incorporates the general scheme of pharmaceutical manufacturing operations.

The organization and personnel, including appropriate qualifications and training, employed in any given system, is evaluated as part of that system's operation. Production, control, or distribution records required to be maintained by the cGMP regulation and selected for review should be included for inspection audit within the context of each of the previously described systems. Inspections of contract companies should be within the systems for which the products or services are contracted as well as their quality systems.

III. PROGRAM MANAGEMENT INSTRUCTIONS

A. Definitions

1. Surveillance Inspections

a. The Full Inspection Option

The Full Inspection Option is a surveillance or compliance inspection that is meant to provide a broad and deep evaluation of the firm's cGMP. This is done when little or no information is known about a firm's cGMP compliance (e.g., for new firms); or for firms where doubt exists about the cGMP compliance in the firm (e.g., a firm with a history of documented short-lived compliance and recidivism); or follow-up to previous regulatory actions. Based on findings of objectionable conditions (as listed in section V) in one or more systems—a minimum of two systems must be completed—a Full Inspection may revert to the Abbreviated Inspection Option, with District concurrence (see section III.B.1.). During the course of a Full Inspection, verification of Quality System activities may require limited coverage in other systems. The Full Inspection Option normally includes an inspection audit of at least four of the systems, one of which must be the Quality

System (the system that includes the responsibility for the annual product reviews).

b. The Abbreviated Inspection Option

The Abbreviated Inspection Option is a surveillance or compliance inspection that is meant to provide an efficient update evaluation of a firm's cGMP. The abbreviated inspection provides documentation for continuing a firm in a satisfactory cGMP compliance status. Generally, this is done when a firm has a record of satisfactory cGMP compliance, with no significant recall or product defect or alert incidents, or with little shift in the manufacturing profiles of the firm within the previous two years (see section III.B.2). A full inspection may revert to an abbreviated inspection based on findings of objectionable conditions as listed in section V in one or more systems. The Abbreviated Inspection Option normally includes an inspection audit of at least two of the systems, one of which must be the Quality System (the system which includes the responsibility for the annual product reviews). The District drug program managers should ensure that the optional systems are rotated in successive abbreviated inspections. During the course of an abbreviated inspection, verification of quality system activities may require limited coverage in other systems. Some firms participate in a limited part of the production of a drug or drug product (e.g., a contract laboratory). Such firms may employ only two of the systems defined. In these cases, the inspection of the two systems comprises inspection of the entire firm; this is considered as the Full Inspection Option.

c. Selecting Systems for Coverage

The selection of the system(s) for coverage will be made by the FDA's Regional District Office based on such factors as a given firm's specific operation, history of previous coverage, history of compliance, or other priorities determined by the District Office.

2. Compliance Inspections

Compliance inspections are inspections conducted to evaluate or verify compliance corrective actions after a regulatory action has been taken. First, the coverage given in compliance inspections must be related to the deficient areas and subjected to corrective actions.

In addition, coverage must be given to systems because a determination must be made on the overall compliance status of the firm after the corrective actions are taken. The firm is expected to address all its operations in its corrective action plan after a previously violative inspection, not just the deficiencies noted in the FDA-483 (inspectional observations). The Full Inspection Option should be used for a compliance inspection, especially if the Abbreviated Inspection Option was used during the violative inspection.

Compliance Inspections include "For Cause Inspections." For Cause Inspections are compliance inspections that are conducted to investigate a specific problem that has come to the attention of some level of the agency. The problems may be indicated in Field Alert Reports (FARs), industry complaints, recalls, indicators of defective products, etc. Coverage of these areas may be assigned under other compliance programs; however, expansion of the coverage to a GMP inspection must be reported under this program. For Cause Inspections may be assigned under this program as the need arises.

3. State of Control

A drug firm is considered to be operating in a "state of control" when it employs conditions and practices that assure compliance with the intent of sections 501(a)(2)(B) of the Act and portions of the cGMP regulations that pertain to their systems. A firm in a state of control produces finished drug products for which there is an adequate level of assurance of quality, strength, identity, and purity. A firm is "out of control" if any one system is out of control. A system is out of control if the quality, identity, strength, and purity of the products resulting from that (those) system(s) cannot be adequately assured. Documented cGMP deficiencies provide the evidence for concluding that a system is not operating in a state of control. See section V, "Regulatory/Administrative Strategy," for a discussion of compliance actions based on inspection findings demonstrating out of control systems/firm.

4. Drug Process

A drug process is a related series of operations that result in the preparation of a drug or drug product. Major operations or steps in a drug process may include mixing, granulation, encapsulation, tabletting, chemical synthesis, fermentation, aseptic filling, sterilization, packing, labeling, and testing.

5. Drug Manufacturing Inspection

A Drug Manufacturing Inspection is a factory inspection in which evaluation of two or more systems, including the Quality System, is done to determine if manufacturing is occurring in a state of control.

B. Inspection Planning

The Field Office will conduct drug manufacturing inspections and maintain profiles or other monitoring systems, which ensures that each drug firm receives biennial inspectional coverage, as provided for in the strategy.

The District Office is responsible for determining the depth of coverage given to each drug firm. cGMP inspectional coverage shall be sufficient to assess the state of compliance for each firm.

The frequency and depth of inspection should be determined by the statutory obligation, the firm's compliance history, the technology employed, and the characteristics of the products. When a system is inspected, the inspection of that system may be considered applicable to all products that use it. Investigators should select an adequate number and type of products to accomplish coverage of the system. Selection of products should be made so that coverage is representative of the firm's overall abilities to manufacture within cGMP requirements.

Review of new drug application/anticipated new drug application (NDA/ANDA) files may assist in selecting significant drug processes for coverage in the various systems. Significant drug processes are those that utilize all the systems in the firm very broadly and contain steps with unique or difficult manipulation in the performance of a step. Products posing special manufacturing features (e.g., low-dose products, narrow therapeutic range drugs, combination drugs, modified release products, etc.) and new products made under an approved drug application should be considered first in selecting products for coverage.

The health significance of certain cGMP deviations may be lower when the drug product involved has no major systemic effect or no dosage limitations, such as in products like calamine lotion or over-the-counter (OTC) medicated

shampoos. Such products should be given inspection coverage with appropriate priority.

Inspections for this compliance program may be performed during visits to a firm when operations are being performed for other compliance programs or other investigations.

C. Profiles

The inspection findings will be used as the basis for updating all profile classes in the profile screen of the FACTS EIR coversheet that is used to record profile/class determinations. Normally, an inspection under this systems approach will result in the update of all profile classes.

IV. INSPECTIONAL OBSERVATIONS

A. Investigational Operations

1. General

Review and use the cGMPs for Finished Pharmaceuticals (21 CFR 210 and 211) to evaluate manufacturing processes. Use the Guides to Inspection published by the Office of Regional Operations for information on technical applications in various manufacturing systems.

The investigator should conduct inspections according to the "Strategy" section in part II of this compliance program. Recognizing that drug firms vary greatly in size and scope, and manufacturing systems are more or less sophisticated, the approach to inspecting each firm should be carefully planned. For example, it may be more appropriate to review the Quality System thoroughly before entering production areas in some firms; in others, the Quality System review should take place concurrently with inspection of another system or systems selected for coverage. The complexity and variability necessitate a flexible inspection approach—one that not only allows the investigator to choose the inspection focus and depth appropriate for a specific firm, but also directs the performance and reporting on the inspection within a framework that will provide for a uniform level of cGMP assessment. Furthermore, this inspection approach provides for fast communication and evaluation of findings.

Inspectional Observations noting cGMP deficiencies should be related to a requirement. Requirements for the manufacture of drug products (dosage forms) are in the cGMP regulation and are amplified by policy in the Compliance Policy Guides or case precedents. cGMP requirements apply to the manufacture of distributed prescription drug products, OTC drug products, approved products, and products not requiring approval, as well as drug products used in clinical trials. The cGMP regulations are not direct requirements for manufacture of active pharmaceutical ingredients (APIs); the regulations should not be referenced as the basis for a GMP deficiency in the manufacture of APIs, but they are guidance for cGMP in API manufacture.

Guidance documents do not establish requirements; they state examples of ways to meet requirements. Guidance documents are not to be referred to as the justification for an inspectional observation. The justification comes from the cGMPs. Current Guides to Inspection and Guidance to Industry documents provide interpretations of requirements, which may assist in the evaluation of the adequacy of cGMP systems.

Current inspectional observation policy as stated in the inspection operations manual (IOM) says that the FDA-483, when issued, should be specific and contain only significant items. For this program, inspection observations should be organized under separate captions by the systems defined in this program. List observations in order of importance within each system. Where repeated or similar observations are made, they should be consolidated under a unified observation. For those Districts utilizing Turbo EIR, a limited number of observations can be common to more than one system (e.g., organization and personnel including appropriate qualifications and training). In these instances, put the observation in the first system reported on the FDA-483 and in the text of the EIR, reference the applicability to other systems where appropriate. This should be done to accommodate the structure of Turbo EIR, which allows individual citation once per FDA-483. Refrain from using unsubstantiated conclusions. Do not use the term "inadequate" without explaining why and how. Refer to the policy in the IOM, chapter 5, section 512 and Field Management Directive 120 for further guidance on the content of Inspectional Observations.

Specific specialized inspectional guidance may be provided as attachments to this program, or in requests for inspection, assignments, etc.

2. Inspection Approaches

This program provides two surveillance inspectional options: Abbreviated Inspection Option and Full Inspection Option (see the definitions of the inspection options in part II of this compliance program).

1. *Selecting the Full Inspection Option*—The Full Inspection Option will include inspection of at least four of the systems as listed in part II "Strategy," one of which must be the Quality System.
   a. Select the Full Inspection Option for an initial FDA inspection of a facility. A full inspection may revert to the Abbreviated Inspection Option, *with District concurrence,* based on the finding of objectionable conditions as listed in part V in one or more systems (a minimum of two systems must be completed).
   b. Select the Full Inspection Option when the firm has a history of fluctuating into and out of compliance. To determine if the firm meets this criterion, the District should utilize all information at its disposal, such as, inspection results, results of sample analyses, complaints, drug quality reporting system (DQRS) reports, recalls, etc., and the compliance actions resulting from them or from past inspections. A Full Inspection may revert to the Abbreviated Inspection Option, *with District concurrence,* based on findings of objectionable conditions as listed in part V in one or more systems (a minimum of two systems must be completed).
   c. Evaluate if important changes have occurred by comparing current operations against the EIR for the previous full inspection. The following types of changes are typical of those that warrant the Full Inspection Option:
      - New potential for cross-contamination arising through change in process or product line
      - Use of new technology requiring new expertise, significant new equipment, or new facilities
   d. A Full Inspection may also be conducted on a surveillance basis at the District's discretion.
   e. The Full Inspection Option will satisfy the biennial inspection requirement.
   f. Follow-up to a Warning Letter or other significant regulatory actions should require a Full Inspection Option.

2. *Selecting the Abbreviated Inspection Option*—The Abbreviated Inspection Option normally will include inspection audit of at least two systems, one of which must be the Quality System. During the course of an abbreviated inspection, verification of quality system activities may require limited coverage in other systems.
   a. This option involves an inspection of the manufacturer to maintain surveillance over the firm's activities and to provide input to the firm on maintaining and improving the GMP level of assurance of quality of its products.
   b. A full inspection may revert to the Abbreviated Inspection Option, *with District concurrence,* based on findings of objectionable conditions as listed in part V in one or more systems (a minimum of two systems must be completed).
   c. An abbreviated inspection is adequate for routine coverage and will satisfy the biennial inspectional requirement.

a. Comprehensive Inspection Coverage

It is not anticipated that full inspections will be conducted every two years. They may be conducted at less frequent intervals, perhaps at every third or fourth inspection cycle. Districts should consider selecting different optional systems for inspection coverage as a cycle of Abbreviated inspections are carried out to build comprehensive information on the firm's total manufacturing activities.

3. System Inspection Coverage

a. Quality System

Assessment of the Quality System is two-phased:

1. The first phase evaluates whether the Quality Control Unit has fulfilled the responsibility to review and approve all procedures related to production, quality control, and quality assurance and assure the procedures are adequate for their intended use. This also includes the associated record-keeping systems.
2. The second phase assesses the data collected to identify quality problems and may link to other major systems for inspectional coverage.

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other major systems that would warrant expansion of coverage. All areas under this system should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- *Product reviews*—at least annually; should include information from areas listed below as appropriate; batches reviewed for each product are representative of all batches manufactured; trends are identified [refer to 21 CFR 211.180(e)]
- *Complaint reviews (quality and medical)*—documented; evaluated; investigated in a timely manner; includes corrective action where appropriate
- *Discrepancy and failure investigations related to manufacturing and testing*—documented; evaluated; investigated in a timely manner; includes corrective action where appropriate
- *Change control*—documented; evaluated; approved; need for revalidation assessed
- *Product improvement projects*—for marketed products
- *Reprocess/rework*—evaluation, review, and approval; impact on validation and stability
- *Returns/salvages*—assessment; investigation expanded where warranted; disposition
- *Rejects*—investigation expanded where warranted; corrective action where appropriate
- *Stability failures*—investigation expanded where warranted; need for field alerts evaluated; disposition
- Quarantine products
- *Validation*—status of required validation/revalidation (e.g., computer, manufacturing process, laboratory methods)
- Training/qualification of employees in quality control unit functions

b. Facilities and Equipment System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

1. *Facilities*
   - Cleaning and maintenance
   - Facility layout and air handling systems for prevention of cross-contamination (e.g., penicillin, beta-lactams, steroids, hormones, cytotoxics, etc.)
   - Specifically designed areas for the manufacturing operations performed by the firm to prevent contamination or mix-ups
   - General air handling systems
   - Control system for implementing changes in the building
   - Lighting, potable water, washing and toilet facilities, sewage and refuse disposal
   - Sanitation of the building, use of rodenticides, fungicides, insecticides, and cleaning and sanitizing agents
2. *Equipment*
   - Equipment installation and operational qualification where appropriate
   - Adequacy of equipment design, size, and location
   - Equipment surfaces should not be reactive, additive, or absorptive
   - Appropriate use of equipment operations substances (lubricants, coolants, refrigerants, etc.), contacting products, containers, etc.
   - Cleaning procedures and cleaning validation
   - Controls to prevent contamination, particularly with any pesticides or any other toxic materials, or other drug or nondrug chemicals
   - Qualification, calibration, and maintenance of storage equipment, such as refrigerators and freezers for ensuring that standards, raw materials, and reagents are stored at the proper temperatures

- Equipment qualification, calibration, and maintenance, including computer qualification/validation and security
- Control system for implementing changes in the equipment
- Equipment identification practices (where appropriate)
- Documented investigation into any unexpected discrepancy

c. Materials System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- Training/qualification of personnel
- Identification of components, containers, and closures
- Inventory of components, containers, and closures
- Storage conditions
- Storage under quarantine until tested or examined and released
- Representative samples collected, tested, or examined using appropriate means
- At least one specific identity test is conducted on each lot of each component
- A visual identification is conducted on each lot of containers and closures
- Testing or validation of supplier's test results for components, containers, and closures
- Rejection of any component, container, or closure not meeting acceptance requirements
- Investigate fully the firm's procedures for verification of the source of components
- Appropriate retesting/reexamination of components, containers, and closures
- First in–first out use of components, containers, and closures
- Quarantine of rejected materials
- Water and process gas supply, design, maintenance, validation, and operation
- Containers and closures should not be additive, reactive, or absorptive to the drug product
- Control system for implementing changes in the materials handling operations
- Qualification/validation and security of computerized or automated processes
- Finished product distribution records by lot
- Documented investigation into any unexpected discrepancy

d. Production System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- Training/qualification of personnel
- Control system for implementing changes in processes
- Adequate procedure and practice for charge-in of components
- Formulation/manufacturing at not less than 100%
- Identification of equipment with contents, and, where appropriate, phase of manufacturing or status
- Validation and verification of cleaning/sterilization/depyrogenation of containers and closures
- Calculation and documentation of actual yields and percentage of theoretical yields
- Contemporaneous and complete batch production documentation
- Establishing time limits for completion of phases of production
- Implementation and documentation of in-process controls, tests, and examinations (e.g., pH, adequacy of mix, weight variation, clarity)
- Justification and consistency of in-process specifications and drug product final specifications
- Prevention of objectionable microorganisms in unsterile drug products
- Adherence to preprocessing procedures (e.g., setup, line clearance, etc.)
- Equipment cleaning and use logs
- Master production and control records
- Batch production and control records
- Process validation, including validation and security of computerized or automated processes
- Change control; the need for revalidation evaluated
- Documented investigation into any unexpected discrepancy

e. Packaging and Labeling System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- Training/qualification of personnel
- Acceptance operations for packaging and labeling materials
- Control system for implementing changes in packaging and labeling operations
- Adequate storage for labels and labeling, both approved and returned after issued
- Control of labels that are similar in size, shape, and color for different products

- Finished product cut labels for immediate containers that are similar in appearance without some type of 100% electronic or visual verification system or the use of dedicated lines
- Labels are not gang printed unless they are differentiated by size, shape, or color
- Control of filled unlabeled containers that are later labeled under multiple private labels
- Adequate packaging records that will include specimens of all labels used
- Control of issuance of labeling, examination of issued labels, and reconciliation of used labels
- Examination of the labeled finished product
- Adequate inspection (proofing) of incoming labeling
- Use of lot numbers and the destruction of excess labeling bearing lot/control numbers
- Physical/spatial separation between different labeling and packaging lines
- Monitoring of printing devices associated with manufacturing lines
- Line clearance, inspection, and documentation
- Adequate expiration dates on the label
- Conformance to tamper-evident packaging (TEP) requirements (see 21CFR 211.132 and Compliance Policy Guide, 7132a.17)
- Validation of packaging and labeling operations, including validation and security of computerized processes
- Documented investigation into any unexpected discrepancy

f. Laboratory Control System

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited only to finished products, but may also incorporate components and in-process materials. These areas may indicate deficiencies not only in this system, but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed next should be covered; however, the depth of coverage may vary depending upon inspectional findings:

- Training/qualification of personnel
- Adequacy of staffing for laboratory operations
- Adequacy of equipment and facility for intended use
- Calibration and maintenance programs for analytical instruments and equipment
- Validation and security of computerized or automated processes
- Reference standards: source, purity and assay, and tests to establish equivalency to current official reference standards as appropriate
- System suitability checks on chromatographic systems [e.g., gas chromatography (GC) or high pressure liquid chromatography (HPLC)]
- Specifications, standards, and representative sampling plans
- Adherence to the written methods of analysis
- Validation/verification of analytical methods
- Control system for implementing changes in laboratory operations
- Required testing is performed on the correct samples
- Documented investigation into any unexpected discrepancy
- Complete analytical records from all tests and summaries of results
- Quality and retention of raw data (e.g., chromatograms and spectra)
- Correlation of result summaries to raw data; presence of unused data
- Adherence to an adequate Out of Specification (OOS) procedure that includes timely completion of the investigation
- Adequate reserve samples; documentation of reserve sample examination
- Stability testing program, including demonstration of stability indicating capability of the test methods

4. Sampling

Samples of defective product constitute persuasive evidence that significant cGMP problems exist. Physical samples may be an integral part of a cGMP inspection where control deficiencies are observed. Physical samples should be correlated with observed control deficiencies. Consider consulting your servicing laboratory for guidance on quantity and type of samples (in-process or finished) to be collected. Documentary samples may be submitted when the documentation illustrates the deficiencies better than a physical sample. Districts may elect to collect, but not analyze, physical samples or to collect documentary samples to document cGMP deficiencies. Physical sample analysis is not necessary to document cGMP deficiencies.

When a large number of products have been produced under deficient controls, collect physical or documentary samples of products that have the greatest therapeutic significance, narrow range of toxicity, or low dosage strength. Include samples of products of minimal therapeutic significance only when they illustrate highly significant cGMP deficiencies.

5. Inspection Teams

An inspection team (see IOM 502.4) composed of experts from within the District, other Districts, or Headquarters is encouraged when it provides needed expertise and experience. Contact the ORO/Division of Field Investigations if technical assistance is needed (see also FMD 142). Participation of an analyst (chemist or microbiologist) on an inspection team is also encouraged, especially where laboratory issues are extensive or complex. Contact your Drug Servicing Laboratory or ORO/Division of Field Science.

6. Reporting

The investigator utilizes Subchapter 590 of the IOM for guidance in reporting of inspectional findings. The Summary of Findings should identify systems covered. The body of the report should identify and explain the rationale for inspecting the profile classes covered. Any adverse findings by systems under separate captions should be reported and discussed in full. Additional information should be provided as needed or desired, for example, a description of any significant changes that have occurred since previous inspections.

Reports with specific, specialized information required should be prepared as instructed within the individual assignment/attachment.

V. ANALYTICAL OBSERVATIONS

A. Analyzing Laboratories

1. Routine chemical analyses—all Servicing Laboratories except WEAC.
2. Sterility testing:
   Region Examining Laboratory
3. Other microbiological examinations—NRL (for the CE Region), SRL, SAN, and DEN; *Salmonella* Serotyping Lab—ARL.
4. Chemical cross-contamination analyses by mass spectrometry (MS)—NRL, SRL, DEN, PRL/NW, and PHI. Non–mass-spectrometry laboratories should call one of their own regional MS-capable laboratories or Division of Field Science (HFC-140) to determine the most appropriate lab for the determinations to be performed.
5. Chemical cross-contamination analyses by nuclear magnetic resonance (NMR) spectroscopy—NRL. Non-NMR laboratories should call one of their own regional labs equipped with NMR or Division of Field Science (HFC-140) to determine the most appropriate lab for the determinations to be performed.
6. Dissolution testing—NRL, KAN, SRL, SJN, DET, PHI, DEN, PRL/SW, and PRL-NW. Districts without dissolution testing capability should use one of their own regional labs for dissolution testing. Otherwise, call DFS.
7. Antibiotic analyses: ORA Examining Laboratory,
   Denver District Lab (HFR-SW260): Tetracyclines, erythromycins
   Northeast Regional Lab (HFR-NE500): Penicillins, cephalosporins
   CDER Examining Laboratory, Office of Testing and Research, Division of Pharmaceutical Analysis (HFD-473): All other antibiotics
8. Bioassays—Division of Testing and Applied Analytical Research, Drug Bioanalysis Branch(HFN-471).
9. Particulate Matter in Injectables—NRL, SRL.
10. Pyrogen/LAL Testing— SRL

B. Analysis

1. Samples must be examined for compliance with applicable specifications as they relate to deficiencies noted during the inspection. The official method should be used for check analyses or, when no official method exists, by other validated procedures.
2. The presence of cross-contamination must be confirmed by a second method. Spectroscopic methods, such as MS, NMR, ultraviolet (UV)-Visible, or infrared (IR) are preferred. A second confirmatory method should be employed by different mechanisms than the initial analysis (i.e., ion-pairing vs. conventional reverse phase HPLC).
3. Check Analysis for dissolution rate must be performed by a second dissolution-testing laboratory.
4. Sterility testing methods should be based on current editions of USP and the *Sterility Analytical Manual*. Other microbiological examinations should be based on appropriate sections of USP and BAM.

VI. REGULATORY/ADMINISTRATIVE STRATEGY

Inspection findings that demonstrate that a firm is not operating in a state of control may be used as evidence for taking appropriate advisory, administrative, or judicial actions.

When the management of the firm is unwilling or unable to provide adequate corrective actions in an appropriate time frame, formal agency regulatory actions will be recommended that are designed to meet the situation encountered.

When deciding the type of action to recommend, the initial decision should be based on the seriousness of the problem and the most effective way to protect consumers. Outstanding instructions in the *Regulatory Procedures Manual* (*RPM*) should be followed.

The endorsement to the inspection report should point out the actions that have been taken or will be taken and when. All deficiencies noted in inspections/audits under this program must be addressed by stating the firm's corrective actions, accomplished or projected, for each as established in the discussion with management at the close of the inspection.

All corrective action approaches in domestic firms are monitored and managed by the District Offices. The approaches may range from shutdown of operations, recall of products, conducting testing programs, development of new procedures, modifications of plants and equipment, to simple immediate corrections of conditions. CDER/DMPQ/CMGB/HFD-325 will assist District Offices as requested.

An inspection report that documents that one or more systems is/are out of control should be classified as OAI. District Offices may issue Warning Letters per RPM to warn firms of violations, to solicit voluntary corrections, and to provide for the initial phase of formal agency regulatory actions.

Issuance of a Warning Letter or taking other regulatory actions pursuant to a surveillance inspection (other than a For Cause Inspection) should result in the classification of all profile classes as unacceptable. Also, the inspection findings will be used as the basis for updating profile classes in FACTS.

The FDA laboratory tests that demonstrate the effects of absent or inadequate cGMPs are strong evidence for supporting regulatory actions. Such evidence development should be considered as an inspection progresses and deficiencies are found; however, the lack of violative physical samples is *not* a barrier to pursuing regulatory or administrative action, provided that cGMP deficiencies have been well documented. Likewise, physical samples found to be in compliance are *not* a barrier to pursuing action under cGMP charges.

Evidence to support significant deficiencies or a trend of deficiencies within a system covered could demonstrate the failure of a system and should result in consideration of the issuance of a Warning Letter or other regulatory action by the District. When deciding the type of action to recommend, the initial decision should be based on the seriousness or the frequency of the problem. Examples include the following:

Quality System

1. Pattern of failure to review/approve procedures
2. Pattern of failure to document execution of operations as required
3. Pattern of failure to review documentation
4. Pattern of failure to conduct investigations and resolve discrepancies/failures/deviations/complaints
5. Pattern of failure to assess other systems to assure compliance with GMP and SOPs

Facilities and Equipment

1. Contamination with filth, objectionable microorganisms, toxic chemicals or other drug chemicals, or a reasonable potential for contamination, with demonstrated

avenues of contamination, such as airborne or through unclean equipment
2. Pattern of failure to validate cleaning procedures for nondedicated equipment; lack of demonstration of effectiveness of cleaning for dedicated equipment
3. Pattern of failure to document investigation of discrepancies
4. Pattern of failure to establish/follow a control system for implementing changes in the equipment
5. Pattern of failure to qualify equipment, including computers

Materials System
1. Release of materials for use or distribution that do not conform to established specifications
2. Pattern of failure to conduct one specific identity test for components
3. Pattern of failure to document investigation of discrepancies
4. Pattern of failure to establish/follow a control system for implementing changes in the materials handling operations
5. Lack of validation of water systems as required depending upon the intended use of the water
6. Lack of validation of computerized processes

Production System
1. Pattern of failure to establish/follow a control system for implementing changes in the production system operations
2. Pattern of failure to document investigation of discrepancies
3. Lack of process validation
4. Lack of validation of computerized processes
5. Pattern of incomplete or missing batch production records
6. Pattern of nonconformance to established in-process controls, tests, and specifications

Packaging and Labeling
1. Pattern of failure to establish/follow a control system for implementing changes in the packaging or labeling operations
2. Pattern of failure to document investigation of discrepancies
3. Lack of validation of computerized processes
4. Lack of control of packaging and labeling operations that may introduce a potential for mislabeling
5. Lack of packaging validation

Laboratory Control System
1. Pattern of failure to establish/follow a control system for implementing changes in the laboratory operations
2. Pattern of failure to document investigation of discrepancies
3. Lack of validation of computerized and/or automated processes
4. Pattern of inadequate sampling practices
5. Lack of validated analytical methods
6. Pattern of failure to follow approved analytical procedures
7. Pattern of failure to follow an adequate OOS procedure
8. Pattern of failure to retain raw data
9. Lack of stability indicating methods
10. Pattern of failure to follow stability programs

Follow-up to a Warning Letter or other significant regulatory action because of an abbreviated inspection should warrant full inspection coverage as defined in this program.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) *(or Drug Substance)*—Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Airlock—An enclosed space with two or more doors, which is interposed between two or more rooms, for example, of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An airlock is designed for use either by people or for goods and/or equipment.

API Starting Material—A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

Authorized person—The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested, and approved for release in compliance with the laws and regulations in force in that country.

Batch (or Lot)—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Batch Number (or Lot Number)—A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

Batch Records—All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and

of all circumstances pertinent to the quality of the final product.

Bioburden—The level and type (e.g., objectionable or not) of micro-organisms that can be present in raw materials, API starting materials, intermediates or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Bulk Product—Any product that has completed all processing stages up to, but not including, final packaging.

Calibration—The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Clean Area—An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Computer System—A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions. A process or operation integrated with a computer system.

Consignment (or Delivery)—The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Contamination—The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage, or transport.

Contract Manufacturer—A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical—Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Critical Operation—An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Cross-Contamination—Contamination of a material or product with another material or product. Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Deviation—Departure from an approved instruction or established standard.

Drug (Medicinal) Product—The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance—See Active Pharmaceutical Ingredient

Expiry Date (or Expiration Date)—The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Fnished Product—A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.

Impurity—Any component present in the intermediate or API that is not the desired entity.

Impurity Profile—A description of the identified and unidentified impurities present in an API.

In-Process Control—Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate—A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Large-Volume Parenterals—Sterile solutions intended for parenteral application with a volume of 100 mL or more in one container of the finished dosage form.

Lot—See Batch

Lot Number—see Batch Number

Manufacture—All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Manufacturer—A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of pharmaceuticals.

Marketing Authorization (Product License, Registration Certificate)—A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling, and shelf-life.

Master Formula—A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master Record—A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Material—A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labeling materials.

Mother Liquor—The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It may be used for further processing.

Packaging—All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be

terminally sterilized, would not normally be regarded as part of packaging.

Packaging Material—Any material intended to protect an intermediate or API during storage and transport. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical Product—Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Procedure—A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids—Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon, etc).

Process Control—See In-Process Control

Production—All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labeling and relabeling, to completion of the finished product.

Qualification—Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)—The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)—Checking or testing that specifications are met.

Quality Unit(s)—An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine—The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Raw Material—A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reconciliation—A comparison between the theoretical quantity and the actual quantity.

Recovery—The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

Reference Standard, Primary—A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity.

Reference Standard, Secondary—A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing—Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch/ lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and preapproved as part of the marketing authorization.

Retest Date—The date when a material should be reexamined to ensure that it is still suitable for use.

Reworking—Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not pre-approved as part of the marketing authorization.

Self-Contained Area—Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well-established procedures, controls, and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

Signature (Signed)—See definition for signed

Signed (Signature)—The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent—An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification—A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Standard Operating Procedure (SOP)—An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g., equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting Material—Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Validation—A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity, or system actually leads to the expected results (see also Qualification).

Validation Protocol—A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing

process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected—The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical—The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

4

Changes to Approved NDAs and ANDAs

I. INTRODUCTION

The holders of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) can make postapproval changes in accordance with added section 506A of the FDA Modernization Act. There are specific reporting requirements for postapproval changes in components and composition, manufacturing sites, manufacturing process, specifications, package labeling, miscellaneous changes, and multiple related changes. Reporting categories for changes relating to specified biotechnology and specified synthetic biological products regulated by the Center for Drug Evaluation and Research (CDER) are found in the guidance for industry entitled *Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products* (July 1997). Information specific to products is developed by an applicant to assess the effect of the change on the identity, strength (e.g., assay, content uniformity), quality (e.g., physical, chemical, and biological properties), purity (e.g., impurities and degradation products), or potency (e.g., biological activity, bioavailability, bioequivalence) of a product as they may relate to the safety or effectiveness of the product. CDER has published guidances, including the SUPAC (scale-up and postapproval changes) guidances that provide recommendations on reporting categories.

II. REPORTING CATEGORIES

Section 506A of the act provides for four reporting categories that are distinguished in the following paragraphs. A "major change" is a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product [506A(c)(2)]. A major change requires the submission of a supplement and approval by the FDA before distribution of the product made using the change [506A(c)(1)]. This type of supplement is called, and should be clearly labeled as, a Prior Approval Supplement. An applicant may ask the FDA to expedite its review of a Prior Approval Supplement for public health reasons (e.g., drug shortage) or if a delay in making the change described in the supplement would impose an extraordinary hardship on the applicant. This type of supplement is called, and should be clearly labeled as, a Prior Approval Supplement—Expedited Review Requested. Requests for expedited review based on extraordinary hardship should be reserved for manufacturing changes made necessary by catastrophic events (e.g., fire) or by events that could not be reasonably foreseen and for which the applicant could not plan.

A "moderate change" is a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. There are two types of moderate change. One type of moderate change requires the submission of a supplement to the FDA at least 30 days before the distribution of the product made using the change [506A(d)(3)(B)(i)]. This type of supplement is called, and should be clearly labeled as, a Supplement—Changes Being Effected in 30 Days. The product made using a moderate change cannot be distributed if the FDA informs the applicant within 30 days of receipt of the supplement that a Prior Approval Supplement is required [506A(d)(3)(B)(i)]. For each change, the supplement must contain information determined by the FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change [506A(b)]. If the FDA informs the applicant within 30 days of receipt of the supplement that information is missing, distribution must be delayed until the supplement has been amended with the missing information. The FDA may identify certain moderate changes for which distribution can occur when the FDA receives the supplement [506A(d)(3)(B)(ii)]. This type of supplement is called, and should be clearly labeled as, a Supplement—Changes Being Effected. If, after review, the FDA disapproves a Changes Being Effected in 30 Days Supplement or a Changes Being Effected Supplement, the FDA may order the manufacturer to cease distribution of the drugs that have been made using the disapproved change [506A(d)(3)(B)(iii)].

A "minor change" is a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product. The applicant must describe minor changes in its next annual report [506A(d)(1)(A) and (d)(2)].

An applicant can submit one or more protocols (i.e., comparability protocols) describing tests, validation studies, and acceptable limits to be achieved to demonstrate the absence of an adverse effect from specified types of changes. A comparability protocol can be used to reduce the reporting category for specified changes. A proposed comparability protocol should be submitted as a Prior Approval Supplement if not approved as part of the original application.

III. GENERAL REQUIREMENTS

Other than for editorial changes in previously submitted information (e.g., correction of spelling or typographical errors, reformatting of batch records), an applicant must notify the FDA about each change in each condition established in an approved application beyond the variations already provided for in the application [506A(a)].

An applicant making a change to an approved application under section 506A of the Act must also conform to other applicable laws and regulations, including current good manufacturing practice (cGMP) requirements of the Act [21 USC 351(a)(2)(B)] and applicable regulations in Title 21 of

the Code of Federal Regulations (e.g., 21 CFR parts 210, 211, 314). For example, manufacturers must comply with relevant cGMP validation and record-keeping requirements and must ensure that relevant records are readily available for examination by authorized FDA personnel during an inspection. A Changes Being Effected Supplement for labeling changes must include 12 copies of the final printed labeling [21 CFR 314.50(e)(2)(ii)].

Except for a supplemental application providing for a change in labeling, an applicant should include a statement in a supplemental application or amendment certifying that the required field copy (21 CFR 314.50) of the supplement or amendment has been provided.

IV. ASSESSING THE EFFECT OF MANUFACTURING CHANGES

A. Assessment of the Effects of the Change

A drug made with a manufacturing change, whether a major manufacturing change or otherwise, may be distributed only after the holder validates (i.e., assesses) the effects of the change on the identity, strength, quality, purity, and potency of the product as these factors may relate to the safety or effectiveness of the product [506A(b)]. For each change, the supplement or annual report must contain information determined by the FDA to be appropriate and must include the information developed by the applicant in assessing the effects of the change [506A(b), (c)(1), (d)(2)(A), and (d)(3)(A)]. Recommendations on the type of information that should be included in a supplemental application or annual report are available in guidance documents. If no guidance is available on the type of information that should be submitted to support a change, the applicant is encouraged to contact the appropriate chemistry or microbiology review staff.

1. Conformance to Specifications

An assessment of the effect of a change on the identity, strength, quality, purity, or potency of the drug product should include a determination that the drug substance intermediates, drug substance, in-process materials, or drug product affected by the change conforms to the approved specifications. A "specification" is a quality standard (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container closure systems and their components and in-process materials. For the purpose of defining specifications, "acceptance criteria" are numerical limits, ranges, or other criteria for the tests described. Conformance to a specification means that the material, when tested according to the analytical procedures listed in the specification, will meet the listed acceptance criteria.

2. Additional Testing

In addition to confirmation that the material affected by manufacturing changes continues to meet its specification, the applicant should perform additional testing, when appropriate, to assess whether the identity, strength, quality, purity, or potency of the product as these factors may relate to the safety or effectiveness of the product have been or will be affected. The assessment should include, as appropriate, evaluation of any changes in the chemical, physical, microbiological, biological, bioavailability, or stability profiles. This additional assessment could involve testing of the postchange drug product itself or, if appropriate, the component directly affected by the change. The type of additional testing that an applicant should perform would depend on the type of manufacturing change, the type of drug substance or drug product, and the effect of the change on the quality of the product. For example:

- Evaluation of changes in the impurity or degradation product profile could first involve profiling using appropriate chromatographic techniques and then, depending on the observed changes in the impurity profile, toxicology tests to qualify a new impurity or degradant or to qualify an impurity that is above a previously qualified level.
- Evaluation of the hardness or friability of a tablet after changes in formulation or manufacturing procedure.
- Assessment of the effect of a change on bioequivalence when required under 21 CFR part 320 could include, for example, multipoint or multimedia dissolution profiling or an in vivo bioequivalence study.
- Evaluation of extractables from new packaging components or moisture permeability of a new container closure system.

B. Equivalence

When testing is performed, the applicant should usually assess the extent to which the manufacturing change has affected the identity, strength, quality, purity, or potency of the drug product. Typically, this is accomplished by comparing test results from prechange and postchange material and determining whether the test results are equivalent or not. Simply stated: Is the product made after the change equivalent to the product made before the change? An exception to this general approach is that when bioequivalence should be redocumented for certain ANDA postapproval changes, the comparator should be the reference-listed drug. Equivalence comparisons frequently require a criterion for comparison with calculation of confidence intervals relative to a predetermined equivalence interval. For this reason, as well as for other reasons, "equivalent" does not necessarily mean "identical." Equivalence may also relate to maintenance of a quality characteristic (e.g., stability) rather than a single performance of a test.

C. Adverse Effect

Sometimes manufacturing changes have an adverse effect on the identity, strength, quality, purity, or potency of the drug product. In many cases, the applicant chooses not to implement these suboptimal manufacturing changes, but sometimes the applicant wishes to put them into practice. If an assessment concludes that a change has adversely affected the identity, strength, quality, purity, or potency of the drug product, the change should be filed in a Prior Approval Supplement, regardless of the recommended reporting category for the change. For example, a type of process change with a recommended filing category of a Supplement—Changes Being Effected in 30 Days could cause a new degradant to be formed that requires qualification or identification. However, the applicant's degradation qualification procedures may indicate that there are no safety concerns relating to the new degradant. The applicant should submit this change in a Prior Approval Supplement with appropriate information to support the continued safety and effectiveness of the product. During the review of the Prior Approval Supplement, the FDA will assess the impact of any adverse effect on the product as it may relate to the safety or effectiveness of the product.

V. COMPONENTS AND COMPOSITION

Changes in the qualitative or quantitative formulation, including inactive ingredients, as provided in the approved application, are considered major changes and should be filed in a Prior Approval Supplement, unless exempted by regulation or guidance [506A(c)(2)(A)]. The deletion or reduction of an ingredient intended to affect only the color of a product may be reported in an annual report. Guidance on changes in components and composition that may be filed in a Changes Being Effected Supplement or annual report is not included in this document because of the complexity of these recommendations, but it may be covered in one or more guidance documents describing postapproval changes (e.g., SUPAC documents).

VI. MANUFACTURING SITES

A. General Considerations

CDER should be notified about a change to a different manufacturing site used by an applicant to manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates; package drug products; label drug products; or test components, drug product containers, closures, packaging materials, in-process materials, or drug products. Sites include those owned by the applicant or contract sites used by an applicant. Testing sites include those performing physical, chemical, biological, and microbiological testing to monitor, accept, or reject materials, as well as those performing stability testing. Sites used to label drug products are considered to be those that perform labeling of the drug product's primary or secondary packaging components. Sites performing operations that place identifying information on the dosage form itself (e.g., ink imprint on a filled capsule) are considered to be facilities that manufacture or process the drug product. The supplement or annual report should identify whether the proposed manufacturing site is an alternative or replacement to those provided for in the approved application.

A move to a different manufacturing site, when it is a type of site routinely subject to FDA inspection, should be filed as a Prior Approval Supplement if the site does not have a satisfactory cGMP inspection for the type of operation being moved. For labeling, secondary packaging, and testing site changes, the potential for adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product is considered to be independent of the type of drug product dosage form or specific type of operation being performed. Therefore, the recommended reporting category for any one of these manufacturing site changes will be the same for all types of drug products and operations. For manufacturing sites used to manufacture or process drug products, in-process materials, drug substances, or drug substance intermediates or perform primary packaging operations, the potential for adverse effect and, consequently, the recommended reporting category depend on various factors such as the type of product and operation being performed. For this reason, recommended reporting categories may differ depending on the type of drug product and operations.

Except for those situations described in sections VI.B.4, VI.C.1.b, and VI.D.5, moving production operations between buildings at the same manufacturing site or within a building, or having construction activities occur at a manufacturing site, do not have to be reported to CDER. A move to a different manufacturing site that involves other changes (e.g., process, equipment) should be evaluated as a multiple related change (see section XII) to determine the appropriate reporting category.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product, as these factors may relate to the safety or effectiveness of the product:

1. A move to a different manufacturing site, except one used to manufacture or process a drug substance intermediate, when the new manufacturing site has never been inspected by the FDA for the type of operation that is being moved, or the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than 2 years.
2. A move to a different manufacturing site, except one used to manufacture or process a drug; substance intermediate, when the new manufacturing site has not had a satisfactory cGMP inspection for the type of operation being moved.
3. A move to a different manufacturing site for (1) the manufacture, processing, or primary packaging of drug products when the primary packaging components control the dose delivered to the patient or when the formulation modifies the rate or extent of availability of the drug; or for (2) the manufacture or processing of in-process materials with modified-release characteristics; examples of these types of drug products include modified-release solid oral dosage forms, transdermal systems, liposomal products, depot products, oral and nasal metered-dose inhalers, dry powder inhalers, and nasal spray pumps.
4. Transfer of manufacturing of an aseptically processed sterile drug substance or aseptically processed sterile drug product to a newly constructed or refurbished aseptic processing facility or area or to an existing aseptic processing facility or area that does not manufacture similar (including container types and sizes) approved products; for example, transferring the manufacture of a lyophilized product to an existing aseptic process area where no approved lyophilized products are manufactured or where the approved lyophilized products being manufactured have dissimilar container types or sizes to the product being transferred.
5. Transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed facility at a different manufacturing site: Once this change has been approved, subsequent site changes to the facility for similar product types and processes may be filed as a Supplement—Changes Being Effected in 30 Days.

C. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

The following manufacturing site changes (excluding changes relating to drug substance intermediate manufacturing sites) should be filed in a Prior Approval Supplement if

the new site does not have a satisfactory cGMP inspection for the type of operation being moved (see sections VI.B.1 and 2):

1. Supplement—Changes Being Effected in 30 Days
   a. A move to a different manufacturing site for the manufacture or processing of any drug product, in-process material, or drug substance that is not otherwise provided for in this guidance
   b. For aseptically processed sterile drug substance or aseptically processed sterile drug product, a move to an aseptic processing facility or area at the same or different manufacturing site, except as provided for in section VI.B.4
   c. A move to a different manufacturing site for the primary packaging of (1) any drug product that is not otherwise listed as a major change and of (2) modified-release solid oral dosage–form products
   d. A move to a different manufacturing site for testing whether (1) the test procedures approved in the application or procedures that have been implemented via an annual report are used, (2) all postapproval commitments made by the applicant relating to the test procedures have been fulfilled (e.g., providing methods validation samples), and (3) the new testing facility has the capability to perform the intended testing
2. Supplement—Changes Being Effected
   a. A move to a different manufacturing site for the manufacture or processing of the final intermediate

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product.

The following manufacturing site changes (excluding changes relating to drug substance intermediate manufacturing sites) should be filed in a Prior Approval Supplement if the new site does not have a satisfactory cGMP inspection for the type of operation being moved (see sections VI.B.1 and 2):

1. A move to a different manufacturing site for secondary packaging.
2. A move to a different manufacturing site for labeling.
3. A move to a different manufacturing site for the manufacture or processing of drug substance intermediates, other than the final intermediate.
4. A change in the contract sterilization site for packaging components when the process is not materially different from that provided for in the approved application, and the facility has a satisfactory cGMP inspection for the type of operation being performed.
5. A transfer of the manufacture of a finished product sterilized by terminal processes to a newly constructed building or existing building at the same manufacturing site.
6. A move to a different manufacturing site for the ink imprinting of solid oral dosage–form products.

VII. MANUFACTURING PROCESS

A. General Considerations

The potential for adverse effects on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the product depends on the type of manufacturing process and the changes being instituted for the drug substance or drug product. In some cases, there may be a substantial potential for adverse effect, regardless of direct testing of the drug substance or drug product for conformance with the approved specification. When there is a substantial potential for adverse effects, a change should be filed in a Prior Approval Supplement.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product:

1. Changes that may affect the controlled (or modified) release, metering, or other characteristics (e.g., particle size) of the dose delivered to the patient, including the addition or deletion of a code imprint by embossing, debossing, or engraving on a modified-release solid oral dosage form.
2. Changes that may affect product sterility assurance including, where appropriate, process changes for sterile drug substances and sterile packaging components, including
   Changes in the sterilization method (e.g., gas, dry heat, irradiation); these include changes from sterile filtered or aseptic processing to terminal sterilization, or vice versa
   Addition, deletion, or substitution of sterilization steps or procedures for handling sterile materials in an aseptic processing operation
   Replacing sterilizers that operate by one set of principles with sterilizers that operate by another principle (e.g., substituting a gravity-displacement steam process with a process using superheated water spray)
   Addition to an aseptic processing line of new equipment made of different materials (e.g., stainless steel vs. glass, changes between plastics) that will come in contact with sterilized bulk solution or sterile drug components, or deletion of equipment from an aseptic processing line
   Replacing a class 100 aseptic fill area with a barrier system or isolator for aseptic filling: Once this change has been approved, subsequent process changes for similar product types in the same barrier system or isolator may be filed as a Supplement—Changes Being Effected in 30 Days
   Replacement or addition of lyophilization equipment of a different size that uses different operating parameters or lengthens the overall process time
   Changes from bioburden-based terminal sterilization to the use of an overkill process, and vice versa
   Changes to aseptic processing methods, including scale, that extend the total processing, including bulk storage time, by more than 50% beyond the validated limits in the approved application
   Changes in sterilizer load configurations that are outside the range of previously validated loads
   Changes in materials or pore size rating of filters used in aseptic processing
3. The following changes for a natural product: Changes in the virus or adventitious agent removal or inactivation methods; this is applicable to any material for which such procedures are necessary, including drug substance, drug product, reagents, and excipients.
4. The following changes for drug substance and drug product: Changes in the source material (e.g., microorganism, plant) or cell line.

5. The following changes for drug substance and drug product: Establishment of a new master cell bank or seed.
6. Any fundamental change in the manufacturing process or technology from that currently used by the applicant, for example:
   a. Drug product
      Dry to wet granulation, or vice versa change from one type of drying process to another (e.g., oven tray, fluid bed, microwave)
   b. Drug substance
      Filtration to centrifugation, or vice versa change in the route of synthesis of a drug substance
7. The following changes for drug substance: Any process change made after the final intermediate processing step in drug substance manufacture.
8. Changes in the synthesis or manufacture of the drug substance that may affect its impurity profile or the physical, chemical, or biological properties.
9. Addition of an ink code imprint or change to or in the ink used for an existing imprint code for a solid oral dosage–form drug product when the ink as changed is not currently used on CDER-approved products.
10. Establishing a new procedure for reprocessing a batch of drug substance or drug product that fails to meet the approved specification.

C. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product:

1. Supplement—Changes Being Effected in 30 Days
   a. For drug products, any change in the process, process parameters, or equipment, except as otherwise provided for in this guidance
   b. For drug substances, any change in process or process parameters, except as otherwise provided for in this guidance
   c. For natural protein drug substances and drug products:
      Any change in the process, process parameters, or equipment, except as otherwise provided for in this guidance
      An increase or decrease in production scale during finishing steps that involves new or different equipment
      Replacement of equipment with that of similar, but not identical, design and operating principle that does not affect the process methodology or process operating parameters
   d. For sterile products, drug substances, and components, as appropriate:
      Changes in dry heat depyrogenation processes for glass container systems for products that are produced by terminal sterilization processes or aseptic processing
      Changes to filtration parameters for aseptic processing (including flow rate, pressure, time, or volume but not filter materials or pore size rating) that require additional validation studies for the new parameters
      Filtration process changes that provide for a change from single to dual product sterilizing filters in series, or for repeated filtration of a bulk
      Changes from one qualified sterilization chamber to another for in-process or terminal sterilization that results in changes to validated operating parameters (time, temperature, F_0, and others)
      Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by more than 50% beyond the validated limits in the approved application when bioburden limits are unchanged
   e. For drug substances, redefinition of an intermediate, excluding the final intermediate, as a starting material
2. Supplement—Changes Being Effected
   a. A change in methods or controls that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports to or is represented to possess
   b. For sterile drug products, elimination of in-process filtration performed as part of the manufacture of a terminally sterilized product

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product:

1. For drug products and protein drug substances, changes to equipment of the same design and operating principle or changes in scale, except as otherwise provided for in this guidance [e.g., section VII.C.1.c; see FDA guidance for industry on the *Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* (November 1994)].
2. A minor change in an existing code imprint for a dosage form; for example, changing from a numeric to alphanumeric code.
3. Addition of an ink code imprint or a change in the ink used in an existing code imprint for a solid oral dosage–form drug product when the ink is currently used on CDER-approved products.
4. Addition or deletion of a code imprint by embossing, debossing, or engraving on a solid dosage–form drug product other than a modified-release dosage form.
5. A change in the order of addition of ingredients for solution dosage forms or solutions used in unit operations (e.g., granulation solutions).
6. Changes in scale of manufacturing for terminally sterilized products that increase the bulk solution storage time by no more than 50% beyond the validated limits in the approved application when bioburden limits are unchanged.

VIII. SPECIFICATIONS

A. General Considerations

All changes in specifications from those in the approved application must be submitted in a Prior Approval Supplement unless otherwise exempted by regulation or guidance [506A(c)(2)(A)].

Specifications (i.e., tests, analytical procedures, and acceptance criteria) are the quality standards provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components, including container and closure systems and in-process materials. For the purpose of defining specifications, acceptance criteria are numerical limits, ranges, or

other criteria for the tests described. Examples of a test, an analytical procedure, and acceptance criteria are an assay, a specific fully described high-pressure liquid chromatography procedure, and 98.0% to 102.0%. The recommendations in this section also apply to specifications associated with sterility assurance that are included in NDA and ANDA submissions. A regulatory analytical procedure is the analytical procedure used to evaluate a defined characteristic of the drug substance or drug product. The analytical procedures in the U.S. Pharmacopeia/National Formulary (USP/NF) are those legally recognized under section 501(b) of the Act as the regulatory analytical procedures for compendial items. The applicant may include in its application alternative analytical procedures to the approved regulatory procedure for testing the drug substance and drug product. However, for purposes of determining compliance with the Act, the regulatory analytical procedure is used. In sections B to D below, the use of the term "analytical procedure" without a qualifier such as "regulatory" or "alternative" refers to analytical procedures used to test materials other than the drug substance or drug product.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes in specifications that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product:

1. Relaxing an acceptance criterion, except as otherwise provided for in this guidance (e.g., section VIII.C.1.b).
2. Deleting any part of a specification, except as otherwise provided for in this guidance (e.g., section VIII.D.2).
3. Establishing a new regulatory analytical procedure.
4. A change in a regulatory analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the regulatory analytical procedure described in the approved application.
5. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as otherwise noted; for example, a change from a high-pressure liquid chromatography procedure that distinguishes impurities to one that does not, to another type of analytical procedure (e.g., titrimetric) that does not, or to one that distinguishes impurities but for which the limit of detection or limit of quantitation is higher.
6. Relating to testing of raw materials for viruses or adventitious agents (1) relaxing an acceptance criteria, (2) deleting a test, or (3) a change in the analytical procedure that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

C. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes in specifications that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product:

1. Supplement—Changes Being Effected in 30 Days
   a. Any change in a regulatory analytical procedure other than editorial or those identified as major changes
   b. Relaxing an acceptance criterion or deleting a test for raw materials used in drug substance manufacturing, in-process materials before the final intermediate, starting materials introduced before the final drug substance intermediate, or drug substance intermediates (excluding final intermediate), except as provided for in section VIII.B.6.
   c. A change in an analytical procedure used for testing raw materials used in drug substance manufacturing, in-process materials before the intermediate, starting materials introduced before the final drug substance intermediate, or drug substance intermediates (excluding final intermediate) that does not provide the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application, except as provided for in section VIII.B.6.
   d. Relaxing an in-process acceptance criterion associated with microbiological monitoring of the production environment, materials, and components that are included in NDA and ANDA submissions; for example, increasing the microbiological alert or action limits for critical processing environments in an aseptic fill facility or increasing the acceptance limit for bioburden in bulk solution intended for filtration and aseptic filling.
2. Supplement—Changes Being Effected
   a. An addition to a specification that provides increased assurance that the drug substance or drug product will have the characteristics of identity, strength, purity, or potency that it purports to or is represented to possess; for example, adding a new test and associated analytical procedure and acceptance criterion
   b. A change in an analytical procedure used for testing components, packaging components, the final intermediate, in-process materials after the final intermediate, or starting materials introduced after the final intermediate that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application

D. Minor Changes (Annual Report)

The following are examples of changes in specifications that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product:

1. Any change in a specification made to comply with an official compendium.
2. For drug substance and drug product, the addition, deletion, or revision of an alternative analytical procedure that provides the same or greater level of assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.
3. Tightening of acceptance criteria.
4. A change in an analytical procedure used for testing raw materials used in drug substance synthesis, starting materials introduced before the final drug substance intermediate, in-process materials before the final intermediate, or

drug substance intermediates (excluding final intermediate) that provides the same or increased assurance of the identity, strength, quality, purity, or potency of the material being tested as the analytical procedure described in the approved application.

IX. PACKAGE

A. General Considerations

The potential for adverse effect on the identity, strength, quality, purity, or potency of a product, as these factors may relate to the safety or effectiveness of the product when making a change to or in the container closure system is generally dependent on the route of administration of the drug product, performance of the container closure system, and likelihood of interaction between the packaging component and the dosage form. In some cases, there may be a substantial potential for adverse effect, regardless of direct product testing for conformance with the approved specification.

A change to or in a packaging component will often result in a new or revised specification for the packaging component. This situation does not have to be considered a multiple related change. Only the reporting category for the packaging change needs to be considered.

B. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product:

1. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms, a change to or in polymeric materials (e.g., plastic, rubber) of primary packaging components, when the composition of the component as changed has never been used in a CDER-approved product of the same dosage form and same route of administration; for example, a polymeric material that has been used in a CDER-approved topical ointment would not be considered CDER-approved for use with an ophthalmic ointment.
2. For liquid (e.g., solution, suspension, elixir) and semisolid (e.g., creams, ointments) dosage forms in permeable or semipermeable container closure systems, a change to an ink or an adhesive used on the permeable or semipermeable packaging component to one that has never been used in a CDER-approved product of the same dosage form, same route of administration, and same type of permeable or semipermeable packaging component (e.g., low-density polyethylene, polyvinyl chloride).
3. A change in the primary packaging components for any product when the primary packaging components control the dose delivered to the patient (e.g., the valve or actuator of a metered-dose inhaler).
4. For sterile products, any other change that may affect product sterility assurance, such as:
   - A change from a glass ampule to a glass vial with an elastomeric closure
   - A change to a flexible container system (bag) from another container system
   - A change to a prefilled syringe dosage form from another container system
   - A change from a single-unit-dose container to a multiple-dose container system
   - Changes that add or delete silicone treatments to container closure systems (such as elastomeric closures or syringe barrels)
   - Changes in the size or shape of a container for a sterile drug product
5. Deletion of a secondary packaging component intended to provide additional protection to the drug product (e.g., carton to protect from light, overwrap to limit transmission of moisture or gases).
6. A change to a new container closure system if the new container closure system does not provide the same or better protective properties than the approved container closure system.

C. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product:

1. Supplement—Changes Being Effected in 30 Days
   a. A change to or in a container closure system, except as otherwise provided for in this guidance
   b. Changes in the size or shape of a container for a sterile drug substance
2. Supplement—Changes Being Effected
   a. A change in the size or shape of a container for a nonsterile drug product, except for solid dosage forms (see section IX.D.2 regarding solid dosage forms)
   b. A change in or addition or deletion of a desiccant

D. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product:

1. A change in the container closure system for a nonsterile drug product, based on a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium.
2. A change in the size or shape of a container containing the same number of dose units, for a nonsterile solid dosage form.
3. The following changes in the container closure system of solid oral dosage–form products as long as the new package provides the same or better protective properties (e.g., light, moisture) and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage–form products:
   - Adding or changing a child-resistant closure, changing from a metal to plastic screw cap, or changing from a plastic to metal screw cap
   - Changing from one plastic container to another of the same type of plastic (e.g., high-density polyethylene container to another high-density polyethylene container)
   - Changes in packaging materials used to control odor (e.g., charcoal packets)
   - Changes in bottle filler (e.g., change in weight of cotton or amount used) without changes in the type of filler (e.g., cotton to rayon)
   - Increasing the wall thickness of the container
   - A change in or addition of a cap liner
   - A change in or addition of a seal (e.g., heat induction seal)

A change in an antioxidant, colorant, stabilizer, or mold-releasing agent for production of the container or closure to one that is used at similar levels in the packaging of CDER-approved solid oral dosage–form products
A change to a new container closure system when the container closure system is already approved in the NDA or ANDA for other strengths of the product

4. The following changes in the container closure system of nonsterile liquid products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved liquid products with the same route of administration (i.e., the material in contact with a liquid topical should already have been used with other CDER-approved liquid topical products):
   Adding or changing a child-resistant closure
   Changing from a metal to plastic screw cap
   Changing from a plastic to metal screw cap
   Increasing the wall thickness of the container
   A change in or addition of a cap liner
   A change in or addition of a seal (e.g., heat induction seal)
5. A change in the container closure system of unit-dose packaging (e.g., blister packs) for nonsterile solid dosage form–products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved products of the same type (e.g., solid oral dosage form, rectal suppository).
6. The following changes in the container closure system of nonsterile semisolid products, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved semisolid products:
   Changes in the closure or cap
   Increasing the wall thickness of the container
   A change in or addition of a cap liner
   A change in or addition of a seal
   A change in the crimp sealant
7. A change in the flip seal cap color, as long as the cap color is consistent with any established color-coding system for that class of drug products.

X. LABELING

A. General Considerations

A drug product labeling change includes changes in the package insert, package labeling, or container label. An applicant should promptly revise all promotional labeling and drug advertising to make it consistent with any labeling change implemented in accordance with the regulations. All labeling changes for ANDA products must be consistent with section 505(j) of the Act.

B. Major Changes (Prior Approval Supplement)

Any proposed change in the labeling, except those that are designated as moderate or minor changes by regulation or guidance, should be submitted as a Prior Approval Supplement. The following list contains some examples of changes that are currently considered by CDER to fall into this reporting category:

1. Changes based on postmarketing study results, including, but not limited to, labeling changes associated with new indications and usage.
2. Change in, or addition of, pharmacoeconomic claims based on clinical studies.
3. Changes to the clinical pharmacology or the clinical study section reflecting new or modified data.
4. Changes based on data from preclinical studies.
5. Revision (expansion or contraction) of population based on data.
6. Claims of superiority to another product.
7. Change in the labeled storage conditions, unless exempted by regulation or guidance.

C. Moderate Changes (Supplement—Changes Being Effected)

A Changes Being Effected Supplement should be submitted for any labeling change that adds or strengthens a contraindication, warning, precaution, or adverse reaction; adds or strengthens a statement about drug abuse, dependence, psychological effect, or overdosage; adds or strengthens an instruction about dosage and administration that is intended to increase the safe use of the product; deletes false, misleading, or unsupported indications for use or claims for effectiveness; or is specifically requested by the FDA. The submission should include 12 copies of final printed labeling. The following list includes some examples of changes that are currently considered by CDER to fall into this reporting category:

1. Addition of an adverse event because of information reported to the applicant or agency.
2. Addition of a precaution arising out of a postmarketing study.
3. Clarification of the administration statement to ensure proper administration of the product.
4. Labeling changes, normally classified as major changes, that the FDA specifically requests be implemented using a Changes Being Effected Supplement.

D. Minor Changes (Annual Report)

Labeling with editorial or similar minor changes or with a change in the information concerning the description of the drug product or information about how the drug is supplied that does not involve a change in the dosage strength or dosage form should be described in an annual report. The following list includes some examples that are currently considered by CDER to fall into this reporting category:

1. Changes in the layout of the package or container label that are consistent with FDA regulations (e.g., 21 CFR part 201) without a change in the content of the labeling.
2. Editorial changes, such as adding a distributor's name.
3. Foreign language versions of the labeling, if no change is made to the content of the approved labeling and a certified translation is included.
4. Labeling changes made to comply with an official compendium.

XI. MISCELLANEOUS CHANGES

A. Major Changes (Prior Approval Supplement)

The following are examples of changes that are considered to have a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product:

1. Changes requiring completion of studies in accordance with 21 CFR part 320 to demonstrate equivalence of the drug to the drug as manufactured without the change or to a reference-listed drug [506A(c)(2)(B)].

2. Addition of a stability protocol or comparability protocol.
3. Changes to an approved stability protocol or comparability protocol unless otherwise provided for in this guidance (e.g., VIII.C, VIII.D, XI.C.2).
4. An extension of an expiration dating period based on data obtained under a new or revised stability testing protocol that has not been approved in the application or on full shelf-life data on pilot-scale batches using an approved protocol.

B. Moderate Changes (Supplement—Changes Being Effected)

The following are examples of changes that are considered to have a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product:

1. Supplement—Changes Being Effected in 30 Days
   a. Reduction of an expiration dating period to provide increased assurance of the identity, strength, quality, purity, or potency of the drug product; extension of an expiration date that has previously been reduced under this provision should be filed in a Supplement—Changes Being Effected in 30 Days even if it is based on data obtained under a protocol approved in the application
2. Supplement—Changes Being Effected
   a. No changes have been identified

C. Minor Changes (Annual Report)

The following are examples of changes that are considered to have a minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as these factors may relate to the safety or effectiveness of the product:

1. An extension of an expiration dating period based on full shelf life data on full production batches obtained under a protocol approved in the application.
2. Addition of time points to the stability protocol or deletion of time points beyond the approved expiration dating period.
3. A change from previously approved stability storage conditions to storage conditions recommended in ICH guidances.
4. Non-USP reference standards:
   Replacement of an in-house reference standard or reference panel (or panel member) according to procedures in an approved application
   Tightening of acceptance criteria for existing reference standards to provide greater assurance of product purity and potency

XII. MULTIPLE RELATED CHANGES

Multiple related changes involve various combinations of individual changes. For example, a site change may also involve equipment and manufacturing process changes, or a component and composition change may necessitate a change in a specification. For multiple related changes for which the recommended reporting categories for the individual changes differ, CDER recommends that the filing be in accordance with the most restrictive of those reporting categories recommended for the individual changes. When the multiple related changes all have the same recommended reporting category, CDER recommends that the filing be in accordance with the reporting category for the individual changes. For the purposes of determining the reporting category for moves between buildings, the terms "different manufacturing site" and "same manufacturing site" are defined as follows. Same manufacturing site: The new and old buildings are included under the same drug establishment registration number, and the same FDA district office is responsible for inspecting the operations in both the new and old buildings. Different manufacturing site: The new and old buildings have different drug establishment registration numbers, or different FDA district offices are responsible for inspecting operations in the new and old building.

The change to a different manufacturing site should be filed in a Prior Approval Supplement when the new manufacturing site has never been inspected by the FDA for the type of operation being moved, the move results in a restart at the new manufacturing site of a type of operation that has been discontinued for more than 2 years, or the new manufacturing site does not have a satisfactory cGMP inspection for the type of operation being moved.

Examples of postapproval manufacturing site changes and filing consequences include

- An applicant wants to move the manufacture of an immediate-release tablet to a different manufacturing site that currently manufactures, and has satisfactory cGMP status for, capsules and powders for oral solution. This manufacturing site change should be filed in a Prior Approval Supplement because the new manufacturing site does not have a satisfactory cGMP inspection for immediate-release tablets.
- An applicant wants to contract out his or her packaging operations for immediate-release tablets and capsules and modified-release capsules. The potential contract packager has a satisfactory cGMP status for immediate-release and modified-release capsules but has never packaged immediate-release tablets. The packaging site change for the immediate-release tablet products should be filed in a Prior Approval Supplement. The packaging site change for the capsule products should be filed as recommended in section VI of this guidance for packaging sites with a satisfactory cGMP inspection.
- An applicant wishes to consolidate his or her product testing to a single analytical laboratory at a manufacturing site. This manufacturing site produces various solid oral dosage–form products, has an operational analytical laboratory currently at the site, and has satisfactory cGMP inspections for the manufacturing occurring at the facility. Some of the products that will be tested at the analytical laboratory when the consolidation occurs are not solid oral dosage form products. Unlike most other production operations, testing laboratories are not inspected on a dosage form/type of drug substance-specific basis. The satisfactory cGMP inspection of the analytical laboratory, which was performed as part of the cGMP inspection for manufacture of the solid oral dosage form products, is considered to apply to all dosage forms, including those not actually produced at the site.

Different reporting categories are proposed for changes to or the addition of certain components based on whether the component/material has been used in and has been in contact with CDER-approved products. Different reporting categories are recommended once CDER has reviewed certain components/materials in association with a product

approval because similar subsequent changes then have a reduced potential to have an adverse effect on the identity, strength, quality, purity, or potency of a product as they may relate to the safety or effectiveness of the product. For example, certain changes in the container closure systems of solid oral dosage form products may be included in the annual report, as long as the new package provides the same or better protective properties and any new primary packaging component materials have been used in and been in contact with CDER-approved solid oral dosage–form products (see section IX.D.3). If the primary packaging component material has not been used in or has not been in contact with CDER-approved solid oral dosage–form products, then submission of the change in an annual report is not recommended. CDER-approved products are considered those subject to an approved NDA or ANDA. When information is not available, an applicant should use reliable sources of information to determine that the component or material has been used in and has been in contact with a CDER-approved product of the same dosage form and route of administration, as appropriate. The applicant should identify in the supplement or annual report the basis for the conclusion that the component or material is used in a CDER-approved product.

If an applicant cannot confirm that a component or material has been used in and has been in contact with a CDER-approved product of the same dosage form and route of administration, the applicant has the option of filing the change for a single NDA or ANDA, using the higher recommended reporting category and, after approval, filing similar subsequent changes for other NDAs and ANDAs, using the lower recommended reporting category.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other criteria for the tests described

Active Ingredient/Drug Substance—Any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to affect the structure or any function of the human body, but does not include intermediates used in the synthesis of such ingredient, including those components that may undergo chemical change in the manufacture of the drug product and are present in the drug product in a modified form intended to furnish the specified activity or effect [21 CFR 210.3(b)(7) and 314.3]

Component—Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product [21 CFR 210.3(b)(3)]

Container Closure System—The sum of packaging components that together contain and protect the dosage form; this includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product

Drug Product—A finished dosage form, for example, tablet, capsule, or solution, that contains an active ingredient, generally, but not necessarily, in association with inactive ingredients [21 CFR 210.3(b)(4)]

Final Intermediate—The last compound synthesized before the reaction that produces the drug substance. The final step forming the drug substance must involve covalent bond formation or breakage; ionic bond formation (i.e., making the salt of a compound) does not qualify. As a consequence, when the drug substance is a salt, the precursors to the organic acid or base, rather than the acid or base itself, should be considered the final intermediate

Inactive Ingredients—Any intended component of the drug product other than an active ingredient

In-Process Material—Any material fabricated, compounded, blended, or derived by chemical reaction that is produced for, and used in, the preparation of the drug product [21 CFR 210.3(b)(9)]. For drug substance, in-process materials are considered those materials that are undergoing change (e.g., molecular, physical)

Intermediate—A material produced during steps of the synthesis of a drug substance that must undergo further molecular change before it becomes a drug substance

Package—The container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons, shrink wrap)

Packaging Component—Any single part of a container closure system

Primary Packaging Component—A packaging component that is or may be in direct contact with the dosage form

Reference-Listed Drug—The listed drug identified by the FDA as the drug product on which an applicant relies in seeking approval of its abbreviated application (21 CFR 314.3)

Satisfactory cGMP Inspection—A satisfactory cGMP inspection is an FDA inspection during which no objectionable conditions or practices were found during (no action indicated), or an inspection during which objectionable conditions were found, but corrective action is left to the firm to take voluntarily, and the objectionable conditions will not be the subject of further administrative or regulatory actions (voluntary action indicated). Information about the cGMP status of a firm may be obtained by requesting a copy of the Quality Assurance Profile (QAP) from the FDAs Freedom of Information (FOI) Office. The QAP reports information on the cGMP compliance status of firms that manufacture, package, assemble, repack, relabel, or test human drugs, devices, biologics, and veterinary drugs. All FOI requests must be in writing and should follow the instructions found in the reference entitled *A Handbook for Requesting Information and Records from FDA*. An electronic version of this reference is available at the Web site http://www.fda.gov/opacom/backgrounders/foiahand.html

Secondary Packaging Component—A packaging component that is not and will not be in direct contact with the dosage form

Specifications—The quality standards (i.e., tests, analytical procedures, and acceptance criteria) provided in an approved application to confirm the quality of drug substances, drug products, intermediates, raw materials, reagents, and other components including container closure systems and in-process materials

Validate the Effects of the Change—To assess the effect of a manufacturing change on the identity, strength, quality, purity, or potency of a drug as these factors relate to the safety or effectiveness of the drug

5

Formulation Considerations of Liquid Products

Liquid formulations offer many advantages, from ease in dosing to ease in administration (easy to swallow), and myriad possibilities of innovative drug delivery systems. One of the most desirable features of liquid formulations, particularly the solution forms, is the relatively lower importance of bioavailability considerations, as the drug molecules are already in the dispersed phase, removing many rate-limiting steps in the absorption of drugs. For the purpose of this volume, liquid formulations include formulations that have liquid characteristics, meaning they can flow and thus include clear liquids, suspensions, and extemporaneous powder suspensions (which could easily be classified as uncompressed solids but for the stability considerations postreconstitution, which are common to liquid preparations). However, all of the advantages of liquid dosage forms are balanced by the many problems in their formulation. These include stability problems, taste masking needs, phase separations, and so forth, all of which require highly specialized formulation techniques.

I. SOLUBILITY

The amount of active drug dissolved per unit of a solvent or liquid base is a critical parameter subject to many factors including temperature, presence of electrolytes (salting-out effect), complexation with other components, state of crystallinity (such as amorphous), nature of crystals (inclusion or imperfections), hydration, or salvation, and so forth. One of the most important studies conducted on new chemical entities is the solubility characteristics, phase conversion studies, and saturation limits under different conditions. Where the amount of drug is above saturation solubility, an equilibrium between the solution (monomolecular dispersion) is established with undissolved particles (often multimolecular dispersions), the direction and extent of which are governed by many physicochemical factors. Because the absorption of drugs takes place only from a monomolecular dispersion (except those instances of pinocytosis, etc.), the equilibrium of the two states is critical to drug absorption. A large number of pH-adjusting buffers are used in the liquid products to modify the solubility of drugs as well as to provide the most optimal pH for drug absorption and drug stability. The dielectric constant of the solvent (or composite dispersion phase) is important in determining the solubility. With available values of dielectric constant, for both pure systems and binary systems, it is easy to project the solubility characteristics of many new drugs. Another factor determining the solubility of drugs is the degree of solubilization in the dispersion phase.

Solubilization is defined as spontaneous passage of poorly water-soluble drugs into an aqueous solution of a detergent, the mechanism being entrapment of drug molecules in the micelles of surface-active agent. As a result, many liquid preparations contain surfactants, not only to solubilize but also to "wet" the powders to allow better mixing with liquid phase. Because the critical micelle concentration of surfactants is highly dependent on the presence of other polar or dielectric molecules, the use of surfactants to solubilized drugs requires extensive compatability studies. The most common solubilizers used include polyoxyethylene sorbital, fatty acid esters, polyoxyethylene monoalklyl ethers, sucrose monoesters, lanolin esters and ethers, and so forth.

Complexation with other components of formulation can give rise to enhanced or reduced solubility. Organic compounds in solution generally tend to associate with each other to some extent, but these are weak bonds, and the complex readily disassociates. Where the drug forms a stronger complex, such as with caffeine or other binders, solubility can be extensively altered. Some polyols are known to disrupt complexes, reducing the solubility. Often complexation results in loss of active drug or a preservative used in the system, leading to serious stability problems. Examples of complexation include when xanthines, polyvinyl pyrrolidone, and so on bind to drugs.

Hydrotrophy is defined as an increase in solubility in water caused by presence of large amounts of additives. It is another type of "solubilization," except the solubilizing agent is not necessarily a surfactant. The phenomenon is closer to complexation, but the change in solvent characteristics play a significant role as well. In general, the quantity of other components must be in the range of 20% to 50% to induce hydrotrophy.

II. CHEMICAL MODIFICATION

Many poorly soluble drugs can be made more water soluble by modifying their chemistry, such as introducing by a hydrophilic group on the molecule. Salts and derivates of poorly soluble drugs are widely used, and modification requires a careful selection because different salts and forms may not have the same chemical stability, and also because the biologic activity may be modified.

III. PRESERVATION

Preservatives are almost always a part of liquid formulations unless there is sufficient preservative efficacy in the formulation itself, such as due to high sugar content, presence of antimicrobial drugs, or solvents that inhibit growth such as alcohol. In all instances a preservative efficacy challenge is needed to prove adequate protection against the growth of microorganisms during the shelf life and use of the product (such as in the case of reconstituted powder suspensions). A large number of approved preservatives are available, including such universal preservatives as parabens, to protect liquid preparations. Among the acidic group, the most

prominent preservatives are phenol, chlorocresol, O-pheyl phenol, alkyl esters of parahydroxybenzoic acid, benzoic acid and its salts, boric acid and its salts, and sorbic acid and its salts; neutral preservatives include chlorbutanol, benzyl alcohol, and β-phenylethyl alcohol; mercurial preservatives include thiomersal, phenylmercuric acetate, and nitrate; and nitromersol and quarternary compounds include benzalkonium chloride and cetylpyridinium chloride. The admissible levels of preservatives are defined in the pharmacopoeia. It should be noted that although preservatives provide an essential function, they often cause an unpleasant taste and allergic reactions in some individuals, requiring proper labeling of all products containing preservatives.

IV. SWEETENING AGENTS

Because taste is of prime importance in the administration of liquid products, sweetening agents ranging from sugar to potassium acesulfame are widely used; appropriate warnings are required when using artificial sweetening agents. Often a combination of sweetening agents is used, in combination with various flavors (which are often included to make the product more palatable), to impart the best taste. When formulating granules for dispersion, solid flavors are preferred.

V. FLAVORS

There are four basic sensations: salty, bitter, sweet, and sour. A combination of efforts is required to mask these tastes. For example, menthol and chloroform act as desensitizing agents; a large number of natural and artificial flavors and their combinations are available to mask the bitterness most often found in organic compounds. Most formulators refer the selection of compatible flavors to companies manufacturing these flavors, as they may allow use of their drug master file for the purpose of filing regulatory applications. The formulator is referred to Givaudan (http://www.givaudan.com/), International Flavors and Fragrances (http://www.iff.com), and Flavors of North America (http://www.fonaflavors.com). Detailed information about other companies can be obtained from the National Association of Flavor and Fragrances (http://www.naffs.org/naffs/public/members.htm). It is noteworthy that as of the end of 2003, all foreign manufacturers of flavors are required to file a registration with the U.S. Food and Drug Administration under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002.

VI. VISCOSITY

Because the flow of liquid for dispensing and dosing is important, an appropriate control of viscosity is required to prevent the liquid from running and, at the same time, to allow good dosing control; many thickening agents are available including carboxymethyl cellulose, methyl cellulose, polyvinylpyrrolidone, and sugar. Because of the significant opportunities available for interacting with salts and other formulation ingredients, the viscosity control should be studied in the final formulation and over the shelf life of the product.

VII. APPEARANCE

The appearance or color of liquid products is often synchronized with the flavors used, for example, green or blue for mint, red for berry, and so forth. Because the amount of dyestuffs allowed in pharmaceutical products is strongly regulated, this presents problems—especially where there is a need to mask features of a preparation. In some instances, solutions are made to "sparkle" by passing them through a filtration process. Often, adsorbents are used in the liquid preparations to remove fine particles, imparting a greater clarity to solutions. Filtration often presents problems, but with the help now available from major filter manufacturers, most problems can be readily solved. The formulators are urged to consult these commercial suppliers.

VIII. CHEMICAL STABILITY

Drugs are more unstable in solution or liquid dispersion than they are in solid state because the molecular interactions are more plausible in liquid surroundings.

IX. PHYSICAL STABILITY

Physically stable liquid products are supposed to retain their color, viscosity, clarity, taste, and odor throughout the shelf life; however, the limits of the specifications for physical attributes are often kept flexible to allow for subjective evaluation criteria often involved and for inevitable, inconsequential, changes in the physical characteristics of these products. Ideally, a freshly prepared product is used as the reference standard; alternately, many companies develop more objective evaluation criteria using instrumental evaluation instead of subjective evaluation. Similar to chemical stability, physical stability can be significantly altered by the packaging type and design; as a result, the New Drug Application for every product requires a package interaction description; obviously, final stability data are to be developed in the final package form. Although glass bottles are fairly resistant to many products, caps and liners are often not. Even the integrity of the caps needs to be evaluated, applying exact torque in closing the bottles intended for stability evaluation; this is important to prevent any cap breakage that might adversely affect stability.

X. RAW MATERIAL

Raw material specifications are more important in liquid products, as the contaminants can adversely affect the formulation more than in solid dosage form. Also, the many features of a liquid product are controlled by including several raw materials such as sweeteners, thickening agents, and so forth, further complicating the matrixing of formulation at the development stage. The microbial quality of raw materials (both solid and liquid) needs to be critically evaluated. It is noteworthy that several raw materials used in liquid products may fall into the "food" category, and even though one is purchasing pharmaceutical-grade material, newly enacted laws in the United States require all foreign manufacturers to make a complete declaration of the composition of materials. Companies are encouraged to revise their specifications

based on this additional information, to control the quality of raw materials more tightly.

Water is the most common raw material used, and it is recommended that the manufacturer fully comply with the standards of at least purified water for inclusion in the formulation, although there is no requirement. Efforts should be made to provide as much microbial-free water as possible; this can be readily achieved by installing a loop system in which the incoming water is first subjected to ultraviolet sterilizer, carbon filter, demineralizer, and a 5-μm filter, and then sent to a heated tank, from which it is passed again through an ultraviolet sterilizer and then a 0.22-μm filter before bringing it into the product; water coming out of the 5-μm filter can be circulated. When using a loop, it is important to establish methods for draining the dead water in the tap and the loop before using it. Also make sure that the flow rate of water does not exceed the sterilizing capacity of the ultraviolet systems installed.

XI. MANUFACTURING EQUIPMENT

Fully sanitizable stainless steel 314 or better quality is recommended. Equipment must be cleaned or sterilized; appropriate disinfectants include dilute solutions of hydrogen peroxide, phenol derivatives, and peracetic acid. Equipment lines can be sterilized by using alcohol, boiling water, autoclaving, steam, or dry heat. Where lids are used, be cautious of the condensate, which may be a source of microbial contamination. Operators must conform to all sanitary presentation requirements, including head covering, gloves, and face masks. Use of portable laminar flow hoods to expose ingredients before addition is often desirable.

XII. MANUFACTURING DIRECTIONS

Provided in this volume are hundreds of formulations with manufacturing directions; in some instances, for the sake of brevity, general details are left out that pertain to basic compounding techniques. For example, the order of addition and techniques of adding solutes to a liquid tank can be very important. Flavors are generally added after first mixing them in a smaller volume of the solvent or liquid base and rinsing them with a portion of liquid as well. This also holds for all other additions, particularly those of smaller quantities of ingredients. Proper mixing is validated; however, unlike solid mixing, where overmixing may result in segregation, the problems in liquid mixing pertain to air entrapment. Appropriate temperature of the liquid phase is often important to ensure that there is no precipitation of the solute added. Classic examples include use of syrup base, which must be heated to bring it to proper viscosity and to allow proper mixing. Parabens, when used as preservatives, must be dissolved in hot water because the quantity used is small and can be readily lost if complete dissolution is not ensured. In most instances, small quantities of solutes should be predissolved in a smaller quantity of solvent before adding it to the main tank. It is customary to bring the batch to the final volume of weight. The gravimetric adjustments are preferred, as they can be done while taring the vessel. Problems arise when solvents like alcohol are used wherein volume contraction and density are subject to temperature changes. Also, formulations are often presented in a volumetric format and require careful conversion calculation, especially where one or two components are used to compensate for the amount of active used (e.g., based on potency factors).

XIII. PACKAGING

Filling of liquid products is determined by their viscosity, surface tension, foam producing, and compatibility with filling machine components. Liquids are often filled at a higher temperature to allow better flow. In most instances, some type of piston filling and delivery is used to fill bottles, for which proper control of volume is required. The filling can be done on the basis of fixed volume or on the level of fill in the container. The filling can be accomplished through positive pressure or through a vacuum created in the container. If the latter is used, care should be taken not to lose any volatile components through the vacuum process; proper validation is required. Liquid product exposed to environment should be protected and filled under a laminar flow hood where possible. All points of contact of product to the environment should be similarly protected; however, once the product has been filled and capped, the bottles can be safely taken to an uncontrolled environment. In most instances, either plastic or aluminum caps are applied to bottles. The liners used in the caps should demonstrate full compatibility with the product, including any adhesive used. Proper torque should be applied to ensure a tight seal. Pilfer-evident packaging where used must comply with the regulatory requirements. It is not uncommon for syrups to crystallize out at the edge of the bottles, which the consumer might think a defect. Efforts should be made to formulate products to avoid this type of crystallization; use of sugar-free formulations is becoming more acceptable and offers a good alternate. However, taste masking without using sugar or liquid glucose remains a challenge. Stability testing in final packaged containers should include trial shipment runs as well to ensure that the caps do not come off or leak during the shipment.

XIV. PARTICLE SIZE AND SHAPE

When suspensions are formulated to provide a stable system, the particle size becomes critical. Flocculated suspensions also require careful particle-size control either in the process of manufacturing or in the starting material. Equally important is the crystal habit—the outward appearance of an agglomeration of crystals. Crystal structure can be altered during the manufacturing process, particularly if the product is subject to temperature cycling, and this can alter the stability of suspensions.

XV. SUSPENSIONS

Suspensions are manufactured either by a precipitation or by dispersed methods requiring use of suspending agents whose characteristic can significantly change because of the presence of other components such as electrolytes.

XVI. EMULSIONS

Heterogeneous systems comprising emulsions offer greater difficulties in manufacturing, where not only a careful calculation of formulation additives such as surfactants is required

but also the manufacturing techniques such as mixing times, intensity of mixing, and temperature become critical in the formation of proper emulsion of the stable type. Microemulsion manufacturing requires special equipment, and recently the use of nanoparticles has created a need for highly specialized handling systems. Homogenizers are used to emulsify liquids along with ultrasonifiers and colloid mills. In some instances, spontaneous emulsification is obtained by a careful order of mixing. The choice of emulsifying agent depends on the type of emulsion desired and determined by the use of hydrophilic–lipophilic balance evaluation. The temperature at which an emulsion is formed can often affect the particle size and, thus, later, the tendency to coalesce or break. Auxiliary emulsification aids include use of fine solids. Hydrophilic colloids are commonly used to impart proper viscosity that enhances stability of emulsions. However, there is a tendency to build up viscosity with time in freshly prepared emulsions. The flow characteristics of emulsions are important and are determined by the emulsion's yield value. Consistency in the density character of emulsion is therefore important. Clear emulsions have a lower proportion of internal phase and require solubilization techniques more frequently than do opaque emulsions. The antimicrobial preservatives used in emulsions are selected on the basis of the type of emulsion manufactured (oil-in-water or water-in-oil). Because water is one of the phases often encountered in emulsions, these must be properly preserved. Classical preservatives are used, but care must be exercised in not selecting preservatives that might interact with surfactants; get adsorbed onto the packaging material such as plastic bottles, caps, or cap liners; and be lost to a point at which they are rendered inactive. Parabens remain a good choice. The presence of oil phase also requires inclusion of antioxidants where necessary, and these may include such examples as gallic acid, propyl gallate, butylated hydroxy-anisole, butylated hydroxytoluene (BHT), ascorbic acid, sulfites, l-tocopherol, butyl phenol, and so forth. Scaling up of emulsion formulations from laboratory scale to manufacturing scales often presents significant problems related to temperature distribution studies; often the two phases are mixed at a specific temperature that may change during the mixing process and thus require a certain mixing rate. Stability testing of emulsions is subject to different protocols than those used for other liquid products, for example, higher-temperature studies may cause an emulsion to break but may not be reflective of the log-linear effect of temperature but, rather, of phase change or inversion. Centrifugation is a common technique to study emulsion stability, and so is the agitation test, which may cause suspended phases to coalesce. Of prime importance in the stability evaluation of emulsions are the phase separation, viscosity changes, changes in light reflection, viscosity, particle size, electrical conductivity, and chemical composition.

XVII. POWDER FOR RECONSTITUTION

Whereas, classically, powder forms would fall under solids, they are included in liquids because of the requirements of formulation after the powder is reconstituted. In some instances, preservatives are required to protect the product during use by the patient. It is important to note that the FDA considers this phase of use of product a part of the product development strategy. The manufacturer must ensure label compliance through the use period, as indicated on the package and under the conditions prescribed, such as keeping it in a refrigerator. Whereas the instructions require the product to be stored in a refrigerator, product development should evaluate a wider range of temperatures, as the temperature inside the consumer's refrigerator may not correspond to the official definition of refrigeration. The method of granulation for the powders intended for resuspension before use is a traditional one, as is used in the preparation of uncompressed or even compressed solids; the difference here is obviously the consideration of the effects of stability on reconstitution, which may require addition of stabilizers. In general, the method of granulation requires wet massing, screening, drying, and screening again; fluid bed dryers may be used as well.

XVIII. NASAL SPRAY PRODUCTS

Nasal spray drug products contain therapeutically active ingredients (drug substances) that are dissolved or suspended in solutions or mixtures of excipients (e.g., preservatives, viscosity modifiers, emulsifiers, and buffering agents) in nonpressurized dispensers that deliver a spray containing a metered dose of the active ingredient. The dose can be metered by the spray pump or can be premetered during manufacture. A nasal spray unit can be designed for unit dosing or can discharge up to several hundred metered sprays of formulation containing the drug substance. Nasal sprays are applied to the nasal cavity for local or systemic effects. Although similar in many features to other drug products, some aspects of nasal sprays may be unique (e.g., formulation, container closure system, manufacturing, stability, controls of critical steps, intermediates, and drug product). These aspects should be considered carefully during the development program because changes can affect the ability of the product to deliver reproducible doses to patients throughout the product's shelf life. Some of the unique features of nasal sprays are listed below:

- Metering and spray producing (e.g., orifice, nozzle, jet) pump mechanisms and components are used for reproducible delivery of drug formulation, and these can be constructed of many parts of different design that are precisely controlled in terms of dimensions and composition.
- Energy is required for dispersion of the formulation as a spray. This is typically accomplished by forcing the formulation through the nasal actuator and its orifice.
- The formulation and the container closure system (container, closure, pump, and any protective packaging) collectively constitute the drug product. The design of the container closure system affects the dosing performance of the drug product.
- The concept of classical bioequivalence and bioavailability may not be applicable for all nasal sprays, depending on the intended site of action. The doses administered are typically so small that blood or serum concentrations are generally undetectable by routine analytical procedures.

A. Inhalation Solutions and Suspensions

Inhalation solution and suspension drug products are typically aqueous-based formulations that contain therapeutically active ingredients and can also contain additional excipients. Aqueous-based oral inhalation solutions and suspension must be sterile (21 CFR 200.51). Inhalation solutions and suspensions are intended for delivery to the lungs by oral inhalation for local or systemic effects and are used with a specified nebulizer. Unit-dose presentation is recommended for these drug products to prevent microbial contamination

during use. The container closure system for these drug products consists of the container and closure and can include protective packaging such as foil overwrap.

B. Inhalation Sprays

An inhalation spray drug product consists of the formulation and the container closure system. The formulations are typically aqueous based and, by definition, do not contain any propellant. Aqueous-based oral inhalation sprays must be sterile (21 CFR 200.51). Inhalation sprays are intended for delivery to the lungs by oral inhalation for local or systemic effects. The products contain therapeutically active ingredients and can also contain additional excipients. The formulation can be in unit-dose or multidose presentations. The use of preservatives or stabilizing agents in inhalation spray formulations is discouraged. If these excipients are included in a formulation, their use should be justified by assessment in a clinical setting to ensure the safety and tolerability of the drug product. The dose is delivered by the integral pump components of the container closure system to the lungs by oral inhalation for local or systemic effects. The container closure system of these drug products consists of the container, closure, and pump, and it can also include protective packaging. Current container closure system designs for inhalation spray drug products include both premetered and device-metered presentations using mechanical or power assistance or energy from patient inspiration for production of the spray plume. Premetered presentations contain previously measured doses or a dose fraction in some type of units (e.g., single or multiple blisters or other cavities) that are subsequently inserted into the device during manufacture or by the patient before use. Typical device-metered units have a reservoir containing formulation sufficient for multiple doses that are delivered as metered sprays by the device itself when activated by the patient. Inhalation spray and nasal spray drug products have many similarities. Many of the characteristics for nasal sprays are also characteristic of inhalation spray drug products. Moreover, the potential wide array of inhalation spray drug product designs with unique characteristics will present a variety of development challenges. Regardless of the design, the most crucial attributes are the reproducibility of the dose, the spray plume, and the particle-/droplet-size distribution, as these parameters can affect the delivery of the drug substance to the intended biological target. Maintaining the reproducibility of these parameters through the expiration dating period and ensuring the sterility of the content and the functionality of the device (e.g., spray mechanism, electronic features, and sensors) through its lifetime under patient-use conditions will probably present the most formidable challenges. Therefore, changes in components of the drug product or changes in the manufacturer or manufacturing process that can affect these parameters should be carefully evaluated for their effect on the safety, clinical effectiveness, and stability of the product. If such changes are made subsequent to the preparation of the batches used in critical clinical, bioequivalence, or primary stability studies, adequate supportive comparative data should be provided to demonstrate equivalency in terms of safety, clinical effectiveness, and stability of the product.

C. Pump Delivery of Nasal Products

A test to assess pump-to-pump reproducibility in terms of drug product performance and to evaluate the delivery from the pump should be performed. The proper performance of the pump should be ensured primarily by the pump manufacturer, who should assemble the pump with parts of precise dimensions. Pump spray weight delivery should be verified by the applicant for the drug product. In general, pump spray weight delivery acceptance criteria should control the weight of individual sprays to within "15% of the target weight" and their USP mean weight to within "10% of the target weight." However, for small-dosage pumps (e.g., 20 mL), other acceptance criteria may be justified. Acceptance testing for pump delivery on incoming pump lots can substitute for the release testing of pump delivery for the drug product, if justified. However, the acceptance criteria for pump delivery should be included in the drug product specification.

D. Spray Content Uniformity for Nasal Products

The spray discharged from the nasal actuator should be thoroughly analyzed for the drug substance content of multiple sprays from beginning to the end of an individual container, among containers, and among batches of drug product. This test should provide an overall performance evaluation of a batch, assessing the formulation, the manufacturing process, and the pump. At most, two sprays per determination should be used except when the number of sprays per minimum dose specified in the product labeling is one. Then the number of sprays per determination should be one spray. To ensure reproducible in vitro dose collection, the procedure should have controls for actuation parameters (e.g., stroke length, actuation force). The test can be performed with units primed following the instructions in the labeling. The amount of drug substance delivered from the nasal actuator should be expressed both as the actual amount and as a percentage of label claim. This test is designed to demonstrate the uniformity of medication per spray (or minimum dose) consistent with the label claim, discharged from the nasal actuator, of an appropriate number ($n = 10$ from beginning and $n = 10$ from end) of containers from a batch. The primary purpose is to ensure spray content uniformity within the same container and among multiple containers of a batch. The following acceptance criteria are recommended, but alternative approaches (e.g., statistical) can be proposed and used if they are demonstrated to provide equal or greater assurance of spray content uniformity. For acceptance of a batch:

- The amount of active ingredient per determination is not outside 80% to 120% of label claim for more than 2 of 20 determinations (10 from beginning and 10 from end) from 10 containers.
- None of the determinations is outside 75% to 125% of the label claim.
- The mean for each of the beginning and end determinations is not outside 85% to 115% of label claim.

If the above acceptance criteria are not met because 3 to 6 of the 20 determinations are outside 80% to 120% of the label claim, 14 units but none are outside 75% to 125% of label claim, and the means for each of the beginning and end determinations are not outside 85% to 115% of label claim, an additional 20 containers should be sampled for second-tier testing.

For the second-tier testing of a batch, the acceptance criteria are met if

- the amount of active ingredient per determination is not outside 80% to 120% of the label claim for more than 6 of all 60 determinations;
- none of the 60 determinations is outside 75% to 125% of label claim; and
- the mean for each of the beginning and end determinations is not outside 85% to 115% of label claim.

E. Spray Pattern and Plume Geometry of Nasal Products

Characterization of spray pattern and plume geometry is important for evaluating the performance of the pump. Various factors can affect the spray pattern and plume geometry, including the size and shape of the nozzle, the design of the pump, the size of the metering chamber, and the characteristics of the formulation. Spray-pattern testing should be performed on a routine basis as a quality control for release of the drug product. However, the characterization of plume geometry typically should be established during the characterization of the product and is not necessarily tested routinely thereafter. The proposed test procedure for spray pattern should be provided in detail to allow duplication by FDA laboratories. For example, in the evaluation of the spray pattern, the spray distance between the nozzle and the collection surface, number of sprays per spray pattern, position and orientation of the collection surface relative to the nozzle, and visualization procedure should be specified. The acceptance criteria for spray pattern should include the shape (e.g., ellipsoid of relative uniform density) as well as the size of the pattern (e.g., no axis is greater than x millimeters and the ratio of the longest to the shortest axes should lie in a specified range). Data should be provided to demonstrate that the collection distance selected for the spray pattern test will provide the optimal discriminatory capability. Variability in the test can be reduced by the development of a sensitive detection procedure and by providing procedure-specific training to the analyst. Acceptance testing for spray pattern on incoming pump lots can substitute for the release testing of spray pattern for the drug product, if justified (e.g., spray patterns from pumps with drug product formulation and with the proposed simulating media are the same).

However, the 15 acceptance criteria for spray pattern should be included in the drug product specification.

F. Droplet-Size Distribution in Nasal Products

For both suspension and solution nasal sprays, the specifications should include an appropriate control for the droplet-size distribution (e.g., three to four cutoff values) of the delivered plume subsequent to spraying under specified experimental and instrumental conditions. If a laser diffraction method is used, droplet-size distribution can be controlled in terms of ranges for the D_{10}, D_{50}, D_{90}, span $[(D_{90} - D_{10})/D_{50}]$, and percentage of droplets less than 10 mm. Appropriate and validated or calibrated droplet-size analytical procedures should be described in sufficient detail to allow accurate assessment by agency laboratories (e.g., apparatus and accessories, calculation theory, correction principles, software version, sample placement, laser trigger condition, measurement range, and beam width). For solution nasal sprays, acceptance testing for droplet-size distribution on incoming pump lots with placebo formulation can substitute for the release testing of droplet-size distribution for the drug product, if justified (i.e., droplet-size distributions from pumps with drug product formulation and those with the placebo are the same). However, the acceptance criteria for droplet-size distribution should be included in the drug product specification.

G. Particle-Size Distribution for Nasal Suspensions

For suspension nasal sprays, the specification should include tests and acceptance criteria for the particle-size distribution of the drug substance particles in the formulation. The quantitative procedure should be appropriately validated, if feasible, in terms of its sensitivity and ability to detect shifts that may occur in the distribution. When examining formulations containing suspending agents in the presence of suspended drug substance, when it is demonstrated that the currently available technology cannot be acceptably validated, a qualitative and semiquantitative method for examination of drug and aggregated drug particle-size distribution can be used. Supportive data, along with available validation information, should be submitted. For example, microscopic evaluation can be used, and such an examination can provide information and data on the presence of large particles, changes in morphology of the drug substance particles, extent of agglomerates, and crystal growth.

XIX. EMULSIFICATION AND SOLUBILIZATION

To solubilize insoluble lypophilic or hydrophobic active substances in an aqueous medium, BASF pharmaceutical excipients offer several possibilities and mechanisms. For microemulsions, Cremophor RH 40, Cremophor EL, and Solutol HS 15 act as surface-active solubilizers in water and form the structures of micelles. The micelle that envelops the active substance is so small that it is invisible, or perhaps visible in the form of opalescence. Typical fields of application are oil-soluble vitamins, antimycotics of the miconazole type, mouth disinfectants (e.g., hexiditin), and etherian oils or fragrances. Solutol HS 15 is recommended for parenteral use of this solubilizing system and has been specially developed for this purpose.

XX. COMPLEXING

The soluble Kollidon products form reversible complexes with many hydrophobic active substances, and clear solutions in water are thus obtained. This may be affected by the molecular weight. The longer the chains or the higher the K-value of the Kollidon type are, the stronger the solubility effect is, and thus the greater the solubility that can be obtained by the active substance. In practice, this effect was mostly exploited for the solubilization of antibiotics in human and veterinary medicine. There are also restrictions on the use of this substance in human parenterals. In many countries the K-value must not exceed 18, and there is also a restriction on the amount to be used for each dose administered in intramuscular application.

XXI. HYDROPHILIZATION

Active substances can also be solubilized by Lutrol F 68 in addition to the Cremophor and Kollidon products. The mechanism is probably based, for the most part, on the principle of hydrophilization. Micelle formation is certainly of minor significance, if it exists at all.

XXII. STABILIZING SUSPENSIONS

Various BASF pharmaceutical excipients with different functions can be used for stabilizing suspensions. The following groups of products can be offered for stabilizing oral and topical suspensions. Soluble Kollidon products can be used at low concentrations, that is, at 2% to 5%, Kollidon

90°F suffices to stabilize aqueous suspensions. A combination consisting of 2% Kollidon 90°F and 5% to 9% Kollidon CL-M has proved to be an effective system for stabilizing suspensions. Kollidon 30 is also used for this purpose. It can be combined with all conventional suspension stabilizers (thickeners, surfactants, etc.). The use of Kollidon CL-M as a suspension stabilizer has nothing whatever to do with the principle of increasing the viscosity. The addition of 5% to 9% Kollidon CL-M has practically no effect in changing the viscosity, but it strongly reduces the rate of sedimentation and facilitates the redispersability, in particular—an effect that is consistent with the low viscosity. One of the reasons for this Kollidon CL-M effect is its low (bulk) density, which is only half of that of conventional crospovidone (e.g., Kollidon CL). The polyoxamers, Lutrol F 68, and Lutrol F 127, in concentrations of 2% to 5%, expressed in terms of the final weight of the suspension, offer a further opportunity of stabilizing suspensions. They also do not increase viscosity when used in these amounts and can be combined with all other conventional suspension stabilizers.

6

Container Closure Systems

I. INTRODUCTION

According to the Federal Food, Drug, and Cosmetic Act (the act), section 501(a)(3), a drug is deemed to be adulterated "if its container is composed, in whole or in part, of any poisonous or deleterious substance which may render the contents injurious to health." In addition, section 502 of the act states that a drug is considered misbranded if there are packaging omissions. Also, section 505 of the act requires a full description of the methods used in, and the facilities and controls used for, the packaging of drugs. Section 505(b)(1)(D) of the act states that an application shall include a full description of the methods used in the manufacturing, processing, and packing of such drug. This includes facilities and controls used in the packaging of a drug product.

A. Definitions

Materials of construction are the substances [e.g., glass, high-density polyethylene (HDPE) resin, metal] used to manufacture a packaging component. A packaging component is any single part of a container closure system. Typical components are containers (e.g., ampoules, vials, bottles), container liners (e.g., tube liners), closures (e.g., screw caps, stoppers), closure liners, stopper overseals, container inner seals, administration ports (e.g., on large-volume parenterals), overwraps, administration accessories, and container labels. A primary packaging component is a packaging component that is or may be in direct contact with the dosage form. A secondary packaging component is a packaging component that is not and will not be in direct contact with the dosage form.

A container closure system is the sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter is intended to provide additional protection to the drug product. A packaging system is equivalent to a container closure system.

A package, or market package, is the container closure system and labeling, associated components (e.g., dosing cups, droppers, spoons), and external packaging (e.g., cartons or shrink-wrap). A market package is the article provided to a pharmacist or retail customer on purchase and does not include packaging used solely for the purpose of shipping such articles.

The term "quality" refers to the physical, chemical, microbiological, biological, bioavailability, and stability attributes that a drug product should maintain if it is to be deemed suitable for therapeutic or diagnostic use. In this guidance, the term is also understood to convey the properties of safety, identity, strength, quality, and purity [see Title 21 Code of Federal Register (CFR) 211.94(a)].

An extraction profile is the analysis (usually by chromatographic means) of extracts obtained from a packaging component. A quantitative extraction profile is one in which the amount of each detected substance is determined.

B. Current Good Manufacturing Practice, the Consumer Product Safety Commission, and Requirements on Containers and Closures

Current good manufacturing practice requirements for the control of drug product containers and closures are included in 21 CFR Parts 210 and 211. The U.S. Food and Drug Administration (FDA) requirement for tamper-resistant closures is included in 21 CFR 211.132 and the Consumer Product Safety Commission requirements for child-resistant closures are included in 16 CFR 1700.

The United States Pharmacopeial Convention has established requirements for containers that are described in many of the drug product monographs in *The United States Pharmacopeia/National Formulary*. For capsules and tablets, these requirements generally relate to the design characteristics of the container (e.g., tight, well closed, or light resistant). For injectable products, materials of construction are also addressed (e.g., "Preserve in single-dose or in multiple-dose containers, preferably of type I glass, protected from light"). These requirements are defined in the "General Notices and Requirements" (Preservation, Packaging, Storage, and Labeling) section of the USP. The requirements for materials of construction are defined in the "General Chapters" of the USP.

C. Additional Considerations

The packaging information in the chemistry, manufacturing, and controls (CMC) section of an investigational new drug application (IND) usually includes a brief description of the components, the assembled packaging system, and any precautions needed to ensure the protection and preservation of the drug substance and drug product during their use in the clinical trials.

A contract packager is a firm retained by the applicant to package a drug product. The applicant remains responsible for the quality of the drug product during shipping, storage, and packaging. The information regarding the container closure system used by a contract packager that should be submitted in the CMC section of an application [new drug application (NDA), abbreviated new drug application (ANDA), or biological license application (BLA)], or in a drug master file (DMF) that is referenced in the application, is no different from that which would be submitted if the applicant performed its own packaging operations. If the information is provided in a DMF, then a copy of the letter of authorization for the DMF should be provided in the application.

II. QUALIFICATION AND QUALITY CONTROL OF PACKAGING COMPONENTS

A packaging system found acceptable for one drug product is not automatically assumed to be appropriate for another. Each application should contain enough information to show

that each proposed container closure system and its components are suitable for its intended use.

The type and extent of information that should be provided in an application will depend on the dosage form and the route of administration. For example, the kind of information that should be provided about a packaging system for an injectable dosage form or a drug product for inhalation is often more detailed than that which should be provided about a packaging system for a solid oral dosage form. More detailed information usually should be provided for a liquid-based dosage form than for a powder or a solid, as a liquid-based dosage form is more likely to interact with the packaging components. There is a correlation between the degree of concern regarding the route of administration and the likelihood of packaging component–dosage form interactions for different classes of drug products:

Highest: inhalation, aerosols, sterile powders, and solutions; powders for injections and injection; and inhalation, injectable, powders, and suspensions
High: ophthalmic solutions and suspensions, transdermal ointments and patches, and nasal aerosols and sprays
Low: topical solutions and topical powders; oral tablets and oral suspensions; and topical oral powders (hard and soft and lingual aerosols; gelatin), capsules, oral solutions, and suspensions

"Suitability" refers to the tests and studies used and accepted for the initial qualification of a component, or a container closure system, for its intended use. "Quality control" refers to the tests typically used and accepted to establish that, after the application is approved, the components and the container closure system continue to possess the characteristics established in the suitability studies. The subsections on associated components and secondary components describe the tests and studies for establishing suitability and quality control for these types of components. However, the ultimate proof of the suitability of the container closure system and the packaging process is established by full shelf-life stability studies.

Every proposed packaging system should be shown to be suitable for its intended use: It should adequately protect the dosage form, it should be compatible with the dosage form, and it should be composed of materials that are considered safe for use with the dosage form and the route of administration. If the packaging system has a performance feature in addition to containing the product, the assembled container closure system should be shown to function properly. Information intended to establish suitability may be generated by the applicant, by the supplier of the material of construction or the component, or by a laboratory under contract to either the applicant or the firm. An adequately detailed description of the tests, methods, acceptance criteria, reference standards, and validation information for the studies should be provided. The information may be submitted directly in the application or indirectly by reference to a DMF. If a DMF is used, a letter authorizing reference (i.e., letter of authorization) to the DMF must be included in the application.

A container closure system should provide the dosage form with adequate protection from factors (e.g., temperature, light) that can cause a degradation in the quality of that dosage form over its shelf life. Common causes of such degradation are exposure to light, loss of solvent, exposure to reactive gases (e.g., oxygen), absorption of water vapor, and microbial contamination. A drug product can also suffer an unacceptable loss in quality if it is contaminated by filth.

Not every drug product is susceptible to degradation by all of these factors: not all drug products are light sensitive. Not all tablets are subject to loss of quality caused by absorption of moisture. Sensitivity to oxygen is most commonly found with liquid-based dosage forms. Laboratory studies can be used to determine which of these factors actually have an influence on a particular drug product.

Light protection is typically provided by an opaque or amber-colored container or by an opaque secondary packaging component (e.g., cartons or overwrap). The test for light transmission (USP <661>) is an accepted standard for evaluating the light transmission properties of a container. Situations exist in which solid- and liquid-based oral drug products have been exposed to light during storage because the opaque secondary packaging component was removed, contrary to the approved labeling and the monograph recommendation. A firm, therefore, may want to consider using additional or alternate measures to provide light protection for these drug products when necessary.

Loss of solvent can occur through a permeable barrier (e.g., a polyethylene container wall), through an inadequate seal, or through leakage. Leaks can develop through rough handling or from inadequate contact between the container and the closure (e.g., because of the buildup of pressure during storage). Leaks can also occur in tubes as a result of failure of the crimp seal. Water vapor or reactive gases (e.g., oxygen) may penetrate a container closure system either by passing through a permeable container surface [e.g., the wall of a low-density polyethylene (LDPE) bottle] or by diffusing past a seal. Plastic containers are susceptible to both routes. Although glass containers would seem to offer better protection, because glass is relatively impermeable, glass containers are more effective only if there is a good seal between the container and the closure.

Protection from microbial contamination is provided by maintaining adequate container integrity after the packaging system has been sealed. An adequate and validated procedure should be used for drug product manufacture and packaging.

Packaging components that are compatible with a dosage form will not interact sufficiently to cause unacceptable changes in the quality of either the dosage form or the packaging component. Examples of interactions include loss of potency, caused by absorption or adsorption of the active drug substance, or degradation of the active drug substance, induced by a chemical entity leached from a packaging component; reduction in the concentration of an excipient caused by absorption, adsorption, or leachable-induced degradation; precipitation; changes in drug product pH; discoloration of either the dosage form or the packaging component; or increase in brittleness of the packaging component.

Some interactions between a packaging component and dosage form will be detected during qualification studies on the container closure system and its components. Others may not show up except in the stability studies. Therefore, any change noted during a stability study that may be attributable to interaction between the dosage form and a packaging component should be investigated, and appropriate action should be taken, regardless of whether the stability study is being conducted for an original application, a supplemental application, or as fulfillment of a commitment to conduct postapproval stability studies.

Packaging components should be constructed of materials that will not leach harmful or undesirable amounts of substances to which a patient will be exposed when being treated with the drug product. This consideration is especially

important for those packaging components that may be in direct contact with the dosage form, but it is also applicable to any component from which substances may migrate into the dosage form (e.g., an ink or adhesive). Making the determination that a material of construction used in the manufacture of a packaging component is safe for its intended use is not a simple process, and a standardized approach has not been established. There is, however, a body of experience that supports the use of certain approaches that depend on the route of administration and the likelihood of interactions between the component and the dosage form. For a drug product such as an injection, inhalation, ophthalmic, or transdermal product, a comprehensive study is appropriate. This involves two parts: first, an extraction study on the packaging component to determine which chemical species may migrate into the dosage form (and at what concentration), and second, a toxicological evaluation of those substances that are extracted to determine the safe level of exposure via the label-specified route of administration. This technique is used by the Center for Food Safety and Applied Nutrition to evaluate the safety of substances that are proposed as indirect food additives (e.g., polymers or additives that may be used in for packaging foods).

The approach for toxicological evaluation of the safety of extractables should be based on good scientific principles and should take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). For many injectable and ophthalmic drug products, data from the Biological Reactivity tests and Elastomeric Closures for Injections tests will typically be considered sufficient evidence of material safety.

For many solid and liquid oral drug products, an appropriate reference to the indirect food additive regulations (21 CFR 174–186) promulgated by Center for Food Safety and Applied Nutrition for the materials of construction used in the packaging component will typically be considered sufficient. Although these regulations do not specifically apply to materials for packaging drug products, they include purity criteria and limitations pertaining to the use of specific materials for packaging foods that may be acceptable for the evaluation of drug product packaging components. Applicants are cautioned that this approach may not be acceptable for liquid oral dosage forms intended for chronic use.

For drug products that undergo clinical trials, the absence of adverse reactions traceable to the packaging components is considered supporting evidence of material safety. Performance of the container closure system refers to its ability to function in the manner for which it was designed. A container closure system is often called on to do more than simply contain the dosage form. When evaluating performance, two major considerations are container closure system functionality and drug delivery.

First, consider container closure system functionality: the container closure system may be designed to improve patient compliance (e.g., a cap that contains a counter), minimize waste (e.g., a two-chamber vial or IV bag), improve ease of use (e.g., a prefilled syringe), or have other functions.

The second consideration is drug delivery: Drug delivery refers to the ability of the packaging system to deliver the dosage form in the amount or at the rate described in the package insert. Some examples of a packaging system for which drug delivery aspects are relevant are a prefilled syringe, a transdermal patch, a metered tube, a dropper or spray bottle, a dry powder inhaler, and a metered dose inhaler.

Container closure system functionality or drug delivery are compromised when the packaging system fails to operate as designed. Failure can result from misuse, faulty design, manufacturing defect, improper assembly, or wear and tear during use. Tests and acceptance criteria regarding dosage form delivery and container closure system functionality should be appropriate to the particular dosage form, route of administration, and design features. If there is a special performance function built into the drug product (e.g., a counter cap), it is of importance for any dosage form or route of administration to show that the container closure system performs that function properly.

In addition to providing data to show that a proposed container closure system is suitable for its intended use, an application should also describe the quality control measures that will be used to ensure consistency in the packaging components. These controls are intended to limit unintended postapproval variations in the manufacturing procedures or the materials of construction for a packaging component and to prevent adverse effects on the quality of a dosage form.

Principal consideration is usually given to consistency in physical characteristics and chemical composition. The physical characteristics of interest include dimensional criteria (e.g., shape, neck finish, wall thickness, design tolerances), physical parameters critical to the consistent manufacture of a packaging component (e.g., unit weight), and performance characteristics (e.g., metering valve delivery volume or the ease of movement of syringe plungers). Unintended variations in dimensional parameters, if undetected, may affect package permeability, drug delivery performance, or the adequacy of the seal between the container and the closure. Variation in any physical parameter is considered important if it can affect the quality of a dosage form.

The chemical composition of the materials of construction may affect the safety of a packaging component. New materials may result in new substances being extracted into the dosage form or in a change in the amount of known extractables. Chemical composition may also affect the compatibility, functional characteristics, or protective properties of packaging components by changing rheological or other physical properties (e.g., elasticity, resistance to solvents, or gas permeability). A composition change may occur as a result of a change in formulation or a change in a processing aid (e.g., using a different mold release agent) or through the use of a new supplier of a raw material. A change in the supplier of a polymeric material or a substance of biological origin is more likely to bring with it an unexpected composition change than is a change in the supplier of a pure chemical compound because polymeric and natural materials are often complex mixtures. A composition change may also occur with a change in the manufacturing process, such as the use of different operating conditions (e.g., a significantly different curing temperature), different equipment, or both. A change in formulation is considered a change in the specifications for the packaging component. Changes in the formulation of a packaging component by its manufacturer should be reported to the firm that purchases that component and to any appropriate DMF. The firm that purchases the component should, in turn, report the change to its application as required under 21 CFR 314.70(a) or 601.12. Manufacturers who supply a raw material or an intermediate packaging component should inform their customers of any intended changes to formulations or manufacturing procedures and should update the DMF in advance of implementing such a change. Changes that seem innocuous may have unintended

consequences on the dosage form marketed in the affected packaging system.

The use of stability studies for monitoring the consistency of a container closure system in terms of compatibility with the dosage form and the degree of protection provided to the dosage form is accepted. At present, there is no general policy concerning the monitoring of a packaging system and components with regard to safety. One exception involves inhalation drug products, for which batch-to-batch monitoring of the extraction profile for the polymeric and elastomeric components is routine.

"Associated components" are packaging components that are typically intended to deliver the dosage form to the patient but that are not stored in contact with the dosage form for its entire shelf life. These components are packaged separately in the market package and are either attached to the container on opening or used only when a dose is to be administered. Measuring spoons, dosing cups, measuring syringes, and vaginal delivery tubes are examples of associated components that typically contact the dosage form only during administration. A hand pump or dropper combined into a closure are examples of an associated component that would contact the dosage form from the time the packaging system is opened until the dosing regimen is completed.

The complete and assembled component and its parts should meet suitability criteria appropriate for the drug product and the actual use of the component. Safety and functionality are the most common factors to be established for suitability. The length of time that the associated component and the dosage form are in direct contact should also be taken into consideration when assessing the suitability of an associated component.

Unlike primary and associated packaging components, secondary packaging components are not intended to make contact with the dosage form. Examples are cartons, which are generally constructed of paper or plastic, and overwraps, which may be fabricated from a single layer of plastic or from a laminate made of metal foil, plastic, or paper. A secondary packaging component generally provides one or more of the following additional services:

- Protection from excessive transmission of moisture or solvents into or out of the packaging system
- Protection from excessive transmission of reactive gases (atmospheric oxygen, inert head-space filler gas, or other organic vapors) into or out of the packaging system
- Light protection for the packaging system
- Protection for a packaging system that is flexible or that needs extra protection from rough handling
- Additional measure of microbiological protection (i.e., by maintaining sterility or by protecting the packaging system from microbial intrusion)

When information on a container closure system is submitted in an application, the emphasis would normally be on the primary packaging components. For a secondary packaging component, a brief description will usually suffice unless the component is intended to provide some additional measure of protection to the drug product. In this case, more complete information should be provided, along with data showing that the secondary packaging component actually provides the additional protection.

Because secondary packaging components are not intended to make contact with the dosage form, there is usually less concern regarding the materials from which they are constructed. However, if the packaging system is relatively permeable, the possibility increases that the dosage form could be contaminated by the migration of an ink or adhesive component or from a volatile substance present in the secondary packaging component. (For example, a solution packaged in an LDPE container was found to be contaminated by a volatile constituent of the secondary packaging components that enclosed it.) In such a case, the secondary packaging component should be considered a potential source of contamination, and the safety of its materials of construction should be taken into consideration.

A. Description

A general description of the entire container closure system should be provided in the CMC section of the application. In addition, the following information should be provided by the applicant for each individual component of the packaging system:

- Identification by product name, product code (if available), name and address of the manufacturer, and a physical description of the packaging component (e.g., type, size, shape, and color)
- Identification of the materials of construction (i.e., plastics, paper, metal, glass, elastomers, coatings, adhesives, and other such materials) should be identified by a specific product designation (code name and/or code number) and the source (name of the manufacturer); alternate materials of construction should be indicated; postconsumer recycled plastic should not be used in the manufacture of a primary packaging component, and if it is used for a secondary or associated component, then the safety and compatibility of the material for its intended use should be addressed appropriately
- Description of any operations or preparations that are performed on a packaging component by the applicant (such as washing, coating, sterilization, or depyrogenation)

B. Information about Suitability

To establish safety and to ensure consistency, the complete chemical composition should be provided for every material used in the manufacture of a packaging component. Test results from appropriate qualification and characterization tests should be provided. Adequate information regarding the tests, methods, acceptance criteria, reference standards, and validation information should also be provided.

To address protection, use of tests for light transmission, moisture permeation, microbial limits, and sterility are generally considered sufficient. Testing for properties other than those described above (e.g., gas transmission, solvent leakage container integrity) may also be necessary.

To address safety and compatibility, the results of extraction/toxicological evaluation studies should be provided for drug products that are likely to interact with the packaging components and to introduce extracted substances into the patient. For drug products less likely to interact, other tests (e.g., Biological Reactivity test) or information (e.g., appropriate reference to the indirect food additive regulations at 21 CFR 174–186) could be used to address the issue of safety and compatibility. For example, an appropriate reference to an indirect food additive regulation is generally sufficient for a solid oral dosage form product.

To address performance, the results of nonfunctionality tests are considered sufficient if the test and acceptance criteria are appropriate for the intended purpose. Tests described there are typically considered sufficient standards for establishing specified properties and characteristics of specified

materials of construction or packaging components. For nonfunctionality tests, an applicant should provide justification for the use of the test, a complete and detailed description of how the test was performed, and an explanation of what the test is intended to establish. If a related test is available, comparative data should be provided using both methods. Supporting data should include a demonstration of the suitability of the test for its intended use and its validation.

Testing on an assembled container closure system is usually performed by the applicant (or a testing laboratory commissioned by the applicant), and the test results are provided in the application. Such tests may include vacuum-leak testing, moisture permeation, and weight loss or media fill. Testing on an individual packaging component is typically performed by the manufacturer of the component and is reported via a DMF (see section V).

The fabricator/manufacturer of a packaging component and the drug product manufacturer who uses this firm share the responsibility for ensuring the quality of packaging components. These firms should have a quality control program in place so that consistent components are produced. The drug product manufacturer must have an inspection program for incoming packaging components and materials (21 CFR 211.22, 211.84, and 211.122). For most drug products, a drug product manufacturer may accept a packaging component lot based on receiving a certificate of analysis (COA) or certificate of certification (COC) from the component supplier and on the performance of an appropriate identification test, provided the supplier's test data are periodically validated [21 CFR 211.84(d)(3)]. Acceptance of a packaging component lot based on a supplier's COA or COC may not be appropriate in all cases (e.g., some packaging components for certain inhalation drug products).

The tests and methods used by the applicant for acceptance of each batch of a packaging component that they receive should be described. If a batch is to be accepted based on a supplier's COA or COC, then the procedure for supplier validation should be described. The data from the supplier's COA or COC should clearly indicate that the lot meets the applicant's acceptance criteria. Acceptance criteria for extractables should also be included, if appropriate.

Dimensional and performance criteria should be provided. Dimensional information is frequently provided via a detailed schematic drawing, complete with target dimensions and tolerances, and it may be provided via the packaging component manufacturer's DMF. A separate drawing may not be necessary if the packaging component is part of a larger unit for which a drawing is provided or if the component is uncomplicated in design (e.g., a cap liner).

Each manufacturer of a packaging component consistency is the physical and chemical characteristics of the component. These measures generally include release criteria (and test methods, if appropriate) and a description of the manufacturing procedure. If the release of the packaging component is based on statistical process control, a complete description of the process (including control criteria) and its validation should be provided.

The description of the manufacturing process is generally brief and should include any operations performed on the packaging component after manufacture but before shipping (e.g., washing, coating, or sterilization). In some cases, it may be desirable for the description to be more detailed and to include in-process controls. This information may be provided via a DMF.

The quality control procedures of the manufacturer of a packaging component may sometimes rely in whole or in part on the quality control procedures of a manufacturer who makes an intermediate packaging component that is used to create the component. If so, each contributor to the final packaging system should provide a description of the quality control measures used to maintain consistency in the physical and chemical characteristics of the separate components and of the assembled packaging system that they provide.

The manufacturer of each material of construction should be prepared to describe the quality control measures used to maintain consistency in the chemical characteristics of their product. This information may be provided via a DMF.

C. Stability Data (Packaging Concerns)

Stability testing of the drug product should be conducted using the container closure systems proposed in the application. The packaging system used in each stability study should be clearly identified, and the container closure system should be monitored for signs of instability. When appropriate, an evaluation of the packaging system should be included in the stability protocol. Even when a formal test for quality of the packaging system is not performed, the applicant should investigate any observed change in the packaging system used in the stability studies. The observations, results of the investigation, and corrective actions should be included in the stability report. If the corrective action requires a change in an approved container closure system, a supplemental application should be submitted.

D. Inhalation Drug Products

Inhalation drug products include inhalation aerosols (metered dose inhalers); inhalation solutions, suspensions, and sprays (administered via nebulizers); inhalation powders (dry powder inhalers); and nasal sprays. The CMC and preclinical considerations for inhalation drug products are unique in that these drug products are intended for respiratory tract-compromised patients. This is reflected in the level of concern given to the nature of the packaging components that may come in contact with the dosage form or the patient.

E. Injection and Ophthalmic Drug Products

These dosage forms share the common attributes that they are generally solutions, emulsions, or suspensions, and that all are required to be sterile. Injectable dosage forms represent one of the highest-risk drug products. Any contaminants present (as a result of contact with a packaging component or caused by the packaging system's failure to provide adequate protection) can be rapidly and completely introduced into the patient's general circulation. Although the risk factors associated with ophthalmics are generally considered to be lower than for injectables, any potential for causing harm to the eyes demands caution.

Injectable drug products may be liquids in the form of solutions, emulsions, suspensions, or dry solids that are to be combined with an appropriate vehicle to yield a solution or suspension. Injections are classified as small-volume parenterals if they have a solution volume of 100 mL or less, or as large-volume parenterals if the solution volume exceeds 100 mL. For solids that must be dissolved or dispersed in an appropriate diluent before being injected, the diluent may be in the same container closure system (e.g., a two-part vial) or be part of the same market package (e.g., a kit containing a vial of diluent). A small-volume parenteral may be packaged in a disposable cartridge, a disposable syringe, a vial, an ampoule, or a flexible bag. A large-volume parenteral may be packaged in a vial, a flexible bag, a glass bottle, or in some cases, as a disposable syringe.

Cartridges, syringes, vials, and ampoules are usually composed of type I or II glass or of polypropylene. Flexible bags are typically constructed with multilayered plastic. Stoppers and septa in cartridges, syringes, and vials are typically composed of elastomeric materials. The input (medication) and output (administration) ports for flexible bags may be plastic or elastomeric materials. An overwrap may be used with flexible bags to retard solvent loss and to protect the flexible packaging system from rough handling.

The potential effects of packaging component/dosage form interactions are numerous. Hemolytic effects may result from a decrease in tonicity, and pyrogenic effects may result from the presence of impurities. The potency of the drug product or the concentration of the antimicrobial preservatives may decrease because of adsorption or absorption. A cosolvent system essential to the solubilization of a poorly soluble drug can also serve as a potent extractant of plastic additives. A disposable syringe may be made of plastic, glass, rubber, and metal components, and such multicomponent construction provides a potential for interaction that is greater than when a container consists of a single material.

Injectable drug products require protection from microbial contamination (loss of sterility or added bioburden) and may also need to be protected from light or from exposure to gases (e.g., oxygen). Liquid-based injectables may need to be protected from solvent loss, whereas sterile powders or powders for injection may need to be protected from exposure to water vapor. For elastomeric components, data showing that a component meets the requirements of elastomeric closures for injections will typically be considered sufficient evidence of safety. For plastic components, data from Biological Reactivity tests will typically be considered sufficient evidence of safety. Whenever possible, the extraction studies should be performed using the drug product. If the extraction properties of the drug product vehicle may reasonably be expected to differ from that of water (e.g., because of high or low pH or a solubilizing excipient), then drug product should be used as the extracting medium. If the drug substance significantly affects extraction characteristics, it may be necessary to perform the extractions using the drug product vehicle. If the total of the extracts significantly exceeds the amount obtained from water extraction, then an extraction profile should be obtained. It may be advisable to obtain a quantitative extraction profile of an elastomeric or plastic packaging component and to compare this periodically to the profile from a new batch of the packaging component. Extractables should be identified whenever possible. For a glass packaging component, data from *Containers: Chemical Resistance—Glass Containers* will typically be considered sufficient evidence of safety and compatibility. In some cases (e.g., for some chelating agents), a glass packaging component may need to meet additional criteria to ensure the absence of significant interactions between the packaging component and the dosage form.

Performance of a syringe is usually addressed by establishing the force to initiate and maintain plunger movement down the barrel and the capability of the syringe to deliver the labeled amount of the drug product.

These drug products are usually solutions marketed in an LDPE bottle with a dropper built into the neck (sometimes referred to as droptainer) or ointments marketed in a metal tube with an ophthalmic tip. A few solution products use a glass container because of stability concerns regarding plastic packaging components. Ophthalmic ointments that are reactive toward metal may be packaged in a tube lined with an epoxy or vinyl plastic coating. A large-volume intraocular solution (for irrigation) may be packaged in a glass or polyolefin (polyethylene or polypropylene) container. The American Academy of Ophthalmology recommended to the FDA that a uniform color coding system be established for the caps and labels of all topical ocular medications. An applicant should either follow this system or provide an adequate justification for any deviations from the system.

Although ophthalmic drug products can be considered topical products, they have been grouped here with injectables because they are required to be sterile [21 CFR 200.50(a)(2)] and the descriptive, suitability, and quality control information is typically the same as that for an injectable drug product. Because ophthalmic drug products are applied to the eye, compatibility and safety should also address the container closure system's potential to form substances which irritate the eye or introduce particulate matter into the product (see USP <771> Ophthalmic Ointments).

F. Liquid-Based Oral and Topical Drug Products and Topical Delivery Systems

A wide variety of drug products falls into this category. The presence of a liquid phase implies a significant potential for the transfer of materials from a packaging component into the dosage form. The higher viscosity of semisolid dosage forms and transdermal systems may cause the rate of migration of leachable substances into these dosage forms to be slower than for aqueous solutions. Because of extended contact, the amount of leachables in these drug products may depend more on a leachable material's affinity for the liquid/semisolid phase than on the rate of migration.

Typical liquid-based oral dosage forms are elixirs, emulsions, extracts, fluid extracts, solutions, gels, syrups, spirits, tinctures, aromatic waters, and suspensions. These products are usually nonsterile but may be monitored for changes in bioburden or for the presence of specific microbes. These dosage forms are generally marketed in multiple-unit bottles or in unit-dose or single-use pouches or cups. The dosage form may be used as is or admixed first with a compatible diluent or dispersant. A bottle is usually glass or plastic, often with a screw cap with a liner, and possibly with a tamper-resistant seal or an overcap that is welded to the bottle. The same cap liners and inner seals are sometimes used with solid oral dosage forms. A pouch may be a single-layer plastic or a laminated material. Both bottles and pouches may use an overwrap, which is usually a laminated material. A single-dose cup may be metal or plastic with a heat-sealed lid made of a laminated material.

A liquid-based oral drug product typically needs to be protected from solvent loss, microbial contamination, and sometimes, from exposure to light or reactive gases (e.g., oxygen). For glass components, data showing that a component meets the requirements of *Containers: Glass Containers* are accepted as sufficient evidence of safety and compatibility. For LDPE components, data from Containers tests are typically considered sufficient evidence of compatibility. The General Chapters do not specifically address safety for polyethylene (HDPE or LDPE), polypropylene, or laminate components. A patient's exposure to substances extracted from a plastic packaging component (e.g., HDPE, LDPE, polypropylene, laminated components) into a liquid-based oral dosage form is expected to be comparable to a patient's exposure to the same substances through the use of the same material when it is used to package food. On the basis of this assumption, an appropriate reference to the indirect food additive regulations (21 CFR 174–186) is typically considered sufficient to establish safety of the material of construction, provided any

limitations specified in the regulations are taken into consideration. This assumption is considered valid for liquid-based oral dosage forms that the patient will take only for a relatively short time (acute dosing regimen). For liquid-based oral drug products that the patient will continue to take for an extended period (i.e., months or years [chronic drug regimen]), a material of construction that meets the requirements for indirect food additives will be considered safe—on that basis alone—only if the patient's exposure to extractables can be expected to be no greater than the exposure through foods or if the length of exposure is supported by toxicological information. For example, if the dosage form is aqueous-based and contains little or no cosolvent (or other substance, including the active drug substance, liable to cause greater extraction of substances from plastic packaging components than would be extracted by water), meeting the requirements of the indirect food additive regulations will usually satisfy the issue of safety.

If the dosage form contains cosolvents (or if, for any reason, it may be expected to extract greater amounts of substances from plastic packaging components than water), then additional extractable information may be needed to address safety issues. Performance is typically not a factor for liquid-based oral drug products.

Topical dosage forms include aerosols, creams, emulsions, gels, lotions, ointments, pastes, powders, solutions, and suspensions. These dosage forms are generally intended for local (not systemic) effect and are generally applied to the skin or oral mucosal surfaces. Topical products also include some nasal and otic preparations as well as some ophthalmic drug products. Vaginal and rectal drug products may be considered to be topical if they are intended to have a local effect. Some topical drug products are sterile or may be subject to microbial limits. In these cases, additional evaluation may be necessary when determining the appropriate packaging.

A liquid-based topical product typically has a fluid or semisolid consistency and is marketed in a single- or multiple-unit container (e.g., a rigid bottle or jar, a collapsible tube, or a flexible pouch). A powder product may be marketed in a sifter-top container. An antibacterial product may be marketed as part of a sterile dressing; there are also a number of products marketed as a pressurized aerosol or a hand-pumped spray. A rigid bottle or jar is usually made of glass or polypropylene with a screw cap. The same cap liners and inner seals are sometimes used as with solid oral dosage forms. A collapsible tube is usually constructed from metal—or is metal-lined, from LDPE, or from a laminated material. Tubes are identified as either blind end or open end. In the former, there is no product contact with the cap on storage. Usually, the size of the tube is controlled by trimming it to an appropriate length for the target fill volume. Fill volume is commonly determined as an in-process measurement, using bulk density. Usually there is no cap liner, although the tube may have a liner. Aluminum tubes usually include a liner. A tube liner is frequently a lacquer or shellac whose composition should be stated. A tube is closed by folding or crimping the open end. The type of fold (roll or saddle) should be described, as well as the type and composition of any sealant. If the tube material is self-sealing through the application of heat alone, this should be stated. If the market package includes a separate applicator device, this should be described. Product contact is possible if the applicator is part of the closure, and therefore, an applicator's compatibility with the drug product should be established as appropriate. Dressings consist of dosage form on a bandage material (e.g., absorbent gauze or gauze bandage) within a flexible pouch. The pouch should maintain the sterility and physical stability of the dressing.

Topical aerosols are not intended to be inhaled; therefore, the droplet size of the spray does not need to be carefully controlled, nor is the dose usually metered. The spray may be used to apply dosage form to the skin (topical aerosol) or mouth (lingual aerosol), and functionality of the sprayer should be addressed. A topical aerosol may be sterile or may conform to acceptance criteria for microbial limits. The packaging system for a liquid-based topical product should deter solvent loss and should provide protection from light when appropriate. Because these dosage forms may be placed in contact with mucosal membranes or with skin that has been broken or otherwise compromised, the safety of the materials of construction for the packaging components should be evaluated. For solid dosage forms, an appropriate reference to the indirect food additive regulations is typically considered sufficient to establish safety.

Topical delivery systems are self-contained, discrete dosage forms that are designed to deliver drug via intact skin or body surface. There are three types of topical delivery systems: transdermal, ocular, and intrauterine.

Transdermal systems are usually applied to the skin with an adhesive and may be in place for an extended period. Ocular systems are inserted under the lower eyelid, typically for 7 days. Intrauterine systems are held in place without adhesive and may stay in place for a year. A transdermal system usually comprises an outer barrier, a drug reservoir (with or without a rate-controlling membrane), a contact adhesive, and a protective liner. An ocular system usually consists of the drug formulation contained in a rate-controlling membrane. An intrauterine system may be constructed of a plastic material impregnated with active ingredients or a coated metal. It is shaped to remain in place after being inserted in the uterus. Each of these systems is generally marketed in a single-unit soft blister pack or a preformed tray with a preformed cover or overwrap.

Compatibility and safety for topical delivery systems are addressed in the same manner as for topical drug products. Performance and quality control should be addressed for the rate-controlling membrane. Appropriate microbial limits should be established and justified for each delivery system. Microbiological standards are under development; therefore, the review division for a specific application should be consulted.

G. Solid Oral Dosage Forms and Powders for Reconstitution

The most common solid oral dosage forms are capsules and tablets. For the purpose of this guidance, oral powders and granules for reconstitution are also included in this group.

The risk of interaction between packaging components and a solid oral dosage form is generally recognized to be small. Powders that are reconstituted in their market container, however, have an additional possibility of an interaction between the packaging components and the reconstituting fluid. Although the contact time will be relatively short when compared with the component/dosage form contact time for liquid-based oral dosage forms, it should still be taken into consideration when the compatibility and safety of the container closure system are being evaluated.

A typical container closure system is a plastic (usually HDPE) bottle with a screw-on or snap-off closure and a flexible packaging system, such as a pouch or a blister package. A typical closure consists of a cap—often with a

liner—frequently with an inner seal. If used, fillers, desiccants, and other absorbent materials are considered primary packaging components.

The most common forms of flexible packaging are the blister package and the pouch. A blister package usually consists of a lid material and a forming film. The lid material is usually a laminate, which includes a barrier layer (e.g., aluminum foil) with a print primer on one side and a sealing agent (e.g., a heat-sealing lacquer) on the other side.

The sealing agent contacts the dosage form and the forming film. The forming film may be a single film, a coated film, or a laminate. A pouch typically consists of film or laminate that is sealed at the edges by heat or adhesive. Leak testing is usually performed on flexible packages as part of the in-process controls.

Solid oral dosage forms generally need to be protected from the potential adverse effects of water vapor. Protection from light and reactive gases may also be needed. For example, the presence of moisture may affect the decomposition rate of the active drug substance or the dissolution rate of the dosage form. The container should have an intrinsically low rate of water vapor permeation, and the container closure system should establish a seal to protect the drug product. Three standard tests for water vapor permeation have been established by the USP for use with solid oral dosage forms.

1. Polyethylene Containers (USP <661>)

This test is conducted on containers heat sealed with foil laminate; therefore, only the properties of the container are evaluated. The level of protection from water vapor permeation provided by a packaging system marketed with a heat-sealed foil laminate inner seal (up to the time the inner seal is removed) is expected to be approximately the same as that determined by this test. The acceptance criteria are those established in USP <671>.

2. Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets (USP <671>)

This test measures the water vapor permeation of a single-unit or unit-dose container closure system and establishes acceptance criteria for five standards (Class A–E containers).

3. Multiple-Unit Containers for Capsules and Tablets (USP <671>)

This test is intended for drugs being dispensed on prescription, but it has also been applied to the drug product manufacturer's container closure system. If the container closure system has an inner seal, it should be removed before testing. The results from this study reflect the contributions to water vapor permeation through the container and through the seal between the container and the closure.

Acceptance criteria have been established for two standards (tight containers and well-closed containers).

For solid oral dosage forms, a reference to the appropriate indirect food additive regulation for each material of construction is typically considered sufficient evidence of safety. However, for a powder for reconstitution dosage form, reference only to the indirect food additive regulations as evidence of safety for the materials of construction is not recommended. Compatibility for solid oral dosage forms and for powders for reconstitution is typically addressed for plastics and glass by meeting the requirements of the Containers test.

The monographs for Purified Cotton and Purified Rayon USP will typically be considered sufficient standards to establish the safety of these materials as fillers in the packaging of tablets or capsules, with the following caveats: cotton need not meet the monograph requirements for sterility, fiber length, or absorbency; and rayon need not meet the monograph requirements for fiber length or absorbency. Appropriate tests and acceptance criteria for identification and for moisture content should be provided for both cotton and rayon filler. Rayon has been found to be a potential source of dissolution problems for gelatin capsules and gelatin-coated tablets, and this characteristic should be considered when choosing filler. The use of other fillers may be considered with appropriate tests and acceptance criteria. If a desiccant or other absorbent material is used, the composition should be provided (or an appropriate DMF referenced). The component should differ in shape or size from the tablets or capsules with which it is packaged. This will help distinguish between the component and the dosage form. Because these are considered primary packaging components, appropriate tests and acceptance criteria to establish suitability should be provided.

H. Other Dosage Forms

The current good manufacturing practice requirements for container closure systems for compressed medical gases are described in 21 CFR 210 and 211. The containers are regulated by the U.S. Department of Transportation. When submitting information for a drug product or dosage form not specifically covered by the sections above, a firm should take into consideration the compatibility and safety concerns raised by the route of administration of the drug product and the nature of the dosage form (e.g., solid or liquid based); the kinds of protection the container closure system should provide to the dosage form; and the potential effect of any treatment or handling that may be unique to the drug product in the packaging system. Quality control procedures for each packaging component should ensure the maintenance of the safety and quality of future production batches of the drug product.

III. POSTAPPROVAL PACKAGING CHANGES

For an approved application (NDA, ANDA, or BLA), a change to a container closure system, to a component of the container closure system, to a material of construction for a component, or to a process involving one of the above must be reported to the application. The filing requirements are specified under 21 CFR 314.70 (supplements and other changes to an approved application) for an NDA or ANDA and under 21 CFR 601.12 (changes to an approved application) for a BLA.

IV. TYPE III DRUG MASTER FILES

The responsibility for providing information about packaging components rests foremost with the applicant of an NDA, ANDA, or BLA, or with the sponsor of an IND. This information may be provided to the applicant by the manufacturer of a packaging component or material of construction and may be included directly in the application. Any information that a manufacturer does not wish to share with the applicant or sponsor (i.e., because it is considered proprietary) may be placed in a type III DMF and incorporated into the application by a letter from the manufacturer to the applicant that authorizes reference to the DMF. The letter of authorization should specify the firm to whom authorization is granted, the component or material of construction being described,

and where the information or data is located in the file by page number or date of submission. This last item is especially important for files that contain information on multiple components or have several volumes. Information in a type III DMF is not restricted to data of a proprietary nature. DMF holders may include in their files as much or as little information as they choose. In addition, a manufacturer of a packaging component is not required to maintain a type III DMF. Without a DMF, there is no procedure for the FDA to review proprietary information except by submission to the application.

The FDA ordinarily reviews a DMF only in connection with an application (IND, NDA, ANDA, or BLA). If the combined information from the application and the DMF is not adequate to support approval of the application or safety for the IND, then the agency may request additional information from the applicant or the DMF holder, as appropriate.

In the event of a change in the DMF, the holder of a DMF must notify the holder of each application supported by the DMF [21 CFR 314.420(c)]. Notice should be provided well before the change is implemented to allow the applicant or sponsor enough time to file a supplement or an amendment to the affected application.

V. BULK CONTAINERS

Drug substances are generally solids, but some are liquids or gases. The container closure system for storage or shipment of a bulk solid drug substance is typically a drum with double LDPE liners that are usually heat sealed or closed with a twist tie. A desiccant may be placed between the bags.

The drum provides protection from light and mechanical strength to protect the liner during shipment and handling. The majority of the protection from air and moisture is provided by the liner. Because LDPE is not a particularly good moisture barrier, a drug substance that is moisture sensitive may need additional protection. An alternative to an LDPE bag is a heat-sealable laminate bag with a comparatively low rate of water vapor transmission.

Qualification of the packaging system is usually based on establishing compatibility and safety of the liner but may also include characterization for solvent or gas transmission. The container closure system for the storage or shipment of a bulk liquid drug substance is typically plastic, stainless steel, a glass-lined metal container, or an epoxy-lined metal container with a rugged, tamper-resistant closure. Qualification of the container closure system may include characterization for solvent and gas permeation, light transmittance, closure integrity, ruggedness in shipment, protection against microbial contamination through the closure, and compatibility and safety of the packaging components as appropriate.

The application (or type II DMF) should include a detailed description of the complete container closure system for the bulk drug substance as well as a description of the specific container, closure, all liners, inner seal, and desiccant (if any), and a description of the composition of each component. A reference to the appropriate indirect food additive regulation is typically considered sufficient to establish the safety of the materials of construction. The tests, methods, and criteria for the acceptance and release of each packaging component should be provided. Stability studies to establish a retest period for bulk drug substance in the proposed container closure system should be conducted with fillers or desiccant packs in place (if used). Smaller versions that simulate the actual container closure system may be used.

A container closure system for bulk drug products may be used for storage before packaging or for shipment to repackagers or contract packagers. In all cases, the container closure system should adequately protect the dosage form and should be constructed of materials that are compatible and safe. Container closure systems for on-site storage have generally been considered a current good manufacturing practice issue under 21 CFR 211.65. However, if a firm plans to hold bulk drug products in storage, then the container closure system and the maximum storage time should be described and justified in the application. In addition, stability data should be provided to demonstrate that extended storage in the described containers does not adversely affect the dosage form. Even when the storage time before packaging will be short, a firm should use a container closure system that provides adequate protection and that is manufactured from materials that are compatible and safe for the intended use.

A container closure system for the transportation of bulk drug products to contract packagers should be described in the application. The container closure system should be adequate to protect the dosage form, be constructed with materials that are compatible with product being stored, and be safe for the intended use. The protective properties of the shipping container are verified by the practice of including annual batches of the packaged product in postapproval stability studies.

A container closure system specifically intended for the transportation of a large volume of drug product to a repackager, whether for a solid or liquid dosage form, is considered a market package. The package should meet the same requirements for protection, compatibility, and safety as a smaller market package; should be included in the stability studies for application approval and in the long-term stability protocol; and should be fully described in the application. The length of time that the dosage form will spend in the bulk container may be a factor in determining the level of detail of the supporting information. Two examples of a large-volume shipping package are a 10,000-tablet HDPE pail with tamper-evident closure and a 10-L polyethylene terephthalate container with a screw-cap closure with dispenser attachment for a liquid drug product. Both are intended for sale to a mass distribution pharmacy.

REFERENCES

FDA guidelines are available at http://www.fda.gov/guidance. Compressed Medical Gases Guideline (February 1989).

FDA Guideline for Drug Master Files (September 1989). http://www.fda.gov/CDER/GUIDANCE/dmf.htm.

FDA Guidance for Industry on the Submission of Documentation for the Sterilization Process Validation in Applications for Human and Veterinary Drug Products (November 1994).

FDA Guidance for Industry on the Content and Format on Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well Characterized, Therapeutic, Biotechnology-Derived Products (November 1995).

FDA Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information for a Therapeutic Recombinant DNA-Derived Product or a Monoclonal Antibody Product for *In Vivo* Use (August 1996).

FDA Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information and Establishment Description for Autologous Somatic Cell Therapy Products (January 1997).

FDA Guidance for the Photostability Testing of New Drug Substance and Products (May 1997).

FDA Guidance for Industry on the Submission of Chemistry, Manufacturing, and Controls Information for Synthetic Peptide Substances (January 1998).

FDA Guidance for Industry on the Content and Format of Chemistry, Manufacturing, and Controls and Establishment Description Information for a Vaccine or Related Product (January 1999).

FDA Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls and Establishment Description Information for Human Plasma-Derived Biological Product or Animal Plasma or Serum-Derived Products (February 1999).

FDA Guidance for Industry on the Content and Format of Chemistry, Manufacturing, and Controls and Establishment Description Information for a Biological *In Vitro* Diagnostic Product (March 1999).

FDA Guidance for Industry on the Content and Format of Chemistry, Manufacturing, and Controls and Establishment Description Information for Allergenic Extract or Allergen Patch Test (April 1999).

FDA Guidance for Industry for the Submission of Chemistry, Manufacturing, and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and for the Completion of the FDA Form 356 h, Application to Market a New Drug, Biologic, or an Antibiotic Drug for Human Use (May 1999).

7

Material for Containers

A container for pharmaceutical use is an article that contains or is intended to contain a product and is, or may be, in direct contact with it. The closure is a part of the container.

The container is so designed that the contents may be removed in a manner appropriate to the intended use of the preparation. It provides a varying degree of protection depending on the nature of the product and the hazards of the environment and minimizes the loss of constituents. The container does not interact physically or chemically with the contents in a way that alters their quality beyond the limits tolerated by official requirements.

Single-dose container. A single-dose container holds a quantity of the preparation intended for total or partial use on one occasion only.

Multidose container. A multidose container holds a quantity of the preparation suitable for two or more doses.

Well-closed container. A well-closed container protects the contents from contamination with extraneous solids and liquids and from loss of contents under ordinary conditions of handling, storage, and transport.

Airtight container. An airtight container is impermeable to solids, liquids, and gases under ordinary conditions of handling, storage, and transport. If the container is intended to be opened on more than one occasion, it must be so designed that it remains airtight after reclosure.

Sealed container. A sealed container is a container closed by fusion of the material of the container.

Tamper-proof container. A tamper-proof container is a closed container fitted with a device that reveals irreversibly whether the container has been opened.

Childproof container. A container that is fitted with a closure that prevents opening by children.

I. GLASS CONTAINERS

Glass containers for pharmaceutical use are glass articles intended to come into direct contact with pharmaceutical preparations. Colorless glass is highly transparent in the visible spectrum. Colored glass is obtained by the addition of small amounts of metal oxides, chosen according to the desired spectral absorbance. *Neutral glass* is a borosilicate glass containing significant amounts of boric oxide, aluminum oxide alkali, and/or alkaline earth oxides. Because of its composition, neutral glass has a high hydrolytic resistance and a high thermal shock resistance. *Soda-lime-silica glass* is a silica glass containing alkali metal oxides, mainly sodium oxide and alkaline earth oxides, mainly calcium oxide. Because of its composition, soda-lime-silica glass has only a moderate hydrolytic resistance. The hydrolytic stability of glass containers for pharmaceutical use is expressed by the resistance to the release of soluble mineral substances into water under the prescribed conditions of contact between the inner surface of the container or glass grains and water. The hydrolytic resistance is evaluated by titrating released alkali. According to their hydrolytic resistance, glass containers are classified as follows:

1. Type I glass containers: Neutral glass, with a high hydrolytic resistance due to the chemical composition of the glass itself.
2. Type II glass containers: Usually of soda-lime-silica glass with a high hydrolytic resistance resulting from suitable treatment of the surface.
3. Type III glass containers: Usually of soda-lime-silica glass with only moderate hydrolytic resistance. The following italicized statements constitute general recommendations concerning the type of glass container that may be used for different types of pharmaceutical preparations. The manufacturer of a pharmaceutical product is responsible for ensuring the suitability of the chosen container.

Type I glass containers are suitable for most preparations whether or not for parenteral use. Type II glass containers are suitable for most acidic and neutral, aqueous preparations whether or not for parenteral use. Type III glass containers are in general suitable for nonaqueous preparations for parenteral use, for powders for parenteral use (except for freeze-dried preparations), and for preparations not for parenteral use. Glass containers with a hydrolytic resistance higher than that recommended earlier for a particular type of preparation may generally also be used. The container chosen for a given preparation shall be such that the glass material does not release substances in quantities sufficient to affect the stability of the preparation or to present a risk of toxicity. In justified cases, it may be necessary to have detailed information on the glass composition, so that the potential hazards can be assessed. Preparations for parenteral use are normally presented in colorless glass, but colored glass may be used for substances known to be light sensitive. Colorless or colored glass is used for the other pharmaceutical preparations. It is recommended that all glass containers for liquid preparations and for powders for parenteral use permit the visual inspection of the contents. The inner surface of glass containers may be specially treated to improve hydrolytic resistance, to confer water repellency. The outer surface may also be treated, for example, to reduce friction and to improve resistance to abrasion. The outer treatment is such that it does not contaminate the inner surface of the container. Except for type I glass containers, glass containers for pharmaceutical preparations are not to be reused. Containers for human blood and blood components must not be reused. Glass containers for pharmaceutical use comply with the relevant test or tests for hydrolytic resistance. When glass containers have nonglass components, the tests apply only to the glass part of the container.

II. NONPLASTICIZED POLY(VINYL CHLORIDE) FOR CONTAINERS FOR NONINJECTABLE AQUEOUS SOLUTIONS

Materials based on nonplasticized poly(vinyl chloride) that comply with the following specifications are suitable for the manufacture of containers for noninjectable aqueous

solutions. They may also be used for solid forms for oral administration and, in some cases, subject to special studies on the compatibility of the container with its contents; these materials may be suitable for the preparation of containers for suppositories. They consist of one or more poly(vinyl chloride/vinyl acetate) or of a mixture of poly(vinyl chloride) and poly(vinyl acetate) or of poly(vinyl chloride). They contain not more than 1 ppm of vinyl chloride. The chlorine content expressed in poly(vinyl chloride) is not less than 80%. They may contain not more than 15% of copolymers based on acrylic and/or methacrylic acids and/or their esters, and/or on styrene and/or butadiene. Materials based on nonplasticized poly(vinyl chloride) are produced by polymerization methods, which guarantee a residual vinyl chloride content of less than 1 ppm.

III. POLYETHYLENE TEREPHTHALATE FOR CONTAINERS FOR PREPARATIONS NOT FOR PARENTERAL USE

Polyethylene terephthalate is obtained from the polymerization of terephthalic acid or dimethyl terephthalate with ethylene glycol. Isophthalic acid, dimethyl isophthalate, 1,4-bis(hydroxymethyl)cyclohexane (cyclohexane-1,4-dimethanol), or diethylene glycol may be used in the polymerization. It may contain not more than 0.5% of silica or silicates and coloring matter approved by the competent authority. The manufacturing process is validated to demonstrate that the residual acetaldehyde content is not greater than 10 ppm in the granules.

IV. NONPLASTICIZED POLY(VINYL CHLORIDE) FOR CONTAINERS FOR DRY DOSAGE FORMS FOR ORAL ADMINISTRATION

Materials based on nonplasticized poly(vinyl chloride) for containers for dry dosage forms for oral administration are suitable for the manufacture of sheets or containers. They consist of one or more poly(vinyl chloride/vinyl acetate) or of a mixture of poly(vinyl chloride) and poly(vinyl acetate) or of poly(vinyl chloride). They contain not more than 1 ppm of vinyl chloride. The chlorine content expressed in poly(vinyl chloride) is not less than 80%. They may contain not more than 15% of copolymers based on acrylic and/or methacrylic acids and/or their esters and/or on styrene and/or butadiene. Materials based on nonplasticized poly(vinyl chloride) are produced by polymerization methods, which guarantee a residual vinyl chloride content of less than 1 ppm.

V. PLASTICIZED POLY(VINYL CHLORIDE) FOR CONTAINERS FOR AQUEOUS SOLUTIONS FOR INTRAVENOUS INFUSION

Materials based on plasticized poly(vinyl chloride) contain not less than 55% of poly(vinyl chloride) and contain various additives, in addition to the high-molecular-mass polymer obtained by polymerization of vinyl chloride. Materials based on plasticized poly(vinyl chloride) for containers for aqueous solutions for intravenous infusion are defined by the nature and the proportions of the substances used in their manufacture. Materials based on plasticized poly(vinyl chloride) are produced by polymerization methods, which guarantee a residual vinyl chloride content of less than 1 ppm.

VI. POLYETHYLENE TEREPHTHALATE FOR CONTAINERS FOR PREPARATIONS NOT FOR PARENTERAL USE

Polyethylene terephthalate is obtained from the polymerization of terephthalic acid or dimethyl terephthalate with ethylene glycol. Isophthalic acid, dimethyl isophthalate, 1,4-bis(hydroxymethyl)cyclohexane (cyclohexane-1,4-dimethanol), or diethylene glycol may be used in the polymerization. It may contain not more than 0.5% of silica or silicates and coloring matter approved by the competent authority. The manufacturing process is validated to demonstrate that the residual acetaldehyde content is not more than 10 ppm in the granules.

VII. POLYOLEFINES

Polyolefines are obtained by polymerization of ethylene or propylene or by copolymerization of these substances with not more than 25% of higher homologues (C_4–C_{10}) or of carboxylic acids or of esters. Certain materials may be mixtures of polyolefines. A certain number of additives are added to the polymer to optimize their chemical, physical, and mechanical properties to adapt them for the intended use. All of these additives are chosen from the appended list, which specifies for each product the maximum allowable content. They may contain at most three antioxidants, one or several lubricants or antiblocking agents, as well as titanium dioxide as an opacifying agent when the material must provide protection from light.

1. Butyl hydroxytoluene (plastic additive 07) (not more than 0.125%)
2. Pentaerythrityl tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] (plastic additive 09) (not more than 0.3%)
3. 1,3,5-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*s*-triazine-2,4,6(1*H*, 3*H*, 5*H*)-trione, (plastic additive 13) (not more than 0.3%)
4. Octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate (plastic additive 11) (not more than 0.3%), ethylene bis[3,3-bis[3-(1,1-dimethylethyl)-4-hydroxyphenyl] butanoate] (plastic additive 08) (not more than 0.3%)
5. Dioctadecyl disulphide (plastic additive 15) (not more than 0.3%)
6. 4,4′,4″-(2,4,6-trimethylbenzene-1,3,5-triyltrismethylene) trio[2,6-bis(1,1-dimethylethyl)phenol] (plastic additive 10) (not more than 0.3%)
7. 2,2′-bis(octadecyloxy)-5,5′-spirobi(1,3,2-dioxaphosphinane) (plastic additive 14) (not more than 0.3%)
8. Didodecyl 3,3′-thiodipropionate (plastic additive 16) (not more than 0.3%),
9. Dioctadecyl 3,3′-thiodipropionate (plastic additive 17) (not more than 0.3%)
10. Tris[2,4-bis(1,1-dimethylethyl)phenyl] phosphite (plastic additive 12) (not more than 0.3%)
11. Plastic additive 18 (not more than 0.1%)

12. Copolymer of dimethyl succinate and (4-hydroxy-2,2,6,6-tetramethylpiperidin-1-yl)ethanol (plastic additive 22) (not more than 0.3%%)

    The total of antioxidant additives listed above does not exceed 0.3%—hydrotalcite (not more than 0.5%).
13. Alkanamides (not more than 0.5%)
14. Alkenamides (not more than 0.5%)
15. Sodium silicoaluminate (not more than 0.5%)
16. Silica (not more than 0.5%)
17. Sodium benzoate (not more than 0.5%)
18. Fatty acid esters or salts (not more than 0.5%)
19. Trisodium phosphate (not more than 0.5%)
20. Liquid paraffin (not more than 0.5%)
21. Zinc oxide (not more than 0.5%)
22. Talc (not more than 0.5%)
23. Magnesium oxide (not more than 0.2%)
24. Calcium stearate or zinc stearate or a mixture of both (not more than 0.5%)
25. Titanium dioxide (not more than 4%)

VIII. POLYETHYLENE WITH ADDITIVES FOR CONTAINERS FOR PARENTERAL PREPARATIONS AND FOR OPHTHALMIC PREPARATIONS

Polyethylene with additives is obtained by the polymerization of ethylene under pressure in the presence of a catalyst or by copolymerization of ethylene with not more than 25% of higher alkene homologues (C_3–C_{10}). A certain number of additives are added to the polymer to optimize their chemical, physical, and mechanical properties to adapt them for the intended use. All these additives are chosen from the appended list, which specifies for each product the maximum allowable content. They may contain at most three antioxidants, one or several lubricants or antiblocking agents, as well as titanium dioxide as an opacifying agent when the material must provide protection from light.

1. Butyl hydroxytoluene (plastic additive 07) (not more than 0.125%).
2. Pentaerythrityl tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] (plastic additive 09) (not more than 0.3%).
3. 1,3,5-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*s*-triazine-2, 4,6(1*H*, 3*H*, 5*H*)-trione (plastic additive 13) (not more than 0.3%).
4. Octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl) propionate, (plastic additive 11) (not more than 0.3%).
5. Ethylene bis[3,3-bis(3-[1,1-dimethylethyl]-4-hydroxyphenyl)butanoate] (plastic additive 08) (not more than 0.3%).
6. Dioctadecyl disulphide (plastic additive 15) (not more than 0.3%).
7. 4,4′,4″-(2,4,6-trimethylbenzene-1,3,5-triyltrismethylene) tris[2,6-bis(1,1-dimethylethyl)phenol] (plastic additive 10) (not more than 0.3%).
8. 2,2′-bis(octadecyloxy)-5,5′-spirobi(1,3,2-dioxaphosphinane) (plastic additive 14) (not more than 0.3%).
9. Didodecyl 3,3′-thiodipropionate (plastic additive 16) (not more than 0.3%).
10. Dioctadecyl 3,3′-thiodipropionate (plastic additive 17) (not more than 0.3%).
11. Tris [2,4-bis(1,1-dimethylethyl)phenyl] phosphite (plastic additive 12) (not more than 0.3%).

    The total of antioxidant additives listed above does not exceed 0.3%.
12. Hydrotalcite (not more than 0.5%).
13. Alkanamides (not more than 0.5%).
14. Alkenamides (not more than 0.5%).
15. Sodium silicoaluminate (not more than 0.5%).
16. Silica (not more than 0.5%).
17. Sodium benzoate (not more than 0.5%).
18. Fatty acid esters or salts (not more than 0.5%).
19. Trisodium phosphate (not more than 0.5%).
20. Liquid paraffin (not more than 0.5%).
21. Zinc oxide (not more than 0.5%).
22. Magnesium oxide (not more than 0.2%).
23. Calcium stearate or zinc stearate or a mixture of both (not more than 0.5%).
24. Titanium dioxide (not more than 4%) only for materials for containers for ophthalmic use. The supplier of the material must be able to demonstrate that the qualitative and quantitative composition of the type sample is satisfactory for each production batch.

IX. POLYPROPYLENE FOR CONTAINERS AND CLOSURES FOR PARENTERAL PREPARATIONS AND OPHTHALMIC PREPARATIONS

Polypropylene consists of the homopolymer of propylene or of a copolymer of propylene with not more than 25% of ethylene or of a mixture (alloy) of polypropylene with not more than 25% of polyethylene. It may contain additives. A certain number of additives are added to the polymer to optimize their chemical, physical, and mechanical properties to adapt them for the intended use. All these additives are chosen from the appended list, which specifies for each product the maximum allowable content. They may contain at most three antioxidants, one or several lubricants or antiblocking agents, as well as titanium dioxide as opacifying agent when the material must provide protection from light.

1. Butyl hydroxytoluene (plastic additive 07) (not more than 0.125%).
2. Pentaerythrityl tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] (plastic additive 09) (not more than 0.3%).
3. 1,3,5-tris(3,5-di-*tert*-butyl-4-hydroxybenzyl)-*s*-triazine-2, 4,6(1*H*,3*H*,5*H*)-trione (plastic additive 13) (not more than 0.3%).
4. Octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate, (plastic additive 11) (not more than 0.3%).
5. Ethylene bis[3,3-bis(3-[1,1-dimethylethyl]-4-hydroxyphenyl)butanoate] (plastic additive 08) (not more than 0.3%).
6. Dioctadecyl disulphide (plastic additive 15) (not more than 0.3%).
7. 2,2′,2″,6,6′,6″-hexa-*tert*-butyl-4,4′,4″-[(2,4,6-trimethyl-1, 3,5-benzenetriyl)trismethylene]triphenol (plastic additive 10) (not more than 0.3%).
8. 2,2′-bis(octadecyloxy)-5,5′-spirobi[1,3,2-dioxaphosphinane] (plastic additive 14) (not more than 0.3%).
9. Didodecyl 3,3′-thiodipropionate (plastic additive 16) (not more than 0.3%).
10. Dioctadecyl 3,3′-thiodipropionate (plastic additive 17) (not more than 0.3%).
11. Tris(2,4-di-*tert*-butylphenyl) phosphite (plastic additive 12) (not more than 0.3%).

The total of antioxidant additives listed above does not exceed 0.3%.

12. Hydrotalcite (not more than 0.5%).
13. Alkanamides (not more than 0.5%).
14. Alkenamides (not more than 0.5%).
15. Sodium silicoaluminate (not more than 0.5%).
16. Silica (not more than 0.5%), sodium benzoate (not more than 0.5%), fatty acid esters or salts (not more than 0.5%).
17. Trisodium phosphate (not more than 0.5%).
18. Liquid paraffin (not more than 0.5%).
19. Zinc oxide (not more than 0.5%), talc (not more than 0.5%).
20. Magnesium oxide (not more than 0.2%).
21. Calcium stearate or zinc stearate or a mixture of both (not more than 0.5%).
22. Titanium dioxide (not more than 4%) only for materials for containers for ophthalmic use. The supplier of the material must be able to demonstrate that the qualitative and quantitative composition of the type sample is satisfactory for each production batch.

X. POLY(ETHYLENE/VINYL ACETATE) FOR CONTAINERS AND TUBING FOR TOTAL PARENTERAL NUTRITION PREPARATIONS

Poly(ethylene/vinyl acetate), complying with the following requirements, is suitable for the manufacture of containers and tubing for total parenteral nutrition preparations. Poly(ethylene/vinyl acetate) is obtained by copolymerization of mixtures of ethylene and vinyl acetate. This copolymer contains a defined quantity of not more than 25% of vinyl acetate for material to be used for containers and not more than 30% for material to be used for tubing. A certain number of additives are added to the polymer to optimize their chemical, physical, and mechanical properties to adapt them for the intended use. All these additives are chosen from the appended list, which specifies for each product the maximum allowable content. Poly(ethylene/vinyl acetate) may contain not more than three of the following antioxidants:

1. Butyl hydroxytoluene (plastic additive 07) (not more than 0.125%)
2. Pentaerythrityl tetrakis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] (plastic additive 09) (not more than 0.2%)
3. Octadecyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate (plastic additive 11) (not more than 0.2%),
4. Tris(2,4-di-*tert*-butylphenyl) phosphite (plastic additive 12) (not more than 0.2%)
5. 2,2′,2″,6,6′,6″-hexa-*tert*-butyl-4,4′,4″-[(2,4,6-trimethyl-1,3,5-benzenetriyl)trismethylene]triphenol (plastic additive 10) (not more than 0.2%). It may also contain
   a. oleamide (plastic additive 20) (not more than 0.5%),
   b. erucamide (plastic additive 21) (not more than 0.5%),
   c. calcium stearate or zinc stearate or a mixture of both (not more than 0.5%),
   d. calcium carbonate or potassium hydroxide (not more than 0.5% of each),
   e. colloidal silica (not more than 0.2%). The supplier of the material must be able to demonstrate that the qualitative and quantitative composition of the type sample is satisfactory for each production batch.

XI. PLASTIC CONTAINERS FOR AQUEOUS SOLUTIONS FOR INFUSION

Plastic containers for aqueous solutions for infusion are manufactured from one or more polymers, if necessary with additives. The containers described in this section are not necessarily suitable for emulsions. The polymers most commonly used are polyethylene, polypropylene, and poly(vinyl chloride). The containers may be bags or bottles. They have a site suitable for the attachment of an infusion set designed to ensure a secure connection. They may have a site that allows an injection to be made at the time of use. They usually have a part that allows them to be suspended and which will withstand the tension occurring during use. The containers must withstand the sterilization conditions to which they will be submitted. The design of the container and the method of sterilization chosen are such that all parts of the containers that may be in contact with the infusion are sterilized. The containers are impermeable to microorganisms after closure. The containers are such that after filling they are resistant to damage from accidental freezing which may occur during transport of the final preparation. The containers are and remain sufficiently transparent to allow the appearance of the contents to be examined at any time, unless otherwise justified and authorized. The empty containers display no defects that may lead to leakage and the filled and closed containers show no leakage. For satisfactory storage of some preparations, the container has to be enclosed in a protective envelope. The initial evaluation of storage has then to be carried out using the container enclosed in the envelope.

A plastic container for pharmaceutical use is a plastic article, which contains or is intended to contain a pharmaceutical product and is, or may be, in direct contact with it. The closure is a part of the container. Plastic containers and closures for pharmaceutical use are made of materials in which may be included certain additives; these materials do not include in their composition any substance that can be extracted by the contents in such quantities as to alter the efficacy or the stability of the product or to present a risk of toxicity. The most commonly used polymers are polyethylene (with and without additives), polypropylene, poly(vinyl chloride), poly(ethylene terephthalate), and poly(ethylene/vinyl acetate). The nature and amount of the additives are determined by the type of the polymer, the process used to convert the polymer into the container, and the intended purpose of the container. Additives may consist of antioxidants, stabilizers, plasticizes, lubricants, coloring matter, and impact modifiers. Antistatic agents and mould-release agents may be used only for containers for preparations for oral use or for external use for which they are authorized Acceptable additives are indicated in the type specification for each material described in the *Pharmacopoeia*. Other additives may be used provided they are approved in each case by the competent authority responsible for the licensing for sale of the preparation. For selection of a suitable plastic container, it is necessary to know the full manufacturing formula of the plastic, including all materials added during formation of the container so that the potential hazards can be assessed. The plastic container chosen for any particular preparation should be such that

1. the ingredients of the preparation in contact with the plastic material are not significantly adsorbed on its surface and do not significantly migrate into or through the plastic,
2. the plastic material does not release substances in quantities sufficient to affect the stability of the preparation or

to present a risk of toxicity. Using material (or materials) selected to satisfy these criteria, a number of identical type samples of the container are made by a well-defined procedure and submitted to practical testing in conditions that reproduce those of the intended use, including, where appropriate, sterilization. To confirm the compatibility of the container and the contents and to ensure that there are no changes detrimental to the quality of the preparation, various tests are carried out, such as verification of the absence of changes in physical characteristics, assessment of any loss or gain through permeation, detection of pH changes, assessment of changes caused by light, chemical tests, and, where appropriate, biological tests. The method of manufacture is such as to ensure reproducibility for subsequent bulk manufacture and the conditions of manufacture are chosen so as to preclude the possibility of contamination with other plastic materials or their ingredients. The manufacturer of the product must ensure that containers made in production are similar in every respect to the type samples.

For the results of the testing on type samples to remain valid, it is important that

1. there is no change in the composition of the material as defined for the type samples,
2. there is no change in the manufacturing process as defined for the type samples, especially as regards the temperatures to which the plastic material is exposed during conversion or subsequent procedures such as sterilization,
3. scrap material is not used. Recycling of excess material of well-defined nature and proportions may be permitted after appropriate validation. Subject to satisfactory testing for compatibility of each different combination of container and contents, the materials described in the *Pharmacopoeia* are recognized as being suitable for the specific purposes indicated, as defined above.

XII. STERILE SINGLE-USE PLASTIC SYRINGES

Sterile single-use plastic syringes are medical devices intended for immediate use for the administration of injectable preparations. They are supplied sterile and pyrogen-free and are not to be resterilized or reused. They consist of a syringe barrel and a piston which may have an elastomer sealing ring; they may be fitted with a needle which may be nondetachable. Each syringe is presented with individual protection for maintaining sterility. The barrel of the syringe is sufficiently transparent to permit dosages to be read without difficulty and allow air bubbles and foreign particles to be discerned. The plastics and elastomer materials of which the barrel and piston are made comply with the appropriate specification or with the requirements of the competent authority. The most commonly used materials are polypropylene and polyethylene. The syringes comply with current standards regarding dimensions and performance. Silicone oil may be applied to the internal wall of the barrel to assist in the smooth operation of the syringe but there remains no excess capable of contaminating the contents at the time of use. The inks, glues, and adhesives for the marking on the syringe or on the package and, where necessary, the assembly of the syringe and its package do not migrate across the walls.

XIII. RUBBER CLOSURES FOR CONTAINERS FOR AQUEOUS PARENTERAL PREPARATIONS, FOR POWDERS, AND FOR FREEZE-DRIED POWDERS

Rubber closures for containers for aqueous parenteral preparations for powders and for freeze-dried powders are made of materials obtained by vulcanization (cross-linking) of macromolecular organic substances (elastomers) with appropriate additives. The specification also applies to closures for containers for powders and freeze-dried products to be dissolved in water immediately before use. The elastomers are produced from natural or synthetic substances by polymerization, polyaddition, or polycondensation. The nature of the principal components and of the various additives (e.g., vulcanizers, accelerators, stabilizers, pigments) depends on the properties required for the finished article. Rubber closures may be classified in two types: type I closures are those which meet the strictest requirements and which are to be preferred; type II closures are those which, having mechanical properties suitable for special uses (e.g., multiple piercing), cannot meet requirements as severe as those for the first category because of their chemical composition. The closures chosen for use with a particular preparation are such that

1. the components of the preparation in contact with the closure are not adsorbed onto the surface of the closure and do not migrate into or through the closure to an extent sufficient to affect the preparation adversely,
2. the closure does not yield to the preparation substances in quantities sufficient to affect its stability or to present a risk of toxicity. The closures are compatible with the preparation for which they are used throughout its period of validity. The manufacturer of the preparation must obtain from the supplier an assurance that the composition of the closure does not vary and that it is identical to that of the closure used during compatibility testing. When the supplier informs the manufacturer of the preparation of changes in the composition, compatibility testing must be repeated, totally or partly, depending on the nature of the changes. The closures are washed and may be sterilized before use.

XIV. SILICONE OIL USED AS A LUBRICANT

Silicone oil used as a lubricant is a poly(dimethylsiloxane) obtained by hydrolysis and polycondensation of dichlorodimethylsilane and chlorotrimethylsilane. Different grades exist which are characterized by a number indicating the nominal viscosity placed after the name. Silicone oil used as lubricants have a degree of polymerization ($n = 400–1200$) such that their kinematic viscosities are nominally between 1000 $mm^2 \cdot s^{-1}$ and 30,000 $mm^2 \cdot s^{-1}$.

XV. SILICONE ELASTOMER FOR CLOSURES AND TUBING

Silicone elastomer complying with the following requirements is suitable for the manufacture of closures and tubing. Silicone elastomer is obtained by cross-linking a linear polysiloxane constructed mainly of dimethylsiloxy units with small quantities of methylvinylsiloxy groups; the chain ends are blocked by trimethylsiloxy or dimethylvinylsiloxy groups. In all cases, appropriate additives are used, such as silica, and sometimes small quantities of organosilicon additives (α,ω-dihydroxypolydimethylsiloxane).

8

Stability Testing of New Drug Substances and Products

I. INTRODUCTION

A. Objectives of the Guideline

The following guideline is a revised version of the ICH Q1A guideline and defines the stability data package for a new drug substance or drug product that is sufficient for a registration application within the three regions of the European Commission, Japan, and the United States. It does not seek necessarily to cover the testing for registration in or export to other areas of the world.

The guideline seeks to exemplify the core stability data package for new drug substances and products, but leaves sufficient flexibility to encompass the variety of different practical situations that may be encountered due to specific scientific considerations and characteristics of the materials being evaluated. Alternative approaches can be used when there are scientifically justifiable reasons.

B. Scope of the Guideline

The guideline addresses the information to be submitted in registration applications for new molecular entities and associated drug products. This guideline does not currently seek to cover the information to be submitted for abbreviated or abridged applications, variations, clinical trial applications, etc.

Specific details of the sampling and testing for particular dosage forms in their proposed container closures are not covered in this guideline.

C. General Principles

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions.

The choice of test conditions defined in this guideline is based on an analysis of the effects of climatic conditions in the three regions of the European Commission, Japan, and the United States. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I to IV. This guideline addresses climatic zones I and II. The principle has been established that stability information generated in any one of the three regions of the European Commission, Japan, and the United States would be mutually acceptable to the other two regions, provided the information is consistent with this guideline and the labeling is in accordance with national/regional requirements.

II. GUIDELINES

A. Drug Substance

1. General

Information on the stability of the drug substance is an integral part of the systematic approach to stability evaluation.

2. Stress Testing

Stress testing of the drug substance can help identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual drug substance and the type of drug product involved.

Stress testing is likely to be carried out on a single batch of the drug substance. It should include the effect of temperatures [in 10°C increments (e.g., 50°C, 60°C) above that for accelerated testing], humidity (e.g., 75% RH or greater) where appropriate, oxidation, and photolysis on the drug substance. The testing should also evaluate the susceptibility of the drug substance to hydrolysis across a wide range of pH values when in solution or suspension. Photostability testing should be an integral part of stress testing.

Examining degradation products under stress conditions is useful in establishing degradation pathways and developing and validating suitable analytical procedures. However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long-term storage conditions.

Results from these studies will form an integral part of the information provided to regulatory authorities.

3. Selection of Batches

Data from formal stability studies should be provided on at least three primary batches of the drug substance. The batches should be manufactured to a minimum of pilot scale by the same synthetic route as, and using a method of manufacture and procedure that simulates the final process to be used for, production batches. The overall quality of the batches of drug substance placed on formal stability studies should be representative of the quality of the material to be made on a production scale.

Other supporting data can be provided.

4. Container Closure System

The stability studies should be conducted on the drug substance packaged in a container closure system that is the same as or simulates the packaging proposed for storage and distribution.

5. Specification

Specification, which is a list of tests, reference to analytical procedures, and proposed acceptance criteria, is addressed in ICH Q6A and Q6B. In addition, specification for degradation products in a drug substance is discussed in Q3A.

Stability studies should include testing of those attributes of the drug substance that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes.

Validated stability indicating analytical procedures should be applied. Whether and to what extent replication should be performed will depend on the results from validation studies.

6. Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug substance. For drug substances with a proposed retest period of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed retest period.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated studies that are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

7. Storage Conditions

In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

The long-term testing should cover a minimum of 12 months duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed retest period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated, and, where appropriate, intermediate storage conditions for drug substances are detailed in the sections below. The general case applies if the drug substance is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

a. General Case

Study	Storage condition	Minimum time period covered by data at submission
Long term[a]	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 mo
Intermediate[b]	30°C ± 2°C/65% RH ± 5% RH	6 mo
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 mo

[a]It is up to the applicant to decide whether long-term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

[b]If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. Testing at the intermediate storage condition should include all tests, unless otherwise justified. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

"Significant change" for a drug substance is defined as failure to meet its specification.

b. Drug Substances Intended for Storage in a Refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 mo
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 mo

Data from refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest period should be based on the real-time data available at the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition, for example, during shipping or handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

c. Drug Substances Intended for Storage in a Freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	−20°C ± 5°C	12 mo

For drug substances intended for storage in a freezer, the retest period should be based on the real-time data obtained at the long term storage condition. In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short term excursions outside the proposed label storage condition, for example, during shipping or handling.

d. Drug Substances Intended for Storage Below −20°C

Drug substances intended for storage below −20°C should be treated on a case-by-case basis.

8. Stability Commitment

When available, long-term stability data on primary batches do not cover the proposed retest period granted at the time

of approval; a commitment should be made to continue the stability studies post approval to firmly establish the retest period.

Where the submission includes long-term stability data on three production batches covering the proposed retest period, a postapproval commitment is considered unnecessary. Otherwise, one of the following commitments should be made.

1. If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue these studies through the proposed retest period.
2. If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue these studies through the proposed retest period and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed retest period.
3. If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long-term stability studies through the proposed retest period.

The stability protocol used for long-term studies for the stability commitment should be the same as that for the primary batches, unless otherwise scientifically justified.

9. Evaluation

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug substance and evaluating the stability information (including, as appropriate, results of the physical, chemical, biological, and microbiological tests), a retest period applicable to all future batches of the drug substance manufactured under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout the assigned retest period.

The data may show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted. Under these circumstances, it is normally unnecessary to go through the formal statistical analysis. Providing a justification for the omission should be sufficient.

An approach for analyzing the data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall retest period should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the retest period can be undertaken at approval time, if justified. This justification should be based on what is known about the mechanism of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should cover not only the assay, but also the levels of degradation products and other appropriate attributes.

10. Statements/Labeling

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug substance. Where applicable, specific instructions should be provided, particularly for drug substances that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" should be avoided.

A retest period should be derived from the stability information, and a retest date should be displayed on the container label if appropriate.

B. Drug Product

1. General

The design of the formal stability studies for the drug product should be based on knowledge of the behavior and properties of the drug substance and from stability studies on the drug substance and on experience gained from clinical formulation studies. The likely changes on storage and the rationale for the selection of attributes to be tested in the formal stability studies should be stated.

2. Photostability Testing

Photostability testing should be conducted on at least one primary batch of the drug product if appropriate. The standard conditions for photostability testing are described in ICH Q1B.

3. Selection of Batches

Data from stability studies should be provided on at least three primary batches of the drug product. The primary batches should be of the same formulation and packaged in the same container closure system as proposed for marketing. The manufacturing process used for primary batches should simulate as that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Two of the three batches should be at least pilot scale batches and the third one can be smaller, if justified. Where possible, batches of the drug product should be manufactured by using different batches of the drug substance.

Stability studies should be performed on each individual strength and container size of the drug product unless bracketing or matrixing is applied.

Other supporting data can be provided.

4. Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on

the drug product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information respectively.

5. Specification

Specification, which is a list of tests, reference to analytical procedures, and proposed acceptance criteria, including the concept of different acceptance criteria for release and shelf life specifications, is addressed in ICH Q6A and Q6B. In addition, specification for degradation products in a drug product is addressed in Q3B.

Stability studies should include testing of those attributes of the drug product that are susceptible to change during storage and are likely to influence quality, safety, and/or efficacy. The testing should cover, as appropriate, the physical, chemical, biological, and microbiological attributes, preservative content (e.g., antioxidant, antimicrobial preservative), and functionality tests (e.g., for a dose delivery system). Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Shelf life acceptance criteria should be derived from consideration of all available stability information. It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration) intended for marketing.A single primary stability batch of the drug product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

6. Testing Frequency

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

Reduced designs, that is, matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified.

7. Storage Conditions

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long-term data will not be available before submission, at 12 months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated, and, where appropriate, intermediate storage conditions for drug products are detailed in the sections below. The general case applies if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used, if justified.

a. General Case

Study	Storage condition	Minimum time period covered by data at submission
Long term[a]	25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH	12 mo
Intermediate[b]	30°C ± 2°C/65% RH ± 5% RH	6 mo
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 mo

[a]It is up to the applicant to decide whether long term stability studies are performed at 25 ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

[b]If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

In general, "significant change" for a drug product is defined as

1. a 5% change in assay from its initial value, or failure to meet the acceptance criteria for potency when using biological or immunological procedures;

2. any degradation product's exceeding its acceptance criterion;
3. failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation); however, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions; and, as appropriate for the dosage form;
4. failure to meet the acceptance criterion for pH; or
5. Failure to meet the acceptance criteria for dissolution for twelve dosage units.

b. Drug Products Packaged in Impermeable Containers

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

c. Drug Products Packaged in Semipermeable Containers

Aqueous-based products packaged in semipermeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based drug products stored in semipermeable containers can withstand low relative humidity environments.

Other comparable approaches can be developed and reported for nonaqueous, solvent-based products.

Study	Storage condition	Minimum time period covered by data at submission
Long term[a]	25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH	12 mo
Intermediate[b]	30°C ± 2°C/65% RH ± 5% RH	6 mo
Accelerated	40°C ± 2°C/not more than (NMT) 25% RH	6 mo

[a]It is up to the applicant to decide whether long-term stability studies are performed at 25 ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH.
[b]If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

For long-term studies conducted at 25°C ± 2°C/40% RH ± 5% RH, additional testing at the intermediate storage condition should be performed as described under the general case to evaluate the temperature effect at 30°C if significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition.A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the drug product will not have significant water loss throughout the proposed shelf life if stored at 25°C and the reference relative humidity of 40% RH.

A 5% loss in water from its initial value is considered a significant change for a product packaged in a semipermeable container after an equivalent of 3 months' storage at 40°C/NMT 25% RH. However, for small containers (1mL or less) or unit-dose products, a water loss of 5% or more after an equivalent of 3 months' storage at 40°C/NMT 25% RH may be appropriate, if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long-term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst-case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

Example of an approach for determining water loss: For a product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative humidity at the same temperature by a water loss rate ratio shown in the table below.A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

For example, at a given temperature, for example, 40°C, the calculated water loss rate during storage at NMT 25% RH is the water loss rate measured at 75% RH multiplied by 3, the corresponding water loss rate ratio.

Alternative relative humidity	Reference relative humidity	Ratio of water loss rates at a given temperature
60% RH	25% RH	1.9
60% RH	40% RH	1.5
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

d. Drug Products Intended for Storage in a Refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C ± 3°C	12 mo
Accelerated	25°C ± 2°C/60% RH ± 5% RH	6 mo

If the drug product is packaged in a semipermeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of this guideline, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real-time data available from the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition, for example, during

shipment and handling. This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period less than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

e. Drug Products Intended for Storage in a Freezer

Study	Storage condition	Minimum time period covered by data at submission
Long term	$-20°C \pm 5°C$	12 mo

For drug products intended for storage in a freezer, the shelf life should be based on the real-time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., $5°C \pm 3°C$ or $25°C \pm 2°C$) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

f. Drug Products Intended for Storage Below $-20°C$

Drug products intended for storage below $-20°C$ should be treated on a case-by-case basis.

8. Stability Commitment

When available, long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval; a commitment should be made to continue the stability studies post approval to firmly establish the shelf life.

Where the submission includes long-term stability data from three production batches covering the proposed shelf life, a postapproval commitment is considered unnecessary. Otherwise, one of the following commitments should be made.

1. If the submission includes data from stability studies on at least three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months.
2. If the submission includes data from stability studies on fewer than three production batches, a commitment should be made to continue the long-term studies through the proposed shelf life and the accelerated studies for 6 months, and to place additional production batches, to a total of at least three, on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.
3. If the submission does not include stability data on production batches, a commitment should be made to place the first three production batches on long-term stability studies through the proposed shelf life and on accelerated studies for 6 months.

The stability protocol used for studies on commitment batches should be the same as that for the primary batches, unless otherwise scientifically justified.

Where intermediate testing is called for by a significant change at the accelerated storage condition for the primary batches, testing on the commitment batches can be conducted at either the intermediate or the accelerated storage condition. However, if significant change occurs at the accelerated storage condition on the commitment batches, testing at the intermediate storage condition should also be conducted.

9. Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including particular attributes of the dosage form (e.g., dissolution rate for solid oral dosage forms).

The purpose of the stability study is to establish, based on testing a minimum of three batches of the drug product, shelf life and label storage instructions applicable to all future batches of the drug product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of the degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Limited extrapolation of the real-time data from the long-term storage condition beyond the observed range to extend the shelf life can be undertaken at approval time, if justified. This justification should be based on what is known about the mechanisms of degradation, the results of testing under accelerated conditions, the goodness of fit of any mathematical model, batch size, existence of supporting stability data, etc. However, this extrapolation assumes that the same degradation relationship will continue to apply beyond the observed data.

Any evaluation should consider not only the assay but also the degradation products and other appropriate attributes. Where appropriate, attention should be paid to reviewing the adequacy of the mass balance and different stability and degradation performance.

10. Statements/Labeling

A storage statement should be established for the labeling in accordance with relevant national/regional requirements. The statement should be based on the stability evaluation of the drug product. Where applicable, specific instruction

should be provided, particularly for drug products that cannot tolerate freezing. Terms such as "ambient conditions" or "room temperature" should be avoided.

There should be a direct link between the label storage statement and the demonstrated stability of the drug product. An expiration date should be displayed on the container label.

GLOSSARY

The following definitions are provided to facilitate interpretation of the guideline.

Accelerated testing—Studies designed to increase the rate of chemical degradation or physical change of a drug substance or drug product by using exaggerated storage conditions as part of the formal stability studies. Data from these studies, in addition to long-term stability studies, can be used to assess longer-term chemical effects at nonaccelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping. Results from accelerated testing studies are not always predictive of physical changes.

Bracketing—The design of a stability schedule such that only samples on the extremes of certain design factors, for example, strength, package size, are tested at all time points as in a full design. The design assumes that the stability of any intermediate level is represented by the stability of the extremes tested. Where a range of strengths is to be tested, bracketing is applicable if the strengths are identical or closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

Climatic zones—The four zones in the world that are distinguished by their characteristic prevalent annual climatic conditions. This is based on the concept described by W. Grimm (*Drugs Made in Germany*, 28:196–202, 1985 and 29:39–47, 1986).

Commitment batches—Production batches of a drug substance or drug product for which the stability studies are initiated or completed post approval through a commitment made in the registration application.

Container closure system—The sum of packaging components that together contain and protect the dosage form. This includes primary packaging components and secondary packaging components, if the latter are intended to provide additional protection to the drug product.A packaging system is equivalent to a container closure system.

Dosage form—A pharmaceutical product type (e.g., tablet, capsule, solution, cream) that contains a drug substance generally, but not necessarily, in association with excipients.

Drug product—The dosage form in the final immediate packaging intended for marketing.

Drug substance—The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.

Excipient—Anything other than the drug substance in the dosage form.

Expiration date—The date placed on the container label of a drug product designating the time prior to which a batch of the product is expected to remain within the approved shelf life specification if stored under defined conditions, and after which it must not be used.

Formal stability studies—Long-term and accelerated (and intermediate) studies undertaken on primary and/or commitment batches according to a prescribed stability protocol to establish or confirm the retest period of a drug substance or the shelf life of a drug product.

Impermeable containers—Containers that provide a permanent barrier to the passage of gases or solvents, for example, sealed aluminum tubes for semisolids, sealed glass ampoules for solutions.

Intermediate testing—Studies conducted at 30°C/65% RH and designed to moderately increase the rate of chemical degradation or physical changes for a drug substance or drug product intended to be stored long term at 25°C.

Long-term testing—Stability studies under the recommended storage condition for the retest period or shelf life proposed (or approved) for labeling.

Mass balance—The process of adding together the assay value and levels of degradation products to see how closely these add up to 100% of the initial value, with due consideration of the margin of analytical error.

Matrixing—The design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations is tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations is tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and, possibly in some cases, different container closure systems.

Mean kinetic temperature—A single derived temperature that, if maintained over a defined period of time, affords the same thermal challenge to a drug substance or drug product as would be experienced over a range of both higher and lower temperatures for an equivalent defined period. The mean kinetic temperature is higher than the arithmetic mean temperature and takes into account the Arrhenius equation.

When establishing the mean kinetic temperature for a defined period, the formula of J. D. Haynes (*J. Pharm. Sci.*, 60:927–929, 1971) can be used.

New molecular entity—An active pharmaceutical substance not previously contained in any drug product registered with the national or regional authority concerned.A new salt, ester, or non–covalent-bond derivative of an approved drug substance is considered a new molecular entity for the purpose of stability testing under this guidance.

Pilot scale batch—A batch of a drug substance or drug product manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100000 tablets or capsules, whichever is the larger.

Primary batch—A batch of a drug substance or drug product used in a formal stability study, from which stability

data are submitted in a registration application for the purpose of establishing a retest period or shelf life respectively.A primary batch of a drug substance should be at least a pilot scale batch. For a drug product, two of the three batches should be at least pilot scale batch, and the third batch can be smaller if it is representative with regard to the critical manufacturing steps. However, a primary batch may be a production batch.

Production batch—A batch of a drug substance or drug product manufactured at production scale by using production equipment in a production facility as specified in the application.

Retest date—The date after which samples of the drug substance should be examined to ensure that the material is still in compliance with the specification and thus suitable for use in the manufacture of a given drug product.

Retest period—The period of time during which the drug substance is expected to remain within its specification and, therefore, can be used in the manufacture of a given drug product, provided that the drug substance has been stored under the defined conditions. After this period, a batch of drug substance destined for use in the manufacture of a drug product should be retested for compliance with the specification and then used immediately.A batch of drug substance can be retested multiple times and a different portion of the batch used after each retest, as long as it continues to comply with the specification. For most biotechnological/biological substances known to be labile, it is more appropriate to establish a shelf life than a retest period. The same may be true for certain antibiotics.

Semipermeable containers—Containers that allow the passage of solvent, usually water, while preventing solute loss. The mechanism for solvent transport occurs by absorption into one container surface, diffusion through the bulk of the container material, and desorption from the other surface. Transport is driven by a partial-pressure gradient. Examples of semipermeable containers include plastic bags and semirigid, low-density polyethylene (LDPE) pouches for large-volume parenterals (LVPs), and LDPE ampoules, bottles, and vials.

Shelf life (also referred to as expiration dating period)—The time period during which a drug product is expected to remain within the approved shelf life specification, provided that it is stored under the conditions defined on the container label.

Specification—See Q6A and Q6B.

Specification Release—The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release.

Specification—Shelf life—The combination of physical, chemical, biological, and microbiological tests and acceptance criteria that determine the suitability of a drug substance throughout its retest period, or that a drug product should meet throughout its shelf life.

Storage condition tolerances—The acceptable variations in temperature and relative humidity of storage facilities for formal stability studies. The equipment should be capable of controlling the storage condition within the ranges defined in this guideline. The actual temperature and humidity (when controlled) should be monitored during stability storage. Short-term spikes caused by opening of doors of the storage facility are accepted as unavoidable. The effect of excursions owing to equipment failure should be addressed, and reported if judged to affect stability results. Excursions that exceed the defined tolerances for more than 24 hours should be described in the study report and their effect assessed.

Stress testing (drug substance)—Studies undertaken to elucidate the intrinsic stability of the drug substance. Such testing is part of the development strategy and is normally carried out under more severe conditions than those used for accelerated testing.

Stress testing (drug product)—Studies undertaken to assess the effect of severe conditions on the drug product. Such studies include photostability testing (see ICH Q1B) and specific testing on certain products, (e.g., metered dose inhalers, creams, emulsions, refrigerated aqueous liquid products).

Supporting data—Data, other than those from formal stability studies, that support the analytical procedures, the proposed retest period or shelf life, and the label storage statements. Such data include (1) stability data on early synthetic route batches of drug substance, small-scale batches of materials, investigational formulations not proposed for marketing, related formulations, and product presented in containers and closures other than those proposed for marketing, (2) information regarding test results on containers, and (3) other scientific rationales.

REFERENCES

Grimm W (1985). Storage Conditions for stability testing—long term testing and stress tests. Drugs Made Germany 28: 196–202; (Part I) and 29: 39–47, 1986 (Part II).

Haynes JD (1971). Worldwide virtual temperature for product stability testing. Pharm Sci 60: 927–929.

ICH Q1B: *Stability Testing: Photostability Testing of New Drug Substances and Products*

ICH Q1C: *Stability Testing of New Dosage Forms*

ICH Q3A: *Impurities in New Drug Substances*

ICH Q3B: *Impurities in New Drug Products*

ICH Q5C: *Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*

ICH Q6A: *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (Including Decision Trees)*

ICH Q6B: *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*

Stability Testing: Photostability Testing of New Drug Substances and Products

I. GENERAL

The ICH Harmonized Tripartite Guideline covering the Stability Testing of New Drug Substances and Products notes that light testing should be an integral part of stress testing.

A. Preamble

The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate that, as appropriate, light exposure does not result in unacceptable change. Normally, photostability testing is carried out on a single batch of material selected as described under Selection of Batches in the Parent Guideline. Under some circumstances these studies should be repeated if certain variations and changes are made to the product (e.g., formulation, packaging). Whether these studies should be repeated depends on the photostability characteristics determined at the time of initial filing and the type of variation and/or change made.

The guideline primarily addresses the generation of photostability information for submission in Registration Applications for new molecular entities and associated drug products. The guideline does not cover the photostability of drugs after administration (i.e., under conditions of use) and those applications not covered by the Parent Guideline. Alternative approaches may be used if they are scientifically sound and justification is provided.

A systematic approach to photostability testing is recommended covering, as appropriate, studies such as:

i. Tests on the drug substance;
ii. Tests on the exposed drug product outside of the immediate pack; and if necessary;
iii. Tests on the drug product in the immediate pack; and if necessary;
iv. Tests on the drug product in the marketing pack.

B. Light Sources

The light sources described below may be used for photostability testing. The applicant should either maintain an appropriate control of temperature to minimize the effect of localized temperature changes or include a dark control in the same environment unless otherwise justified. For both options 1 and 2, a pharmaceutical manufacturer/applicant may rely on the spectral distribution specification of the light source manufacturer.

Option 1

Any light source that is designed to produce an output similar to the D65/ID65 emission standard such as an artificial daylight fluorescent lamp combining visible and ultraviolet (UV) outputs, xenon, or metal halide lamp. D65 is the internationally recognized standard for outdoor daylight as defined in ISO 10977 (1993). ID65 is the equivalent indoor indirect daylight standard. For a light source emitting significant radiation below 320 nm, an appropriate filter(s) may be fitted to eliminate such radiation.

Option 2

For option 2 the same sample should be exposed to both the cool white fluorescent and near UV lamp.

1. A cool white fluorescent lamp designed to produce an output similar to that specified in ISO 10977(1993); and
2. A near UV fluorescent lamp having a spectral distribution from 320 nm to 400 nm with a maximum energy emission between 350 nm and 370 nm; a significant proportion of UV should be in both bands of 320 to 360 nm and 360 to 400 nm.

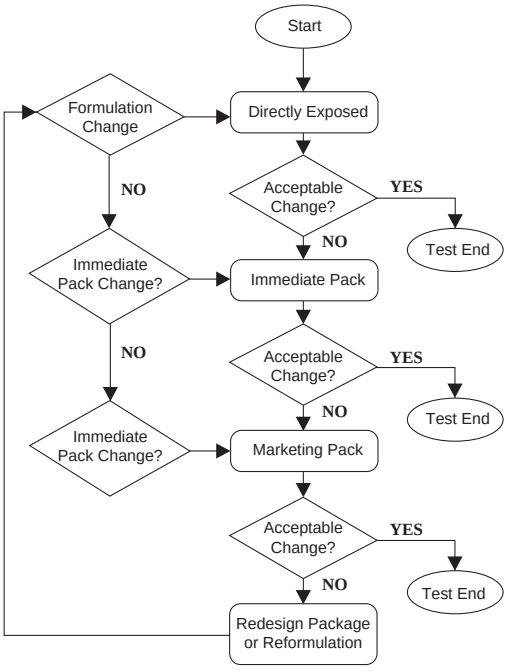
C. Procedure

For confirmatory studies, samples should be exposed to light providing an overall illumination of not less than 1.2 million lux hours and an integrated near UV energy of not less than 200 W hr/m^2 to allow direct comparisons to be made between the drug substance and drug product.

Samples may be exposed side-by-side with a validated chemical actinometric system to ensure the specified light exposure is obtained, or for the appropriate duration of time when conditions have been monitored using calibrated radiometers/lux meters. An example of an actinometric procedure is provided in the Annex.

If protected samples (e.g., wrapped in aluminum foil) are used as dark controls to evaluate the contribution of thermally induced change to the total observed change, these should be placed alongside the authentic sample.

Decision Flow Chart for Photostability Testing of Drug Products



II. DRUG SUBSTANCE

For drug substances, photostability testing should consist of two parts: forced degradation testing and confirmatory testing.

The purpose of forced degradation testing studies is to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation. This testing may involve the drug substance alone and/or in simple solutions/suspensions to validate the analytical procedures. In these studies, the samples should be in chemically inert and transparent containers. In these forced degradation studies, a variety of exposure conditions may be used, depending on the photosensitivity of the drug substance involved and the intensity of the light sources used. For development and validation purposes, it is appropriate to limit exposure and end the studies if extensive decomposition occurs. For photostable materials, studies may be terminated after an appropriate exposure level has been used. The design of these experiments is left to the applicant's discretion although the exposure levels used should be justified.

Under forcing conditions, decomposition products may be observed that are unlikely to be formed under the conditions used for confirmatory studies. This information may be useful in developing and validating suitable analytical methods. If in practice it has been demonstrated that they are not formed in the confirmatory studies, these degradation products need not be further examined.

Confirmatory studies should then be undertaken to provide the information necessary for handling, packaging, and labeling (see section I.C., Procedure, and II. A., Presentation, for information on the design of these studies).

Normally, only one batch of drug substance is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the Parent Guideline if the drug is clearly photostable or photolabile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted. Samples should be selected as described in the Parent Guideline.

A. Presentation of Samples

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account and efforts should be made, such as cooling and/or placing the samples in sealed containers, to ensure that the effects of the changes in physical states such as sublimation, evaporation or melting are minimized. All such precautions should be chosen to provide minimal interference with the exposure of samples under test. Possible interactions between the samples and any material used for containers or for general protection of the sample should also be considered and eliminated wherever not relevant to the test being carried out.

As a direct challenge for samples of solid drug substances, an appropriate amount of sample should be taken and placed in a suitable glass or plastic dish and protected with a suitable transparent cover if considered necessary. Solid drug substances should be spread across the container to give a thickness of typically not more than 3 mL. Drug substances that are liquids should be exposed in chemically inert and transparent containers.

B. Analysis of Samples

At the end of the exposure period, the samples should be examined for any changes in physical properties (e.g., appearance, clarity, or color of solution) and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes.

Where solid drug substance samples are involved, sampling should ensure that a representative portion is used in individual tests. Similar sampling considerations, such as homogenization of the entire sample, apply to other materials that may not be homogeneous after exposure. The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark controls if these are used in the test.

C. Judgement of Results

The forced degradation studies should be designed to provide suitable information to develop and validate test methods for the confirmatory studies. These test methods should be capable of resolving and detecting photolytic degradants that appear during the confirmatory studies. When evaluating the results of these studies, it is important to recognize that they form part of the stress testing and are not therefore designed to establish qualitative or quantitative limits for change.

The confirmatory studies should identify precautionary measures needed in manufacturing or in formulation of the drug product, and if light resistant packaging is needed. When evaluating the results of confirmatory studies to determine whether change due to exposure to light is acceptable, it is important to consider the results from other formal stability studies in order to assure that the drug will be within justified limits at time of use (see the relevant ICH Stability and Impurity Guidelines).

III. DRUG PRODUCT

Normally, the studies on drug products should be carried out in a sequential manner starting with testing the fully exposed product then progressing as necessary to the product in the immediate pack and then in the marketing pack. Testing should progress until the results demonstrate that the drug product is adequately protected from exposure to light. The drug product should be exposed to the light conditions described under the procedure in section I.C.

Normally, only one batch of drug product is tested during the development phase, and then the photostability characteristics should be confirmed on a single batch selected as described in the Parent Guideline if the product is clearly photostable or photolabile. If the results of the confirmatory study are equivocal, testing of up to two additional batches should be conducted.

For some products where it has been demonstrated that the immediate pack is completely impenetrable to light, such as aluminum tubes or cans, testing should normally only be conducted on directly exposed drug product.

It may be appropriate to test certain products such as infusion liquids, dermal creams, etc., to support their photostability in-use. The extent of this testing should depend on and relate to the directions for use, and is left to the applicant's discretion.

The analytical procedures used should be suitably validated.

A. Presentation of Samples

Care should be taken to ensure that the physical characteristics of the samples under test are taken into account and efforts, such as cooling and/or placing the samples in sealed

containers, should be made to ensure that the effects of the changes in physical states are minimized, such as sublimation, evaporation, or melting. All such precautions should be chosen to provide a minimal interference with the irradiation of samples under test. Possible interactions between the samples and any material used for containers or for general protection of the sample should also be considered and eliminated wherever not relevant to the test being carried out.

Where practicable when testing samples of the drug product outside of the primary pack, these should be presented in a way similar to the conditions mentioned for the drug substance. The samples should be positioned to provide maximum area of exposure to the light source. For example, tablets, capsules, etc., should be spread in a single layer.

If direct exposure is not practical (e.g., due to oxidation of a product), the sample should be placed in a suitable protective inert transparent container (e.g., quartz).

If testing of the drug product in the immediate container or as marketed is needed, the samples should be placed horizontally or transversely with respect to the light source, whichever provides for the most uniform exposure of the samples. Some adjustment of testing conditions may have to be made when testing large volume containers (e.g., dispensing packs).

B. Analysis of Samples

At the end of the exposure period, the samples should be examined for any changes in physical properties (e.g., appearance, clarity or color of solution, dissolution/disintegration for dosage forms such as capsules, etc.) and for assay and degradants by a method suitably validated for products likely to arise from photochemical degradation processes.

When powder samples are involved, sampling should ensure that a representative portion is used in individual tests. For solid oral dosage form products, testing should be conducted on an appropriately sized composite of, for example, 20 tablets or capsules. Similar sampling considerations, such as homogenization or solubilization of the entire sample, apply to other materials that may not be homogeneous after exposure (e.g., creams, ointments, suspensions, etc.). The analysis of the exposed sample should be performed concomitantly with that of any protected samples used as dark controls if these are used in the test.

C. Judgement of Results

Depending on the extent of change special labeling or packaging may be needed to mitigate exposure to light. When evaluating the results of photostability studies to determine whether change due to exposure to light is acceptable, it is important to consider the results obtained from other formal stability studies in order to assure that the product will be within proposed specifications during the shelf life (see the relevant ICH Stability and Impurity Guidelines).

IV. ANNEX

A. Quinine Chemical Actinometry

The following provides details of an actinometric procedure for monitoring exposure to a near UV fluorescent lamp (based on FDA/National Institute of Standards and Technology study). For other light sources/actinometric systems, the same approach may be used, but each actinometric system should be calibrated for the light source used.

Prepare a sufficient quantity of a 2% weight/volume aqueous solution of quinine monohydrochloride dihydrate (if necessary, dissolve by heating).

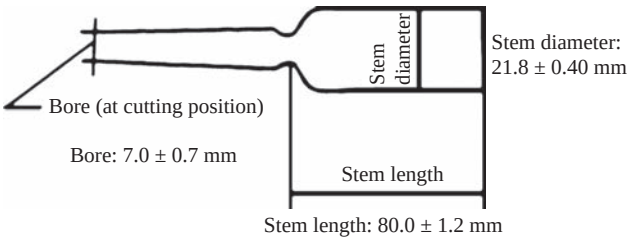
Option 1

Put 10 mL of the solution into a 20 mL colorless ampoule seal it hermetically, and use this as the sample. Separately, put 10 mL of the solution into a 20 mL colorless ampoule (see note 1), seal it hermetically, wrap in aluminum foil to protect completely from light, and use this as the control. Expose the sample and control to the light source for an appropriate number of hours. After exposure determine the absorbances of the sample (AT) and the control (Ao) at 400 nm using a 1 cm path length. Calculate the change in absorbance, $\Delta A = AT - Ao$. The length of exposure should be sufficient to ensure a change in absorbance of at least 0.9.

Option 2

Fill a 1 cm quartz cell and use this as the sample. Separately fill a 1 cm quartz cell, wrap in aluminum foil to protect completely from light, and use this as the control. Expose the sample and control to the light source for an appropriate number of hours. After exposure determine the absorbances of the sample (AT) and the control (Ao) at 400 nm. Calculate the change in absorbance, $\Delta A = AT - Ao$. The length of exposure should be sufficient to ensure a change in absorbance of at least 0.5.

Alternative packaging configurations may be used if appropriately validated. Alternative validated chemical actinometers may be used.



Note 1: Shape and Dimensions (See Japanese Industry Standard (JIS) R3512 (1974) for ampoule specifications).

10

Stability Testing for New Dosage Forms

I. GENERAL

This document discusses stability guideline and addresses the recommendations on what should be submitted regarding stability of new dosage forms by the owner of the original application, after the original submission for new drug substances and products.

II. NEW DOSAGE FORMS

A new dosage form is defined as a drug product, which is a different pharmaceutical product type, but contains the same active substance as included in the existing drug product approved by the pertinent regulatory authority.

Such pharmaceutical product types include products of different administration route (e.g., oral to parenteral), new specific functionality/delivery systems (e.g., immediate-release tablet to modified-release tablet), and different dosage forms of the same administration route (e.g., capsule to tablet, solution to suspension).

Stability protocols for new dosage forms should follow the guidance in the parent stability guideline in principle. However, a reduced stability database at submission time (e.g., 6 months accelerated and 6 months long-term data from ongoing studies) may be acceptable in certain justified cases.

GLOSSARY

Immediate (primary) pack is that constituent of the packaging that is in direct contact with the drug substance or drug product, and includes any appropriate label.

Marketing pack is the combination of immediate pack and other secondary packaging such as a carton.

Forced degradation testing studies are those undertaken to degrade the sample deliberately. These studies, which may be undertaken in the development phase normally on the drug substances, are used to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation.

Confirmatory studies are those undertaken to establish photostability characteristics under standardized conditions. These studies are used to identify precautionary measures needed in manufacturing or formulation and whether light resistant packaging and/or special labeling is needed to mitigate exposure to light. For the confirmatory studies, the batches should be selected according to batch selection for long-term and accelerated testings, which is described in the Parent Guideline.

BIBLIOGRAPHY

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11

Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products

I. INTRODUCTION

A. Objectives of the Guideline

This guideline is intended to address recommendations on the application of bracketing and matrixing to stability studies conducted in accordance with principles outlined in the ICH Q1A(R) Harmonised Tripartite guideline on Stability Testing of New Drug Substances and Products (hereafter referred to as the parent guideline).

B. Background

The parent guideline notes that the use of matrixing and bracketing can be applied, if justified, to the testing of new drug substances and products, but provides no further guidance on the subject.

C. Scope of the Guideline

This document provides guidance on bracketing and matrixing study designs. Specific principles are defined in this guideline for situations in which bracketing or matrixing can be applied. Sample designs are provided for illustrative purposes, and should not be considered the only, or the most appropriate, designs in all cases.

II. GUIDELINES

A. General

A full study design is one in which samples for every combination of all design factors are tested at all time points. A reduced design is one in which samples for every factor combination are not all tested at all time points. A reduced design can be a suitable alternative to a full design when multiple design factors are involved. Any reduced design should have the ability to adequately predict the retest period or shelf life. Before a reduced design is considered, certain assumptions should be assessed and justified. The potential risk should be considered of establishing a shorter retest period or shelf life than could be derived from a full design due to the reduced amount of data collected.

During the course of a reduced design study, a change to full testing or to a less reduced design can be considered if a justification is provided and the principles of full designs and reduced designs are followed. However, proper adjustments should be made to the statistical analysis, where applicable, to account for the increase in sample size as a result of the change. Once the design is changed, full testing or less reduced testing should be carried out through the remaining time points of the stability study.

B. Applicability of Reduced Designs

Reduced designs can be applied to the formal stability study of most types of drug products, although additional justification should be provided for certain complex drug delivery systems where there are a large number of potential drug-device interactions. For the study of drug substances, matrixing is of limited utility and bracketing is generally not applicable.

Whether bracketing or matrixing can be applied depends on the circumstances, as discussed in detail below. The use of any reduced design should be justified. In certain cases, the condition described in this guideline is sufficient justification for use, while in other cases, additional justification should be provided. The type and level of justification in each of these cases will depend on the available supporting data. Data variability and product stability, as shown by supporting data, should be considered when a matrixing design is applied.

Bracketing and matrixing are reduced designs based on different principles. Therefore, careful consideration and scientific justification should precede the use of bracketing and matrixing together in one design.

C. Bracketing

As defined in the glossary to the parent guideline, bracketing is the design of a stability schedule such that only samples on the extremes of certain design factors (e.g., strength, container size, and/or fill) are tested at all time points as in a full design. The design assumes that the stability of any intermediate levels is represented by the stability of the extremes tested.

The use of a bracketing design would not be considered appropriate if it cannot be demonstrated that the strengths or container sizes and/or fills selected for testing are indeed the extremes.

1. Design Factors

Design factors are variables (e.g., strength, container size, and/or fill) to be evaluated in a study design for their effect on product stability.

a. Strength

Bracketing can be applied to studies with multiple strengths of identical or closely related formulations. Examples include but are not limited to (1) capsules of different strengths made with different fill plug sizes from the same powder blend, (2) tablets of different strengths manufactured by compressing varying amounts of the same granulation, and (3) oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colorants, flavorings).

With justification, bracketing can be applied to studies with multiple strengths where the relative amounts of drug substance and excipients change in a formulation. Such justification can include a demonstration of comparable stability profiles among the different strengths of clinical or development batches.

In cases where different excipients are used among strengths, bracketing generally should not be applied.

Table 11.1 Example of a Bracketing Design

Strength		50 mg			75 mg			100 mg		
Batch		1	2	3	1	2	3	1	2	3
Container size	15 mL	T	T	T				T	T	T
	100 mL									
	500 mL	T	T	T				T	T	T

Key: T = Sample tested.

b. Container Closure Sizes and/or Fills

Bracketing can be applied to studies of the same container closure system where either container size or fill varies while the other remains constant. However, if a bracketing design is considered where both container size and fill vary, it should not be assumed that the largest and smallest containers represent the extremes of all packaging configurations. Care should be taken to select the extremes by comparing the various characteristics of the container closure system that may affect product stability. These characteristics include container wall thickness, closure geometry, surface area to volume ratio, headspace to volume ratio, water vapor permeation rate or oxygen permeation rate per dosage unit or unit fill volume, as appropriate.

With justification, bracketing can be applied to studies for the same container when the closure varies. Justification could include a discussion of the relative permeation rates of the bracketed container closure systems.

2. Design Considerations and Potential Risks

If, after starting the studies, one of the extremes is no longer expected to be marketed, the study design can be maintained to support the bracketed intermediates. A commitment should be provided to carry out stability studies on the marketed extremes postapproval.

Before a bracketing design is applied, its effect on the retest period or shelf life estimation should be assessed. If the stability of the extremes is shown to be different, the intermediates should be considered no more stable than the least stable extreme (i.e., the shelf life for the intermediates should not exceed that for the least stable extreme).

3. Design Example

An example of a bracketing design is given in Table 11.1. This example is based on a product available in three strengths and three container sizes. In this example, it should be demonstrated that the 15 and 500 mL high-density polyethylene container sizes truly represent the extremes. The batches for each selected combination should be tested at each time point as in a full design.

D. Matrixing

As defined in the glossary of the parent guideline, matrixing is the design of a stability schedule such that a selected subset of the total number of possible samples for all factor combinations would be tested at a specified time point. At a subsequent time point, another subset of samples for all factor combinations would be tested. The design assumes that the stability of each subset of samples tested represents the stability of all samples at a given time point. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same container closure system, and possibly, in some cases, different container closure systems.

When a secondary packaging system contributes to the stability of the drug product, matrixing can be performed across the packaging systems.

Each storage condition should be treated separately under its own matrixing design. Matrixing should not be performed across test attributes. However, alternative matrixing designs for different test attributes can be applied if justified.

1. Design Factors

Matrixing designs can be applied to strengths with identical or closely related formulations. Examples include but are not limited to (1) capsules of different strengths made with different fill plug sizes from the same powder blend, (2) tablets of different strengths manufactured by compressing varying amounts of the same granulation, and (3) oral solutions of different strengths with formulations that differ only in minor excipients (e.g., colorants or flavorings).

Other examples of design factors that can be matrixed include batches made by using the same process and equipment, and container sizes and/or fills in the same container closure system.

With justification, matrixing designs can be applied, for example, to different strengths where the relative amounts of drug substance and excipients change or where different excipients are used or to different container closure systems. Justification should generally be based on supporting data. For example, to matrix across two different closures or container closure systems, supporting data could be supplied showing relative moisture vapor transmission rates or similar protection against light. Alternatively, supporting data could be supplied to show that the drug product is not affected by oxygen, moisture, or light.

2. Design Considerations

A matrixing design should be balanced as far as possible so that each combination of factors is tested to the same extent over the intended duration of the study and through the last time point prior to submission. However, due to the recommended full testing at certain time points, as discussed below, it may be difficult to achieve a complete balance in a design where time points are matrixed.

In a design where time points are matrixed, all selected factor combinations should be tested at the initial and final time points, while only certain fractions of the designated combinations should be tested at each intermediate time point. If full long-term data for the proposed shelf life will not be available for review before approval, all selected combinations of batch, strength, container size, and fill, among other things, should also be tested at 12 months or at the last time point prior to submission. In addition, data from at least three time points, including initial, should be available for each selected combination through the first 12 months of the study. For matrixing at an accelerated or intermediate storage condition, care should be taken to ensure testing occurs at a minimum of three time points, including initial and final, for each selected combination of factors.

When a matrix on design factors is applied, if one strength or container size and/or fill is no longer intended for marketing, stability testing of that strength or container size and/or fill can be continued to support the other strengths or container sizes and/or fills in the design.

3. Design Examples

Examples of matrixing designs on time points for a product in two strengths (S1 and S2) are shown in Table 11.2. The terms "one-half reduction" and "one-third reduction" refer to the

Table 11.2 Examples of Matrixing Designs on Time Points for a Product with Two Strengths

Time Point (Months)			0	3	6	9	12	18	24	36
One-half reduction										
	S1	Batch 1	T	T		T	T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T	T		T
Strength	S2	Batch 1	T		T		T		T	T
		Batch 2	T	T		T	T	T		T
		Batch 3	T		T		T		T	T
One-third reduction										
	S1	Batch 1	T	T		T	T		T	T
		Batch 2	T	T	T		T	T		T
		Batch 3	T		T	T	T	T	T	T
Strength	S2	Batch 1	T		T	T	T	T	T	T
		Batch 2	T	T		T	T		T	T
		Batch 3	T	T	T		T	T		T

Key: T = Sample tested.

reduction strategy initially applied to the full study design. For example, a "one-half reduction" initially eliminates one in every two time points from the full study design and a "one-third reduction" initially removes one in every three. In the examples shown in Table 11.2, the reductions are less than one-half and one-third due to the inclusion of full testing of all factor combinations at some time points as discussed in section 2.4.2. These examples include full testing at the initial, final, and 12-month time points. The ultimate reduction is therefore less than one-half (24/48) or one-third (16/48), and is actually 15/48 or 10/48, respectively.

Additional examples of matrixing designs for a product with three strengths and three container sizes are given in Table 11.3. Table 11.3(A) shows a design with matrixing on time points only and Table 11.3(B) depicts a design with matrixing on time points and factors. In Table 11.3(A), all combinations of batch, strength, and container size are tested, while in Table 11.3(B), certain combinations of batch, strength, and container size are not tested.

4. Applicability and Degree of Reduction

The following, although not an exhaustive list, should be considered when a matrixing design is contemplated:

- Knowledge of data variability
- Expected stability of the product
- Availability of supporting data
- Stability differences in the product within a factor or among factors

and/or

- Number of factor combinations in the study

In general, a matrixing design is applicable if the supporting data indicate predictable product stability. Matrixing is appropriate when the supporting data exhibit only small variability. However, where the supporting data exhibit moderate variability, a matrixing design should be statistically justified. If the supportive data show large variability, a matrixing design should not be applied.

Table 11.3 Examples of Matrixing Designs for a Product with Three Strengths and Three Container Sizes

Strength	S1			S2			S3		
A. Matrixing on time points									
Container size	A	B	C	A	B	C	A	B	C
Batch 1	T1	T2	T3	T2	T3	T1	T3	T1	T2
Batch 2	T2	T3	T1	T3	T1	T2	T1	T2	T3
Batch 3	T3	T1	T2	T1	T2	T3	T2	T3	T1
B. Matrixing on time points and factors									
Container size	A	B	C	A	B	C	A	B	C
Batch 1	T1	T2		T2		T1		T1	T2
Batch 2		T3	T1	T3	T1		T1		T3
Batch 3	T3		T2		T2	T3	T2	T3	
Time-point (months)	0	3	6	9	12	18	24	36	
T1	T		T	T	T	T	T	T	
T2	T	T		T	T		T	T	
T3	T	T	T		T	T		T	

S1, S2, and S3 are different strengths. A, B, and C are different container sizes.
Key: T = Sample tested.

A statistical justification could be based on an evaluation of the proposed matrixing design with respect to its power to detect differences among factors in the degradation rates or its precision in shelf life estimation.

If a matrixing design is considered applicable, the degree of reduction that can be made from a full design depends on the number of factor combinations being evaluated. The more factors associated with a product and the more levels in each factor, the larger the degree of reduction that can be considered. However, any reduced design should have the ability to adequately predict the product shelf life.

5. Potential Risk

Because of the reduced amount of data collected, a matrixing design on factors other than time points generally has less precision in shelf life estimation and yields a shorter shelf life than the corresponding full design. In addition, such a matrixing design may have insufficient power to detect certain main or interaction effects, thus leading to incorrect pooling of data from different design factors during shelf life estimation. If there is an excessive reduction in the number of factor combinations tested and data from the tested factor combinations cannot be pooled to establish a single shelf life, it may be impossible to estimate the shelf lives for the missing factor combinations.

A study design that matrixes on time points only would often have similar ability to that of a full design to detect differences in rates of change among factors and to establish a reliable shelf life. This feature exists because linearity is assumed and because full testing of all factor combinations would still be performed at both the initial time point and the last time point prior to submission.

E. Data Evaluation

Stability data from studies in a reduced design should be treated in the same manner as data from full design studies.

12

Evaluation of Stability Data

I. INTRODUCTION

A. Objectives of the Guideline

This guideline is intended to provide recommendations on how to use stability data generated in accordance with the principles detailed in the ICH guideline "Q1A(R) Stability Testing of New Drug Substances and Products" (hereafter referred to as the parent guideline) to propose a retest period or shelf life in a registration application. This guideline describes when and how extrapolation can be considered when proposing a retest period for a drug substance or a shelf life for a drug product that extends beyond the period covered by "available data from the stability study under the long-term storage condition" (hereafter referred to as long-term data).

B. Background

The guidance on the evaluation and statistical analysis of stability data provided in the parent guideline is brief in nature and limited in scope. The parent guideline states that regression analysis is an appropriate approach to analyzing quantitative stability data for retest period or shelf-life estimation and recommends that a statistical test for batch poolability be performed using a level of significance of 0.25. However, the parent guideline includes few details and does not cover situations where multiple factors are involved in a full- or reduced-design study.

This guideline is an expansion of the guidance presented in the Evaluation sections of the parent guideline.

C. Scope of the Guideline

This guideline addresses the evaluation of stability data that should be submitted in registration applications for new molecular entities and associated drug products. The guideline provides recommendations on establishing retest periods and shelf lives for drug substances and drug products intended for storage at or below "room temperature"*. It covers stability studies using single- or multifactor designs and full or reduced designs.

ICH Q6A and Q6B should be consulted for recommendations on the setting and justification of acceptance criteria, and ICH Q1D should be referenced for recommendations on the use of full- versus reduced-design studies.

II. GUIDELINES

A. General Principles

The design and execution of formal stability studies should follow the principles outlined in the parent guideline. The purpose of a stability study is to establish, based on testing a minimum of three batches of the drug substance or product, a retest period or shelf life and label storage instructions applicable to all future batches manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within acceptance criteria throughout its retest period or shelf life.

Although normal manufacturing and analytical variations are to be expected, it is important that the drug product be formulated with the intent to provide 100% of the labeled amount of the drug substance at the time of batch release. If the assay values of the batches used to support the registration application are higher than 100% of label claim at the time of batch release, after taking into account manufacturing and analytical variations, the shelf life proposed in the application can be overestimated. On the other hand, if the assay value of a batch is lower than 100% of label claim at the time of batch release, it might fall below the lower acceptance criterion before the end of the proposed shelf life.

A systematic approach should be adopted in the presentation and evaluation of the stability information. The stability information should include, as appropriate, results from the physical, chemical, biological, and microbiological tests, including those related to particular attributes of the dosage form (e.g., dissolution rate for solid oral dosage forms). The adequacy of the mass balance should be assessed. Factors that can cause an apparent lack of mass balance should be considered, including, for example, the mechanisms of degradation and the stability-indicating capability and inherent variability of the analytical procedures.

The basic concepts of stability data evaluation are the same for single- versus multifactor studies and for full- versus reduced-design studies. Data from formal stability studies and, as appropriate, supporting data should be evaluated to determine the critical quality attributes likely to influence the quality and performance of the drug substance or product. Each attribute should be assessed separately, and an overall assessment should be made of the findings for the purpose of proposing a retest period or shelf life. The retest period or shelf life proposed should not exceed that predicted for any single attribute.

The decision tree in Appendix A outlines a stepwise approach to stability data evaluation and when and how much extrapolation can be considered for a proposed retest period or shelf life. Appendix B provides (1) information on how to analyze long-term data for appropriate quantitative test attributes from a study with a multifactor, full, or reduced design; (2) information on how to use regression analysis for retest period or shelf life estimation; and (3) examples of statistical procedures to determine poolability of data from different batches or other factors. Additional guidance can be found in the references listed; however, the examples and references do not cover all applicable statistical approaches.

In general, certain quantitative chemical attributes (e.g., assay, degradation products, preservative content) for a drug

*_Note_: The term "room temperature" refers to the general customary environment and should not be inferred to be the storage statement for labeling.

substance or product can be assumed to follow zero-order kinetics during long-term storage (Carstensen, 1977). Data for these attributes are therefore amenable to the type of statistical analysis described in Appendix B, including linear regression and poolability testing. Although the kinetics of other quantitative attributes (e.g., pH, dissolution) is generally not known, the same statistical analysis can be applied, if appropriate. Qualitative attributes and microbiological attributes are not amenable to this kind of statistical analysis.

The recommendations on statistical approaches in this guideline are not intended to imply that use of statistical evaluation is preferred when it can be justified to be unnecessary. However, statistical analysis can be useful in supporting the extrapolation of retest periods or shelf lives in certain situations and can be called for to verify the proposed retest periods or shelf lives in other cases.

B. Data Presentation

Data for all attributes should be presented in an appropriate format (e.g., tabular, graphical, narrative) and an evaluation of such data should be included in the application. The values of quantitative attributes at all time points should be reported as measured (e.g., assay as percent of label claim). If a statistical analysis is performed, the procedure used and the assumptions underlying the model should be stated and justified. A tabulated summary of the outcome of statistical analysis and/or graphical presentation of the long-term data should be included.

C. Extrapolation

Extrapolation is the practice of using a known data set to infer information about future data. Extrapolation to extend the retest period or shelf life beyond the period covered by long-term data can be proposed in the application, particularly if no significant change is observed at the accelerated condition. Whether extrapolation of stability data is appropriate depends on the extent of knowledge about the change pattern, the goodness of fit of any mathematical model, and the existence of relevant supporting data. Any extrapolation should be performed such that the extended retest period or shelf life will be valid for a future batch released with test results close to the release acceptance criteria.

An extrapolation of stability data assumes that the same change pattern will continue to apply beyond the period covered by long-term data. The correctness of the assumed change pattern is critical when extrapolation is considered. When estimating a regression line or curve to fit the long-term data, the data themselves provide a check on the correctness of the assumed change pattern, and statistical methods can be applied to test the goodness of fit of the data to the assumed line or curve. No such internal check is possible beyond the period covered by long-term data. Thus, a retest period or shelf life granted on the basis of extrapolation should always be verified by additional long-term stability data as soon as these data become available. Care should be taken to include in the protocol for commitment batches a time point that corresponds to the end of the extrapolated retest period or shelf life.

D. Data Evaluation for Retest Period or Shelf-Life Estimation for Drug Substances or Products Intended for Room Temperature Storage

A systematic evaluation of the data from formal stability studies should be performed as illustrated in this section. Stability data for each attribute should be assessed sequentially. For drug substances or products intended for storage at room temperature, the assessment should begin with any significant change at the accelerated condition and, if appropriate, at the intermediate condition, and progress through the trends and variability of the long-term data. The circumstances are delineated under which extrapolation of retest period or shelf life beyond the period covered by long-term data can be appropriate. A decision tree is provided in Appendix A as an aid.

1. No Significant Change at Accelerated Condition

Where no significant change occurs at the accelerated condition, the retest period or shelf life would depend on the nature of the long-term and accelerated data.

a. Long-Term and Accelerated Data Showing Little or No Change Over Time and Little or No Variability

Where the long-term data and accelerated data for an attribute show little or no change over time and little or no variability, it might be apparent that the drug substance or product will remain well within the acceptance criteria for that attribute during the proposed retest period or shelf life. In these circumstances, a statistical analysis is normally considered unnecessary but justification for the omission should be provided. Justification can include a discussion of the change pattern or lack of change, relevance of the accelerated data, mass balance, and/or other supporting data as described in the parent guideline. Extrapolation of the retest period or shelf life beyond the period covered by long-term data can be proposed. The proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data.

b. Long-Term or Accelerated Data Showing Change Over Time and/or Variability

If the long-term or accelerated data for an attribute show change over time and/or variability within a factor or among factors, statistical analysis of the long-term data can be useful in establishing a retest period or shelf life. Where there are differences in stability observed among batches or among other factors (e.g., strength, container size, and/or fill) or factor combinations (e.g., strength-by-container size and/or fill) that preclude the combining of data, the proposed retest period or shelf life should not exceed the shortest period supported by any batch, other factor, or factor combination. Alternatively, where the differences are readily attributed to a particular factor (e.g., strength), different shelf lives can be assigned to different levels within the factor (e.g., different strengths). A discussion should be provided to address the cause for the differences and the overall significance of such differences on the product. Extrapolation beyond the period covered by long-term data can be proposed; however, the extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

- *Data not amenable to statistical analysis:* Where long-term data are not amenable to statistical analysis, but relevant supporting data are provided, the proposed retest period or shelf life can be up to one-and-a-half times, but should not be more than 6 months beyond, the period covered by long-term data. Relevant supporting data include satisfactory long-term data from development batches that are (1) made with a closely related formulation to, (2)

manufactured on a smaller scale than, or (3) packaged in a container closure system similar to, that of the primary stability batches.

- *Data amenable to statistical analysis:* If long-term data are amenable to statistical analysis but no analysis is performed, the extent of extrapolation should be the same as when data are not amenable to statistical analysis. However, if a statistical analysis is performed, it can be appropriate to propose a retest period or shelf life of up to twice, but not more than 12 months beyond, the period covered by long-term data, when the proposal is backed by the result of the analysis and relevant supporting data.

2. Significant Change at Accelerated Condition

Where significant change* occurs at the accelerated condition, the retest period or shelf life would depend on the outcome of stability testing at the intermediate condition, as well as at the long-term condition.

However, if phase separation of a semisolid dosage form occurs at the accelerated condition, testing at the intermediate condition should be performed. Potential interaction effects should also be considered in establishing that there is no other significant change.

a. No Significant Change at Intermediate Condition

If there is no significant change at the intermediate condition, extrapolation beyond the period covered by long-term data can be proposed; however, the extent of extrapolation would depend on whether long-term data for the attribute are amenable to statistical analysis.

- *Data not amenable to statistical analysis:* When the long-term data for an attribute are not amenable to statistical analysis, the proposed retest period or shelf life can be up to 3 months beyond the period covered by long-term data, if backed by relevant supporting data.
- *Data amenable to statistical analysis:* When the long-term data for an attribute are amenable to statistical analysis but no analysis is performed, the extent of extrapolation should be the same as when data are not amenable to statistical analysis. However, if a statistical analysis is performed, the proposed retest period or shelf life can be up to one-and-half times, but should not be more than 6 months beyond, the period covered by long-term data, when backed by statistical analysis and relevant supporting data.

b. Significant Change at Intermediate Condition

Where significant change occurs at the intermediate condition, the proposed retest period or shelf life should not exceed the period covered by long-term data. In addition, a retest period or shelf life shorter than the period covered by long-term data could be called for.

Note: The following physical changes can be expected to occur at the accelerated condition and would not be considered significant change that calls for intermediate testing if there is no other significant change:

- softening of a suppository that is designed to melt at 37°C, if the melting point is clearly demonstrated and
- failure to meet acceptance criteria for dissolution for 12 units of a gelatin capsule or gel-coated tablet if the failure can be unequivocally attributed to cross-linking.

E. Data Evaluation for Retest Period or Shelf-Life Estimation for Drug Substances or Products Intended for Storage Below Room Temperature

1. Drug Substances or Products Intended for Storage in a Refrigerator

Data from drug substances or products intended to be stored in a refrigerator should be assessed according to the same principles as described in section D for drug substances or products intended for room temperature storage, except where explicitly noted in the section below. The decision tree in Appendix A can be used as an aid.

a. No Significant Change at Accelerated Condition

Where no significant change occurs at the accelerated condition, extrapolation of retest period or shelf life beyond the period covered by long-term data can be proposed based on the principles outlined in subsection 1 of section D, except that the extent of extrapolation should be more limited.

If the long-term and accelerated data show little change over time and little variability, the proposed retest period or shelf life can be up to one-and-a-half times, but should not be more than 6 months beyond, the period covered by long-term data normally without the support of statistical analysis.

Where the long-term or accelerated data show change over time and/or variability, the proposed retest period or shelf life can be up to 3 months beyond the period covered by long-term data if (1) the long-term data are amenable to statistical analysis but a statistical analysis is not performed, or (2) the long-term data are not amenable to statistical analysis but relevant supporting data are provided.

Where the long-term or accelerated data show change over time and/or variability, the proposed retest period or shelf life can be up to one-and-a-half times, but should not be more than 6 months beyond, the period covered by long-term data if (1) the long-term data are amenable to statistical analysis and a statistical analysis is performed, and (2) the proposal is backed by the result of the analysis and relevant supporting data.

b. Significant Change at Accelerated Condition

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest period or shelf life should be based on the long-term data. Extrapolation is not considered appropriate. In addition, a retest period or shelf life shorter than the period covered by long-term data could be called for. If the long-term data show variability, verification of the proposed retest period or shelf life by statistical analysis can be appropriate.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, the proposed retest period or shelf life should be based on long-term data. Extrapolation is not considered appropriate. A retest period or shelf life shorter than the period covered by long-term data could be called for. If the long-term data show variability, verification of the proposed retest period or shelf life by statistical analysis can be appropriate. In addition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipping or handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance or product at the accelerated condition for a period shorter than 3 months.

2. Drug Substances or Products Intended for Storage in a Freezer

For drug substances or products intended for storage in a freezer, the retest period or shelf life should be based on long-term data. In the absence of an accelerated storage condition for drug substances or products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition (e.g., during shipping or handling).

3. Drug Substances or Products Intended for Storage Below −20°C

For drug substances or products intended for storage below −20°C, the retest period or shelf life should be based on long-term data and should be assessed on a case-by-case basis.

F. General Statistical Approaches

Where applicable, an appropriate statistical method should be employed to analyze the long-term primary stability data in an original application. The purpose of this analysis is to establish, with a high degree of confidence, a retest period or shelf life during which a quantitative attribute will remain within acceptance criteria for all future batches manufactured, packaged, and stored under similar circumstances.

In cases where a statistical analysis was employed to evaluate long-term data due to a change over time and/or variability, the same statistical method should also be used to analyze data from commitment batches to verify or extend the originally approved retest period or shelf life.

Regression analysis is considered an appropriate approach to evaluating the stability data for a quantitative attribute and establishing a retest period or shelf life. The nature of the relationship between an attribute and time will determine whether data should be transformed for linear regression analysis. The relationship can be represented by a linear or nonlinear function on an arithmetic or logarithmic scale. In some cases, a nonlinear regression can better reflect the true relationship.

An appropriate approach to retest period or shelf-life estimation is to analyze a quantitative attribute (e.g., assay, degradation products) by determining the earliest time at which the 95% confidence limit for the mean intersects the proposed acceptance criterion.

For an attribute known to decrease with time, the lower one-sided 95% confidence limit should be compared to the acceptance criterion. For an attribute known to increase with time, the upper one-sided 95% confidence limit should be compared to the acceptance criterion. For an attribute that can either increase or decrease, or whose direction of change is not known, two-sided 95% confidence limits should be calculated and compared to the upper and lower acceptance criteria.

The statistical method used for data analysis should take into account the stability study design to provide a valid statistical inference for the estimated retest period or shelf life. The approach described above can be used to estimate the retest period or shelf life for a single batch or for multiple batches when the data are combined after an appropriate statistical test. Examples of statistical approaches to the analysis of stability data from single or multifactor, full- or reduced-design studies are included in Appendix B. References to current literature sources can be found in Appendix B.6.

III. APPENDICES

Appendix A: Decision Tree for Data Evaluation for Retest Period or Shelf-Life Estimation for Drug Substances or Products (Excluding Frozen Products)

(See chart on page 72.)

Appendix B: Examples of Statistical Approaches to Stability Data Analysis

Linear regression, poolability tests, and statistical modeling, described below, are examples of statistical methods and procedures that can be used in the analysis of stability data that are amenable to statistical analysis for a quantitative attribute for which there is a proposed acceptance criterion.

B.1. DATA ANALYSIS FOR A SINGLE BATCH

In general, the relationship between certain quantitative attributes and time is assumed to be linear (Carstensen, 1977). Figure 12.1 shows the regression line for assay of a drug product with upper and lower acceptance criteria of 105% and 95% of label claim, respectively, with 12 months of long-term data and a proposed shelf life of 24 months. In this example, two-sided 95% confidence limits for the mean are applied because it is not known ahead of time whether the assay would increase or decrease with time (e.g., in the case of an aqueous-based product packaged in a semipermeable container). The lower confidence limit intersects the lower acceptance criterion at 30 months, while the upper confidence limit does not intersect with the upper acceptance criterion until later. Therefore, the proposed shelf life of 24 months can be supported by the statistical analysis of the assay, provided the recommendations in sections D and E are followed.

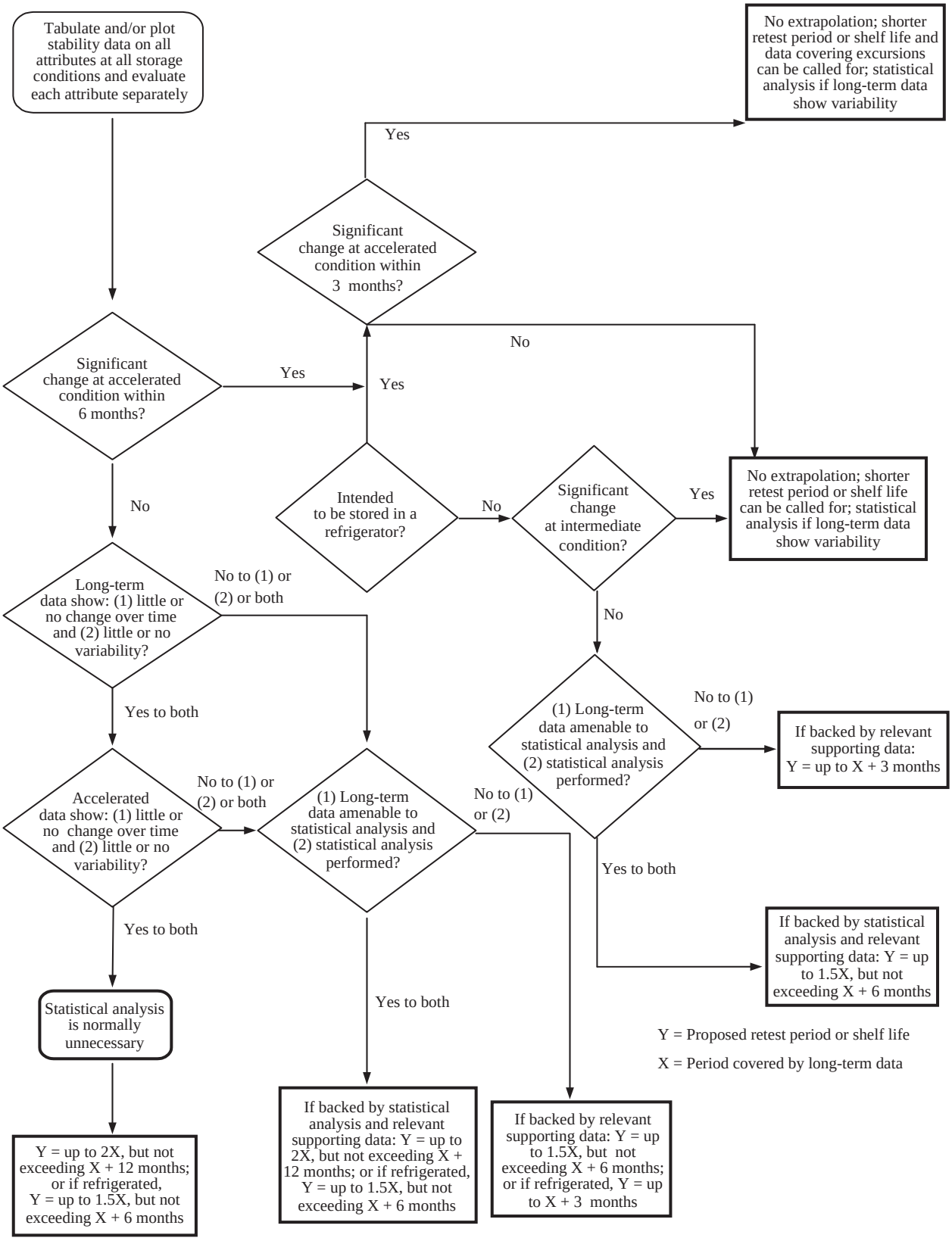
When data for an attribute with only an upper or a lower acceptance criterion are analyzed, the corresponding one-sided 95% confidence limit for the mean is recommended. Figure 12.2 shows the regression line for a degradation product in a drug product with 12 months of long-term data and a proposed shelf life of 24 months, where the acceptance criterion is not more than 1.4%. The upper one-sided 95% confidence limit for the mean intersects the acceptance criterion at 31 months. Therefore, the proposed shelf life of 24 months can be supported by statistical analysis of the degradation product data, provided the recommendations in sections D and E are followed.

If the above approach is used, the mean value of the quantitative attribute (e.g., assay, degradation products) can be expected to remain within the acceptance criteria through the end of the retest period or shelf life at a confidence level of 95%.

The approach described above can be used to estimate the retest period or shelf life for a single batch, individual batches, or multiple batches when combined after appropriate statistical tests described in sections B.2 through B.5.

B.2. DATA ANALYSIS FOR ONE-FACTOR, FULL-DESIGN STUDIES

For a drug substance or for a drug product available in a single strength and a single container size and/or fill, the retest period or shelf life is generally estimated based on the stability data from a minimum of three batches. When


Tabulate and/or plot stability data on all attributes at all storage conditions and evaluate each attribute separately
No extrapolation; shorter retest period or shelf life and data covering excursions can be called for; statistical analysis if long-term data show variability
Yes
Significant change at accelerated condition within 3 months?
No
Significant change at accelerated condition within 6 months?
Yes
Yes
No
Intended to be stored in a refrigerator?
No
Significant change at intermediate condition?
Yes
No extrapolation; shorter retest period or shelf life can be called for; statistical analysis if long-term data show variability
No
Long-term data show: (1) little or no change over time and (2) little or no variability?
No to (1) or (2) or both
Yes to both
(1) Long-term data amenable to statistical analysis and (2) statistical analysis performed?
No to (1) or (2)
If backed by relevant supporting data: Y = up to X + 3 months
Accelerated data show: (1) little or no change over time and (2) little or no variability?
No to (1) or (2) or both
(1) Long-term data amenable to statistical analysis and (2) statistical analysis performed?
No to (1) or (2)
Yes to both
If backed by statistical analysis and relevant supporting data: Y = up to 1.5X, but not exceeding X + 6 months
Yes to both
Statistical analysis is normally unnecessary
Yes to both
Y = Proposed retest period or shelf life
X = Period covered by long-term data
Y = up to 2X, but not exceeding X + 12 months; or if refrigerated, Y = up to 1.5X, but not exceeding X + 6 months
If backed by statistical analysis and relevant supporting data: Y = up to 2X, but not exceeding X + 12 months; or if refrigerated, Y = up to 1.5X, but not exceeding X + 6 months
If backed by relevant supporting data: Y = up to 1.5X, but not exceeding X + 6 months; or if refrigerated, Y = up to X + 3 months

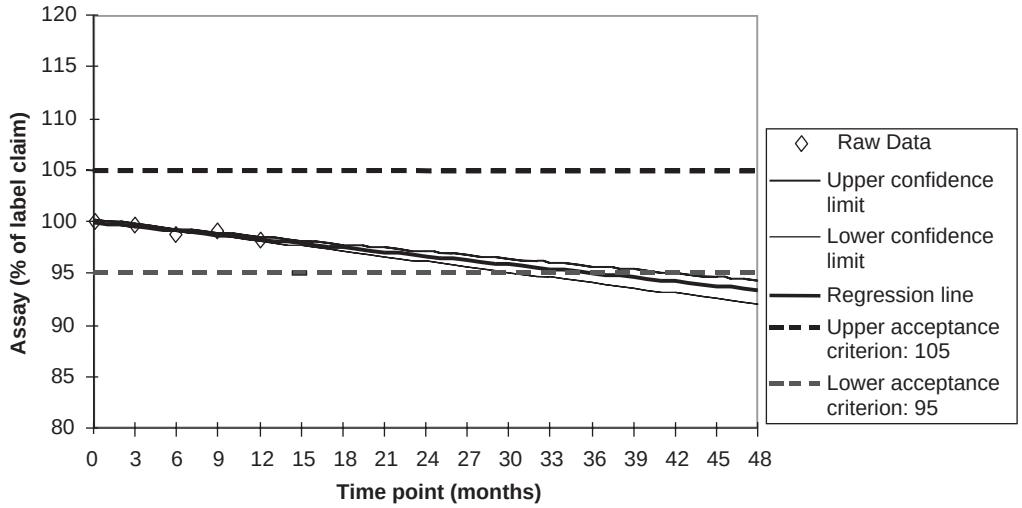


Figure 12.1 Shelf-life estimation with upper and lower acceptance criteria based on assay at 25°C/60% RH.

analyzing data from such one-factor, batch-only, full-design studies, two statistical approaches can be considered:

- The objective of the first approach is to determine whether the data from all batches support the proposed retest period or shelf life.
- The objective of the second approach, testing for poolability, is to determine whether the data from different batches can be combined for an overall estimate of a single retest period or shelf life.

B.2.1. Evaluating whether all batches support the proposed retest period or shelf life

The objective of this approach is to evaluate whether the estimated retest periods or shelf lives from all batches are longer than the one proposed. Retest periods or shelf lives for individual batches should first be estimated using the procedure described in section B.1 with individual intercepts, individual slopes, and the pooled mean square error calculated from all batches. If each batch has an estimated retest period or shelf life longer than that proposed, the proposed retest period or shelf life will generally be considered appropriate, as long as the guidance for extrapolation in sections D and E is followed. There is generally no need to perform poolability tests or identify the most reduced model. If, however, one or more of the estimated retest periods or shelf lives are shorter than that proposed, poolability tests can be performed to determine whether the batches can be combined to estimate a longer retest period or shelf life.

Alternatively, the above approach can be taken during the pooling process described in section B.2.2. If the regression lines for the batches are found to have a common slope and the estimated retest periods or shelf lives based on the common slope and individual intercepts are all longer than the proposed retest period or shelf life, there is generally no need to continue to test the intercepts for poolability.

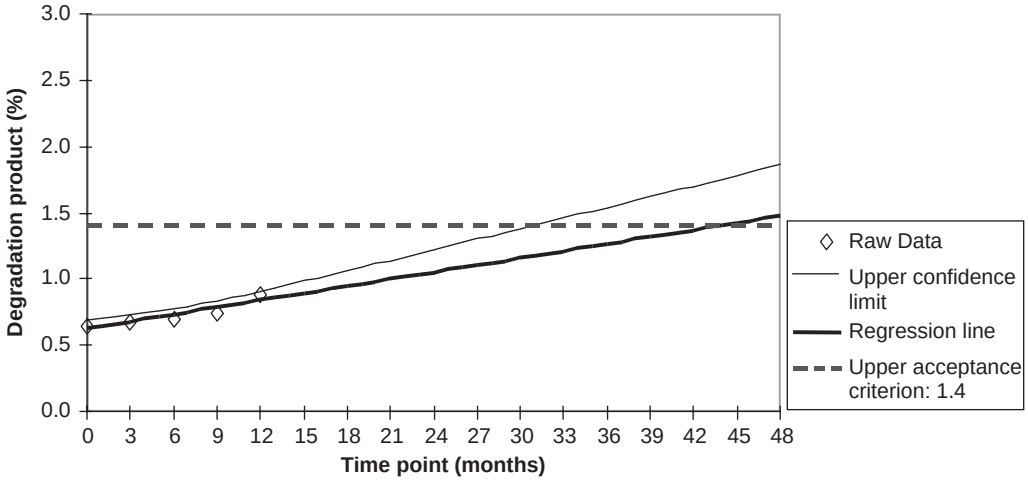


Figure 12.2 Shelf-life estimation with upper acceptance criterion based on a degradation product at 25°C/60% RH.

B.2.2. Testing for poolability of batches

B.2.2.1. Analysis of covariance

Before pooling the data from several batches to estimate a retest period or shelf life, a preliminary statistical test should be performed to determine whether the regression lines from different batches have a common slope and a common time-zero intercept. Analysis of covariance (ANCOVA) can be employed, where time is considered the covariate, to test the differences in slopes and intercepts of the regression lines among batches. Each of these tests should be conducted using a significance level of 0.25 to compensate for the expected low power of the design due to the relatively limited sample size in a typical formal stability study.

If the test rejects the hypothesis of equality of slopes (i.e., if there is a significant difference in slopes among batches), it is not considered appropriate to combine the data from all batches. The retest periods or shelf lives for individual batches in the stability study can be estimated by applying the approach described in section B.1 using individual intercepts and individual slopes and the pooled mean square error calculated from all batches. The shortest estimate among the batches should be chosen as the retest period or shelf life for all batches.

If the test rejects the hypothesis of equality of intercepts but fails to reject that the slopes are equal (i.e., if there is a significant difference in intercepts but no significant difference in slopes among the batches), the data can be combined for the purpose of estimating the common slope. The retest periods or shelf lives for individual batches in the stability study should be estimated by applying the approach described in section B.1, using the common slope and individual intercepts. The shortest estimate among the batches should be chosen as the retest period or shelf life for all batches.

If the tests for equality of slopes and equality of intercepts do not result in rejection at a level of significance of 0.25 (i.e., if there is no significant difference in slope and intercepts among the batches), the data from all batches can be combined. A single retest period or shelf life can be estimated from the combined data by using the approach described in section B.1 and applied to all batches. The estimated retest period or shelf life from the combined data is usually longer than that from individual batches because the width of the confidence limit(s) for the mean will become narrower as the amount of data increases when batches are combined.

The pooling tests described above should be performed in a proper order such that the slope terms are tested before the intercept terms. The most reduced model (i.e., individual slopes, common slope with individual intercepts, or common slope with common intercept, as appropriate) can be selected for retest period or shelf-life estimation.

B.2.2.2. Other methods

Statistical procedures other than those described above can be used in retest period or shelf-life estimation (Murphy and Weisman, 1990; Ruberg and Stegeman, 1991; Ruberg and Hsu, 1992; Shao and Chow, 1994; Yoshioka et al., 1997). For example, if it is possible to decide in advance the acceptable difference in slope or in mean retest period or shelf life among batches, an appropriate procedure for assessing the equivalence in slope or in mean retest period or shelf life can be used to determine the data poolability. However, such a procedure should be prospectively defined, evaluated, and justified and, where appropriate, discussed with the regulatory authority. A simulation study can be useful, if applicable, to demonstrate that the statistical properties of the alternative procedure selected are appropriate (Chen et al., 1997).

B.3. DATA ANALYSIS FOR MULTIFACTOR, FULL-DESIGN STUDIES

The stability of the drug product could differ to a certain degree among different factor combinations in a multifactor, full-design study. Two approaches can be considered when analyzing such data.

- The objective of the first approach is to determine whether the data from all factor combinations support the proposed shelf life.
- The objective of the second approach, testing for poolability, is to determine whether the data from different factor combinations can be combined for an overall estimate of a single shelf life.

B.3.1. Evaluating whether all factor combinations support the proposed shelf life

The objective of this approach is to evaluate whether the estimated shelf lives from all factor combinations are longer than the one proposed. A statistical model that includes all appropriate factors and factor combinations should be constructed as described in section B.3.2.2.1, and the shelf life should be estimated for each level of each factor and factor combination.

If all shelf lives estimated by the original model are longer than the proposed shelf life, further model building is considered unnecessary and the proposed shelf life will generally be appropriate as long as the guidance in sections D and E is followed. If one or more of the estimated shelf lives fall short of the proposed shelf life, model building as described in section B.3.2.2.1 can be employed. However, it is considered unnecessary to identify the final model before evaluating whether the data support the proposed shelf life. Shelf lives can be estimated at each stage of the model building process, and if all shelf lives at any stage are longer than the one proposed, further attempts to reduce the model are considered unnecessary.

This approach can simplify the data analysis of a complicated multifactor stability study compared to the data analysis described in section B.3.2.2.1.

B.3.2. Testing for poolability

The stability data from different combinations of factors should not be combined unless supported by statistical tests for poolability.

B.3.2.1. Testing for poolability of batch factor only

If each factor combination is considered separately, the stability data can be tested for poolability of batches only, and the shelf life for each nonbatch factor combination can be estimated separately by applying the procedure described in section B.2. For example, for a drug product available in two strengths and four container sizes, eight sets of data from the 2×4 strength-size combinations can be analyzed and eight separate shelf lives should be estimated accordingly. If a single shelf life is desired, the shortest estimated shelf life among all factor combinations should become the shelf life for the product. However, this approach does not take advantage of the available data from all factor combinations, thus generally resulting in shorter shelf lives than does the approach in section B.3.2.2.

B.3.2.2. Testing for poolability of all factors and factor combinations

If the stability data are tested for poolability of all factors and factor combinations and the results show that the data can be combined, a single shelf life longer than that estimated based on individual factor combinations is generally obtainable. The shelf life is longer because the width of the confidence limit(s) for the mean will become narrower as the amount of data increases when batches, strengths, container sizes and/or fills, and so forth are combined.

B.3.2.2.1. Analysis of covariance

Analysis of covariance can be employed to test the difference in slopes and intercepts of the regression lines among factors and factor combinations (Chen et al., 1997; Fairweather et al., 1995). The purpose of the procedure is to determine whether data from multiple factor combinations can be combined for the estimation of a single shelf life.

The full statistical model should include the intercept and slope terms of all main effects and interaction effects and a term reflecting the random error of measurement. If it can be justified that the higher-order interactions are very small, there is generally no need to include these terms in the model. In cases where the analytical results at the initial time point are obtained from the finished dosage form prior to its packaging, the container intercept term can be excluded from the full model because the results are common among the different container sizes and/or fills.

The tests for poolability should be specified to determine whether there are statistically significant differences among factors and factor combinations. Generally, the pooling tests should be performed in a proper order such that the slope terms are tested before the intercept terms and the interaction effects are tested before the main effects. For example, the tests can start with the slope and then the intercept terms of the highest-order interaction, and proceed to the slope and then the intercept terms of the simple main effects. The most reduced model, obtained when all remaining terms are found to be statistically significant, can be used to estimate the shelf lives.

All tests should be conducted using appropriate levels of significance. It is recommended that a significance level of 0.25 be used for batch-related terms, and a significance level of 0.05 be used for non-batch-related terms. If the tests for poolability show that the data from different factor combinations can be combined, the shelf life can be estimated according to the procedure described in section B.1 using the combined data.

If the tests for poolability show that the data from certain factors or factor combinations should not be combined, either of two alternatives can be applied: (1) a separate shelf life can be estimated for each level of the factors and of the factor combinations remaining in the model; or (2) a single shelf life can be estimated based on the shortest estimated shelf life among all levels of factors and factor combinations remaining in the model.

B.3.2.2.2. Other methods

Alternative statistical procedures to those described above can be applied (Murphy and Weisman, 1990; Ruberg and Stegeman, 1991; Ruberg and Hsu, 1992; Shao and Chow, 1994; Yoshioka et al., 1997). For example, an appropriate procedure for assessing the equivalence in slope or in mean shelf life can be used to determine the data poolability. However, such a procedure should be prospectively defined, evaluated, properly justified, and, where appropriate, discussed with the regulatory authority. A simulation study can be useful, if applicable, to demonstrate that the statistical properties of the alternative procedure selected are appropriate (Chen et al., 1997).

B.4. DATA ANALYSIS FOR BRACKETING DESIGN STUDIES

The statistical procedures described in section B.3 can be applied to the analysis of stability data obtained from a bracketing design study. For example, for a drug product available in three strengths (S1, S2, and S3) and three container sizes (P1, P2, and P3) and studied according to a bracketing design where only the two extremes of the container sizes (P1 and P3) are tested, six sets of data from the 3×2 strength-size combinations will be obtained. The data can be analyzed separately for each of the six combinations for shelf-life estimation according to section B.3.2.1, or tested for poolability prior to shelf-life estimation according to section B.3.2.2.

The bracketing design assumes that the stability of the intermediate strengths or sizes is represented by the stability at the extremes. If the statistical analysis indicates that the stability of the extreme strengths or sizes is different, the intermediate strengths or sizes should be considered no more stable than the least stable extreme. For example, if P1 from the above bracketing design is found to be less stable than P3, the shelf life for P2 should not exceed that for P1. No interpolation between P1 and P3 should be considered.

B.5. DATA ANALYSIS FOR MATRIXING DESIGN STUDIES

A matrixing design has only a fraction of the total number of samples tested at any specified time point. Therefore, it is important to ascertain that all factors and factor combinations that can have an impact on shelf-life estimation have been appropriately tested. For a meaningful interpretation of the study results and shelf-life estimation, certain assumptions should be made and justified. For instance, the assumption that the stability of the samples tested represents the stability of all samples should be valid. In addition, if the design is not balanced, some factors or factor interactions might not be estimable. Furthermore, for different levels of factor combinations to be poolable, it might have to be assumed that the higher-order factor interactions are negligible. Because it is usually impossible to statistically test the assumption that the higher-order terms are negligible, a matrixing design should be used only when it is reasonable to assume that these interactions are indeed very small, based on supporting data.

The statistical procedure described in section B.3 can be applied to the analysis of stability data obtained from a matrixing design study. The statistical analysis should clearly identify the procedure and assumptions used. For instance, the assumptions underlying the model in which interaction terms are negligible should be stated. If a preliminary test is performed for the purpose of eliminating factor interactions from the model, the procedure used should be provided and justified. The final model on which the estimation of shelf life will be based should be stated. The estimation of shelf life should be performed for each of the terms remaining in the model. The use of a matrixing design can result in an estimated shelf life shorter than that resulting from a full design.

Where bracketing and matrixing are combined in one design, the statistical procedure described in section B.3 can be applied.

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13

Stability Data Package for Registration Applications in Climatic Zones III and IV

I. INTRODUCTION

A. Objectives of the Guideline

This guideline describes an approach to broader use of the ICH guideline "Q1A(R) Stability Testing of New Drug Substances and Products" (hereafter referred to as the parent guideline) and outlines the stability data package for a new drug substance or drug product that is considered sufficient for a registration application in territories in Climatic Zones III and IV (Schumacher, 1974; Grimm, 1985).

B. Background

The parent guideline describes the stability data package for the ICH tripartite regions (EC, Japan, and the United States), which are in Climatic Zones I and II. The parent guideline can be followed to generate stability data packages for registration applications in other countries or regions in Zones I and II. For territories in Climatic Zones III and IV, the data package as described in the parent guideline can be considered applicable except for certain storage conditions. An approach for classification of countries according to Climatic Zones I, II, III, and IV can be found in the literature (Dietz et al., 1993; Grimm, 1998).

The World Health Organization (WHO) has published a guideline "Stability testing of pharmaceutical products containing well-established drug substances in conventional dosage forms" (WHO Technical Report Series, No 863, Annex 5), updated in the Report of the thirty-seventh meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations, Geneva, 22–26 October 2001. The WHO guideline describes stability testing recommendations, including storage conditions for all four climatic zones.

The stability testing recommendations in this guideline are based on the parent guideline and the WHO guideline. To harmonize with the long-term storage condition for Zones III and IV, the intermediate storage condition in the General Case for Zones I and II in the parent guideline is changed to 30°C ± 2°C/65% RH ± 5% RH. This condition of 30°C ± 2°C/65% RH ± 5% RH can also be a suitable alternative to 25°C ± 2°C/60% RH ± 5% RH as the long-term storage condition for Zones I and II.

C. Scope of the Guideline

This document is an annex to the parent guideline and recommends the long-term storage condition for stability testing of a new drug substance or drug product for a registration application in territories in Climatic Zones III and IV.

II. GUIDELINES

A. Continuity with the Parent Guideline

This guideline should be used in conjunction with the parent guideline and subsequently published annexes (Q1B, Q1C, Q1D, Q1E, Q5C). The recommendations in the parent guideline and annexes should be followed unless specific alternatives are described within this guideline. The following sections of the parent guideline can be considered common to any territory in the world and are not reproduced here.

- Stress testing
- Selection of batches
- Container closure system
- Specification
- Testing frequency
- Storage conditions for drug substance or product in a refrigerator
- Storage conditions for drug substance or product in a freezer
- Stability commitment
- Evaluation
- Statements/labelling

B. Storage Conditions

1. General Case

For the "General case" (as described in the parent guideline), the recommended long-term and accelerated storage conditions for Climatic Zones III and IV are shown below:

Study	Storage Condition	Minimum Time Period Covered by Data at Submission
Long-term	30°C ± 2°C/65% RH ± 5% RH	12 mo
Accelerated	40°C ± 2°C/75% RH ± 5% RH	6 mo

No intermediate storage condition for stability studies is recommended for Climatic Zones III and IV. Therefore, the intermediate storage condition is not relevant when the principles of retest period or shelf life extrapolation described in Q1E are applied.

2. Aqueous-Based Drug Products Packaged in Semipermeable Containers

For aqueous-based drug products packaged in semipermeable containers (as described in the parent guideline), the recommended long-term and accelerated storage conditions for Climatic Zones III and IV are shown below:

Study	Storage Condition	Minimum Time Period Covered by Data at Submission
Long-term	30°C ± 2°C/35% RH ± 5% RH	12 mo
Accelerated	40°C ± 2°C/not more than 25% RH ± 5% RH	6 mo

As described in the parent guideline, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured

at an alternative relative humidity at the same temperature by a water loss rate ratio (see table below for examples).

The ratio of water loss rates at a given temperature is calculated by the general formula (100 – reference% RH)/(100 – alternative% RH).

Alternative Relative Humidity	Reference Relative Humidity	Ratio of Water Loss Rates at a Given Temperature
65% RH	35% RH	1.9
75% RH	25% RH	3.0

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can be used. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated.

3. Tests at Elevated Temperature and/or Extremes of Humidity

Special transportation and climatic conditions outside the storage conditions recommended in this guideline should be supported by additional data. For example, these data can be obtained from studies on one batch of drug product conducted for up to 3 months at 50°C/ambient humidity to cover extremely hot and dry conditions and at 25°C/80% RH to cover extremely high humidity conditions (Grimm, 1985).

Stability testing at a high humidity condition, for example, 25°C/80% RH, is recommended for solid dosage forms in water-vapor permeable packaging, for example, tablets in PVC/aluminum blisters, intended to be marketed in territories with extremely high humidity conditions in Zone IV. However, for solid dosage forms in primary containers designed to provide a barrier to water vapor, for example, aluminum/aluminum blisters, stability testing at a storage condition of extremely high humidity is not considered necessary.

C. Additional Considerations

If it cannot be demonstrated that the drug substance or drug product will remain within its acceptance criteria when stored at 30°C ± 2°C/65% RH ± 5% RH for the duration of the proposed retest period or shelf life, the following options should be considered: (1) a reduced retest period or shelf life, (2) a more protective container closure system, or (3) additional cautionary statements in the labeling.

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Schumacher P (1974). Aktuelle Fragen zur Haltbarkeit von Arzneimitteln [Current questions on drug stability]. Pharm Ztg 119:321–324.

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EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use

I. INTRODUCTION

The pharmaceutical industry of the European Union maintains high standards of quality assurance in the development, manufacture, and control of medicinal products. A system of Marketing Authorizations ensures that all medicinal products are assessed by a competent authority to ensure compliance with contemporary requirements of safety, quality, and efficacy. A system of manufacturing authorizations ensures that all products authorized on the European market are manufactured only by authorized manufacturers, whose activities are regularly inspected by the competent authorities. Manufacturing authorizations are required by all pharmaceutical manufacturers in the European Community whether the products are sold within or outside the Community.

Two directives laying down principles and guidelines of good manufacturing practice (GMP) for medicinal products were adopted by the Commission. Directive 2003/94/EC applies to medicinal products for human use and Directive 91/412/EEC for veterinary use. Detailed guidelines in accordance with those principles are published in the *Guide to Good Manufacturing Practice*, which will be used in assessing applications for manufacturing authorizations and as a basis for inspection of manufacturers of medicinal products.

The principles of GMP and the detailed guidelines are applicable to all operations which require the authorization referred to in Article 40 of Directive 2001/83/EC and in Article 44 of Directive 2001/82/EC, as amended by Directives 2004/27/EC and 2004/28/EC, respectively. They are also relevant for all other large-scale pharmaceutical manufacturing processes, such as that undertaken in hospitals, and for the preparation of products for use in clinical trials.

All member states and the industry agreed that the GMP requirements applicable to the manufacture of veterinary medicinal products are the same as those applicable to the manufacture of medicinal products for human use. Certain detailed adjustments to the GMP guidelines are set out in two annexes specific to veterinary medicinal products and to immunological veterinary medicinal products.

The guide is presented in two parts of basic requirements and specific annexes. Part I covers GMP principles for the manufacture of medicinal products. Part II covers GMP for active substances used as starting materials.

Chapters of Part I on "basic requirements" are headed by principles as defined in Directives 2003/94/EC and 91/412/EEC. Chapter 1 on Quality Management outlines the fundamental concept of quality assurance as applied to the manufacture of medicinal products. Thereafter, each chapter has a principle outlining the quality assurance objectives of that chapter and a text which provides sufficient detail for manufacturers to be made aware of the essential matters to be considered when implementing the principle.

Part II was established newly on the basis of a guideline developed on the level of ICH and published as ICH Q7a on "active pharmaceutical ingredients," which was implemented as GMP Annex 18 for voluntary application in 2001. According to the revised Article 47 and Article 51, respectively, of the Directive 2001/83/EC and Directive 2001/82/EC, as amended, detailed guidelines on the principles of GMP for active substances used as starting materials shall be adopted and published by the Commission. The former Annex 18 has been replaced by the new Part II of the GMP guide, which has an extended application both for the human and the veterinary sector.

In addition to the general matters of good manufacturing practice outlined in Part I and II, a series of annexes providing detail about specific areas of activity is included. For some manufacturing processes, different annexes will apply simultaneously (e.g., annex on sterile preparations and on radiopharmaceuticals and/or on biological medicinal products).

GMP Part I, Chapter 1 on Quality Management, has been revised to include aspects of quality risk management within the quality system framework. In future revisions of the guide, the opportunity will be taken to introduce quality risk management elements when appropriate.

The new GMP Annex 20, which corresponds to the ICH Q9 guideline, provides guidance on a systematic approach to quality risk management leading to compliance with GMP and other quality requirements. It includes principles to be used and options for processes, methods, and tools, which may be used when applying a formal quality risk management approach. While the GMP guide is primarily addressed to manufacturers, the ICH Q9 guideline has relevance for other quality guidelines and includes specific sections for regulatory agencies. However, for reasons of coherence and completeness the ICH Q9 guideline has been transferred completely into GMP Annex 20.

A glossary of some terms used in the guide has been incorporated after the annexes.

The guide is not intended to cover security aspects for the personnel engaged in manufacture. This may be particularly important in the manufacture of certain medicinal products such as highly active, biological and radioactive medicinal products. However, those aspects are governed by other provisions of Community or national law.

Throughout the guide it is assumed that the requirements of the Marketing Authorization relating to the safety, quality, and efficacy of the products are systematically incorporated into all the manufacturing, control, and release for sale arrangements of the holder of the manufacturing authorization.

The manufacture of medicinal products has for many years taken place in accordance with guidelines for Good Manufacturing Practice and the manufacture of medicinal products is not governed by CEN/ISO standards. Harmonized standards as adopted by the European standardization organizations CEN/ISO may be used at industry's discretion

as a tool for implementing a quality system in the pharmaceutical sector. The CEN/ISO standards have been considered but the terminology of these standards has not been implemented in this edition. It is recognized that there are acceptable methods, other than those described in the guide, which are capable of achieving the principles of quality assurance. The guide is not intended to place any restraint upon the development of any new concepts or new technologies which have been validated and which provide a level of quality assurance at least equivalent to those set out in this guide. With its principles, methods, and tools, Annex 20 provides a systematic approach, which may be used to demonstrate such equivalence.

The GMP guide will be regularly revised. Revisions will be made publicly available on the Web site of the European Commission (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev4.htm).

Part I: Chapter 1: Quality Management

Principle

The holder of a manufacturing authorization must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorization, and do not place patients at risk due to inadequate safety, quality, or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers, and by the distributors. To achieve the quality objective reliably there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice, Quality Control, and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance system should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment, and facilities. There are additional legal responsibilities for the holder of the manufacturing authorization and for the Qualified Person(s).

The basic concepts of Quality Assurance, Good Manufacturing Practice, Quality Control, and Quality Risk Management are interrelated. They are described here in order to emphasize their relationships and their fundamental importance to the production and control of medicinal products.

Quality Assurance

1.1 Quality Assurance is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this guide.

The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that

(i) medicinal products are designed and developed in a way that takes account of the requirements of GMP;
(ii) production and control operations are clearly specified and GMP adopted;
(iii) managerial responsibilities are clearly specified;
(iv) arrangements are made for the manufacture, supply, and use of the correct starting and packaging materials;
(v) all necessary controls on intermediate products, and any other in-process controls and validations are carried out;
(vi) the finished product is correctly processed and checked, according to the defined procedures;
(vii) medicinal products are not sold or supplied before a Qualified Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorization and any other regulations relevant to the production, control, and release of medicinal products;
(viii) satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed, and subsequently, handled so that quality is maintained throughout their shelf life; and
(ix) there is a procedure for Self-Inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Quality Assurance system.

Good Manufacturing Practice for Medicinal Products (GMP)

1.2 Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorization or product specification.

Good Manufacturing Practice is concerned with both production and Quality Control. The basic requirements of GMP are as follows:

(i) All manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications.
(ii) Critical steps of manufacturing processes and significant changes to the process are validated.
(iii) All necessary facilities for GMP are provided including
appropriately qualified and trained personnel;
adequate premises and space;
suitable equipment and services;
correct materials, containers, and labels;
approved procedures and instructions; and
suitable storage and transport.
(iv) Instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided.
(v) Operators are trained to carry out procedures correctly.
(vi) Records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated.
(vii) Records of manufacture including distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form.
(viii) The distribution (wholesaling) of the products minimizes any risk to their quality.
(ix) A system is available to recall any batch of product, from sale or supply.
(x) Complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

Quality Control

1.3 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications, and testing, and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of Quality Control are as follows:

(i) Adequate facilities, trained personnel, and approved procedures are available for sampling, inspecting, and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.
(ii) Samples of starting materials, packaging materials, intermediate products, bulk products, and finished products are taken by personnel and by methods approved by Quality Control.
(iii) Test methods are validated.
(iv) Records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting, and testing procedures were actually carried out. Any deviations are fully recorded and investigated.
(v) The finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorization, are of the purity required, and are enclosed within their proper containers and correctly labeled.
(vi) Records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures.
(vii) No batch of product is released for sale or supply prior to certification by a Qualified Person that it is in accordance with the requirements of the relevant authorizations.
(viii) Sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

Product Quality Review

1.4 Regular periodic or rolling quality reviews of all licensed medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends, and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least

(i) a review of starting materials including packaging materials used in the product, especially those from new sources;
(ii) a review of critical in-process controls and finished product results;
(iii) a review of all batches that failed to meet established specification(s) and their investigation;
(iv) a review of all significant deviations or nonconformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken;
(v) a review of all changes carried out to the processes or analytical methods;
(vi) a review of Marketing Authorization variations submitted/granted/refused, including those for third country (export only) dossiers;
(vii) a review of the results of the stability monitoring program and any adverse trends;
(viii) a review of all quality-related returns, complaints, and recalls and the investigations performed at the time;
(ix) a review of adequacy of any other previous product process or equipment corrective actions;
(x) for new Marketing Authorizations and variations to Marketing Authorizations, a review of postmarketing commitments;
(xi) the qualification status of relevant equipment and utilities, for example, HVAC, water, compressed gases; and
(xii) a review of any contractual arrangements as defined in Chapter 7 to ensure that they are up-to-date.

The manufacturer and Marketing Authorization holder should evaluate the results of this review, where different, and an assessment made of whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type, for example, solid dosage forms, liquid dosage forms, sterile products, where scientifically justified.

Where the Marketing Authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The Qualified Person responsible for final batch certification together with the Marketing Authorization holder should ensure that the quality review is performed in a timely manner and is accurate.

Quality Risk Management

1.5 Quality Risk Management is a systematic process for the assessment, control, communication, and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

1.6 The Quality Risk Management system should ensure that

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process, and ultimately links to the protection of the patient and
- the level of effort, formality, and documentation of the Quality Risk Management process is commensurate with the level of risk.

Chapter 2: Personnel

Principle

The establishment and maintenance of a satisfactory system of Quality Assurance and the correct manufacture of medicinal products relies upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and

recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

General

2.1 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

2.2 The manufacturer must have an organization chart. People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.

Key Personnel

2.3 Key Personnel include the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the duties described in Article 51 of Directive 2001/83/EC1, the Qualified Person(s) designated for the purpose. Normally, key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organizations, it may be necessary to delegate some of the functions listed in 2.5, 2.6, and 2.7.

2.4 The duties of the Qualified Person(s) are fully described in Article 51 of Directive 2001/83/EC, and can be summarized as follows:

(a) For medicinal products manufactured within the European Community, a Qualified Person must ensure that each batch has been produced and tested/checked in accordance with the directives and the Marketing Authorization (2).
(b) For medicinal products manufactured outside the European Community, a Qualified Person must ensure that each imported batch has undergone, in the importing country, the testing specified in paragraph 1 (b) of Article 51; Article 55 of Directive 2001/82/EC (2) According to Directive 75/319/EEC (now codified Directive 2001/83/EC) and the Ruling (Case 247/81) of the Court of Justice of the European Communities, medicinal products which have been properly controlled in the EU by a Qualified Person do not have to be recontrolled or rechecked in any other member state of the Community.
(c) A Qualified Person must certify in a register or equivalent document, as operations are carried out and before any release, that each production batch satisfies the provisions of Article 51. The persons responsible for these duties must meet the qualification requirements laid down in Article 493 of the same Directive, they shall be permanently and continuously at the disposal of the holder of the manufacturing authorization to carry out their responsibilities. Their responsibilities may be delegated, but only to other Qualified Person(s).

2.5 The head of the Production Department generally has the following responsibilities:

(i) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
(ii) to approve the instructions relating to production operations and to ensure their strict implementation;
(iii) to ensure that the production records are evaluated and signed by an authorized person before they are sent to the Quality Control Department;
(iv) to check the maintenance of his department, premises, and equipment;
(v) to ensure that the appropriate validations are done; and
(vi) to ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

2.6 The head of the Quality Control Department generally has the following responsibilities:

(i) to approve or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk and finished products;
(ii) to evaluate batch records;
(iii) to ensure that all necessary testing is carried out;
(iv) to approve specifications, sampling instructions, test methods, and other Quality Control procedures;
(v) to approve and monitor any contract analysts;
(vi) to check the maintenance of his department, premises, and equipment;
(vii) to ensure that the appropriate validations are done; and
(viii) to ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

Other duties of the Quality Control Department are summarized in Chapter 6.

2.7 The heads of Production and Quality Control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, subject to any national regulations,

the authorization of written procedures and other documents, including amendments;
the monitoring and control of the manufacturing environment;
plant hygiene;
process validation;
training;
the approval and monitoring of suppliers of materials;
the approval and monitoring of contract manufacturers;
the designation and monitoring of storage conditions for materials and products;
the retention of records;
the monitoring of compliance with the requirements of Good Manufacturing Practice; and
the inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality.

Training

2.8 The manufacturer should provide training for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance, and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.9 Besides the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programs should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.

2.10 Personnel working in areas where contamination is a hazard, for example, clean areas or areas where highly active, toxic, infectious, or sensitizing materials are handled, should be given specific training.

2.11 Visitors or untrained personnel should, preferably, not be taken into the production and Quality Control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

2.12 The concept of Quality Assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

Personnel Hygiene

2.13 Detailed hygiene programs should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices, and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production and control areas. Hygiene programs should be promoted by management and widely discussed during training sessions.

2.14 All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.

2.15 Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.

2.16 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

2.17 Eating, drinking, chewing, or smoking, or the storage of food, drink, smoking materials, or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected should be forbidden.

2.18 Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.

2.19 Personnel should be instructed to use the handwashing facilities.

2.20 Any specific requirements for the manufacture of special groups of products, for example, sterile preparations, are covered in the annexes.

Chapter 3: Premises and Equipment

Principle

Premises and equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt, and in general, any adverse effect on the quality of products.

Premises

General

3.1 Premises should be situated in an environment which, when considered together with measures to protect the manufacture, presents minimal risk of causing contamination of materials or products.

3.2 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3.3 Lighting, temperature, humidity, and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage or the accurate functioning of equipment.

3.4 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.5 Steps should be taken in order to prevent the entry of unauthorized people. Production, storage, and Quality Control areas should not be used as a right of way by personnel who do not work in them.

Production Area

3.6 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitizing materials (e.g., penicillins) or biological preparations (e.g., from live microorganisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs and nonmedicinal products, should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

3.7 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.8 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

3.9 Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors, and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

3.10 Pipework, light fittings, ventilation points, and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

3.11 Drains should be of adequate size and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

3.12 Production areas should be effectively ventilated, with air-control facilities (including temperature and, where necessary, humidity and filtration) appropriate both to the products handled, to the operations undertaken within them, and to the external environment.

3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.

3.14 In cases where dust is generated (e.g., during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross-contamination and facilitate cleaning.

3.15 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

3.16 Production areas should be well lit, particularly where visual controls are carried out.

3.17 In-process controls may be carried out within the production area provided they do not carry any risk for the production.

Storage Areas

3.18 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk and finished products, and products in quarantine, released, rejected, returned, or recalled.

3.19 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g., temperature, humidity), these should be provided, checked, and monitored.

3.20 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

3.21 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

3.22 There should normally be a separate sampling area for starting materials. If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

3.23 Segregated areas should be provided for the storage of rejected, recalled, or returned materials or products.

3.24 Highly active materials or products should be stored in safe and secure areas.

3.25 Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

Quality Control Areas

3.26 Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals, and radioisotopes, which should also be separated from each other.

3.27 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

3.28 Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, and so forth.

3.29 Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

Ancillary Areas

3.30 Rest and refreshment rooms should be separate from other areas.

3.31 Facilities for changing clothes, washing, and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.

3.32 Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

3.33 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

Equipment

3.34 Manufacturing equipment should be designed, located, and maintained to suit its intended purpose.

3.35 Repair and maintenance operations should not present any hazard to the quality of the products.

3.36 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.

3.37 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.

3.38 Equipment should be installed in such a way as to prevent any risk of error or of contamination.

3.39 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.

3.40 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.

3.41 Measuring, weighing, recording, and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.

3.42 Fixed pipework should be clearly labeled to indicate the contents and, where applicable, the direction of flow.

3.43 Distilled, deionized, and, where appropriate, other water pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

3.44 Defective equipment should, if possible, be removed from production and Quality Control areas, or at least be clearly labeled as defective.

Chapter 4: Documentation

Principle

Good documentation constitutes an essential part of the Quality Assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications, Manufacturing Formulae and instructions, procedures, and records must be free from

errors and available in writing. The legibility of documents is of paramount importance.

General

4.1 *Specifications* describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Manufacturing Formulae, Processing, and Packaging Instructions state all the starting materials used and lay down all processing and packaging operations.

Procedures give directions for performing certain operations, for example, cleaning, clothing, environmental control, sampling, testing, equipment operation.

Records provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product.

4.2 Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of the manufacturing and Marketing Authorization dossiers.

4.3 Documents should be approved, signed, and dated by appropriate and authorized persons.

4.4 Documents should have unambiguous contents; title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

4.5 Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.

4.6 Documents should not be handwritten, although, where documents require the entry of data, these entries may be made in clear, legible, and indelible handwriting. Sufficient space should be provided for such entries.

4.7 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

4.8 The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable. They should be retained for at least one year after the expiry date of the finished product.

4.9 Data may be recorded by electronic data processing systems or photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer and there should be a record of changes and deletions; access should be restricted by passwords or other means and the result of entry of critical data should be independently checked. Batch records electronically stored should be protected by backup transfer on magnetic tape, microfilm, paper, or other means. It is particularly important that the data are readily available throughout the period of retention.

4.10 There should be appropriately authorized and dated specifications for starting and packaging materials, and finished products; where appropriate, they should be also available for intermediate or bulk products.

Specifications for Starting and Packaging Materials

4.11 Specifications for starting and primary or printed packaging materials should include, if applicable,

- a description of the materials, including
- the designated name and the internal code reference;
- the reference, if any, to a pharmacopoeia monograph;
- the approved suppliers and, if possible, the original producer of the products;
- (a) specimen of printed materials, (b) directions for sampling and testing or reference to procedures, (c) qualitative and quantitative requirements with acceptance limits, and (d) storage conditions and precautions; and
- the maximum period of storage before reexamination.

Specifications for Intermediate and Bulk Products

4.12 Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used for the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for Finished Products

4.13 Specifications for finished products should include (a) the designated name of the product and the code reference where applicable; (b) the formula or a reference to; (c) a description of the pharmaceutical form and package details; (d) directions for sampling and testing or a reference to procedures; e) the qualitative and quantitative requirements, with the acceptance limits; (f) the storage conditions and any special handling precautions, where applicable; and (g) the shelf-life.

Manufacturing Formula and Processing Instructions

Formally authorized Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured. They are often combined in one document.

4.14 The Manufacturing Formula should include (a) the name of the product, with a product reference code relating to its specification; (b) a description of the pharmaceutical form, strength of the product, and batch size; (c) a list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material; mention should be made of any substance that may disappear in the course of processing; and (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

4.15 The Processing Instructions should include (a) a statement of the processing location and the principal equipment to be used; (b) the methods, or reference to the methods, to be used for preparing the critical equipment (e.g., cleaning, assembling, calibrating, sterilizing); (c) detailed stepwise processing instructions (e.g., checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures); (d) the instructions for any in-process controls with their limits; (e) where necessary, the requirements for bulk storage of the products; including the container, labeling, and special storage conditions where applicable; and (f) any special precautions to be observed.

Packaging Instructions

4.16 There should be formally authorized Packaging Instructions for each product, pack size, and type. These should normally include, or have a reference to, the following:

(a) name of the product;
(b) description of its pharmaceutical form, and strength where applicable;

(c) the pack size expressed in terms of the number, weight, or volume of the product in the final container;
(d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes, and types, with the code or reference number relating to the specifications of each packaging material;
(e) where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;
(f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
(g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used; and
(h) details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Records

4.17 A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions. The method of preparation of such records should be designed to avoid transcription errors. The record should carry the number of the batch being manufactured.

Before any processing begins, there should be recorded checks that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that equipment is clean and suitable for use.

During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations:

(a) the name of the product;
(b) dates and times of commencement, of significant intermediate stages and of completion of production;
(c) name of the person responsible for each stage of production;
(d) initials of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g., weighing);
(e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
(f) any relevant processing operation or event and major equipment used;
(g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
(h) the product yield obtained at different and pertinent stages of manufacture; and
(i) notes on special problems including details, with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions.

Batch Packaging Records

4.18 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions and the method of preparation of such records should be designed to avoid transcription errors. The record should carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained.

Before any packaging operation begins, there should be recorded checks that the equipment and work station are clear of previous products, documents, or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.

The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

(a) the name of the product;
(b) the date(s) and times of the packaging operations;
(c) the name of the responsible person carrying out the packaging operation;
(d) the initials of the operators of the different significant steps;
(e) records of checks for identity and conformity with the packaging instructions including the results of in-process controls;
(f) details of the packaging operations carried out, including references to equipment and the packaging lines used;
(g) whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating, and any additional overprinting;
(h) notes on any special problems or unusual events including details, with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions; and
(i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed, or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

Procedures and Records

Receipt

4.19 There should be written procedures and records for the receipt of each delivery of each starting and primary and printed packaging material.

4.20 The records of the receipts should include (a) the name of the material on the delivery note and the containers; (b) the "in-house" name and/or code of material (if different from a); (c) date of receipt; (d) supplier's name and, if possible, manufacturer's name; (e) manufacturer's batch or reference number; (f) total quantity, and number of containers received; (g) the batch number assigned after receipt; and (h) any relevant comment (e.g., state of the containers).

4.21 There should be written procedures for the internal labeling, quarantine and storage of starting materials, packaging materials, and other materials, as appropriate.

Sampling

4.22 There should be written procedures for sampling, which include the person(s) authorized to take samples, the methods and equipment to be used, the amounts to be taken, and any precautions to be observed to avoid contamination of the material or any deterioration in its quality (see Chapter 6, item 13).

Testing

4.23 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded (see Chapter 6, item 17).

Other

4.24 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by the Qualified Person(s) in accordance with the requirements of Article 51 of Directive 2001/83/EC[1].

4.25 Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

4.26 There should be written procedures and the associated records of actions taken or conclusions reached, where appropriate, for

— validation;
— equipment assembly and calibration;
— maintenance, cleaning, and sanitation;
— personnel matters including training, clothing, and hygiene;
— environmental monitoring;
— pest control;
— complaints;
— recalls; and
— returns.

4.27 Clear operating procedures should be available for major items of manufacturing and test equipment.

4.28 Logbooks should be kept for major or critical equipment recording, as appropriate, any validations, calibrations, maintenance, cleaning or repair operations, including the dates and identity of people who carried these operations out.

4.29 Logbooks should also record in chronological order the use of major or critical equipment and the areas where the products have been processed.

Chapter 5: Production

Principle

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and Marketing Authorizations.

General

5.1 Production should be performed and supervised by competent people.

5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labeling, dispensing, processing, packaging, and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled with the prescribed data.

5.4 Damage to containers and any other problem which might adversely affect the quality of a material should be investigated, recorded, and reported to the Quality Control Department.

5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

5.6 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

5.7 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

5.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

5.9 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

5.10 At every stage of processing, products and materials should be protected from microbial and other contamination.

5.11 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials.

5.12 At all times during processing, all materials, bulk containers, major items of equipment, and, where appropriate, rooms used should be labeled or otherwise identified with an indication of the product or material being processed, its strength (where applicable), and batch number. Where applicable, this indication should also mention the stage of production and batch number.

5.13 Labels applied to containers, equipment, or premises should be clear, unambiguous, and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colors to indicate status (e.g., quarantined, accepted, rejected, clean, under processing, etc.).

5.14 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

5.15 Any deviation from instructions or procedures should be avoided as far as possible. If a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.

5.16 Access to production premises should be restricted to authorized personnel.

5.17 Normally, the production of nonmedicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

Prevention of Cross-Contamination in Production

5.18 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapors, sprays, or organisms from materials and products in process, from residues on equipment, and from "operators" clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses, and/or over a long time.

5.19 Cross-contamination should be avoided by appropriate technical or organizational measures, for example, (a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations, and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning; (b) providing appropriate air locks and air extraction; (c) minimizing the risk of contamination caused by recirculation or reentry

of untreated or insufficiently treated air; (d) keeping protective clothing inside areas where products with special risk of cross-contamination are processed; (e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination; (f) using "closed systems" of production; and (g) testing for residues and use of cleaning status labels on equipment.

5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

Validation

5.21 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

5.22 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.23 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.

5.24 Processes and procedures should undergo periodic critical revalidation to ensure that they remain capable of achieving the intended results.

Starting Materials

5.25 The purchase of starting materials is an important operation which should involve staff who have a particular and thorough knowledge of the suppliers.

5.26 Starting materials should only be purchased from approved suppliers named in the relevant specification and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labeling, and packaging requirements, as well as complaints and rejection procedures are discussed with the manufacturer and the supplier.

5.27 For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.

5.28 lf one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing, and release.

5.29 Starting materials in the storage area should be appropriately labeled (see Chapter 5, item 13). Labels should bear at least the following information:

— the designated name of the product and the internal code reference where applicable;
— a batch number given at receipt;
— where appropriate, the status of the contents (e.g., in quarantine, on test, released, rejected); and
— where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerized storage systems are used, all the above information need not necessarily be in a legible form on the label.

5.30 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Chapter 6, item 13).

5.3l Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used.

5.32 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers.

5.33 Each dispensed material and its weight or volume should be independently checked and the check recorded.

5.34 Materials dispensed for each batch should be kept together and conspicuously labeled as such. Processing operations: intermediate and bulk products.

5.35 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, or documents not required for the current operation.

5.36 Intermediate and bulk products should be kept under appropriate conditions.

5.37 Critical processes should be validated (see "VALIDATION" in this Chapter).

5.38 Any necessary in-process controls and environmental controls should be carried out and recorded.

5.39 Any significant deviation from the expected yield should be recorded and investigated.

Packaging Materials

5.40 The purchase, handling, and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

5.41 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorized personnel following an approved and documented procedure.

5.42 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

5.43 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

Packaging Operations

5.44 When setting up a program for the packaging operations, particular attention should be given to minimizing the risk of cross-contamination, mix-ups, or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

5.45 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines, and other equipment are clean and free from any products, materials, or documents previously used, if these are not required for the current operation. The line clearance should be performed according to an appropriate checklist.

5.46 The name and batch number of the product being handled should be displayed at each packaging station or line.

5.47 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity, and conformity with the Packaging Instructions.

5.48 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

5.49 Normally, filling and sealing should be followed as quickly as possible by labeling. If it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.

5.50 The correct performance of any printing operation (e.g., code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be rechecked at regular intervals.

5.51 Special care should be taken when using cut labels and when overprinting is carried out off-line. Rollfeed labels are normally preferable to cut labels, in helping to avoid mix-ups.

5.52 Checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly.

5.53 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.54 Online control of the product during packaging should include at least checking the following:

(a) general appearance of the packages;
(b) whether the packages are complete;
(c) whether the correct products and packaging materials are used;
(d) whether any overprinting is correct; and
(e) correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

5.55 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation, and approval by authorized personnel. Detailed record should be kept of this operation.

5.56 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

5.57 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

Finished Products

5.58 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

5.59 The evaluation of finished products and documentation which is necessary before release of product for sale are described in Chapter 6 (Quality Control).

5.60 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

Rejected, Recovered, and Returned Materials

5.61 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorized personnel.

5.62 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. Record should be kept of the reprocessing.

5.63 The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

5.64 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.65 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for resale, relabeling, or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken should be appropriately recorded.

Chapter 6: Quality Control

Principle

Quality Control is concerned with sampling, specifications, and testing as well as the organization, documentation, and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control (see also Chapter 1).

General

6.1 Each holder of a manufacturing authorization should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

6.2 The principal duties of the head of Quality Control are summarized in Chapter 2. The Quality Control Department as a whole will also have other duties, such as to establish, validate, and implement all Quality Control procedures, keep the reference samples of materials and products, ensure the correct labeling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, and so forth. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of

in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification, and examination of the final finished pack.

6.4 Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

Good Quality Control Laboratory Practice

6.5 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3.

6.6 The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in Chapter 7, Contract Analysis, can be accepted for particular reasons, but this should be stated in the Quality Control records.

Documentation

6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:

- specifications;
- sampling procedures;
- testing procedures and records (including analytical worksheets and/or laboratory notebooks);
- analytical reports and/or certificates;
- data from environmental monitoring, where required;
- validation records of test methods, where applicable; and
- procedures for and records of the calibration of instruments and maintenance of equipment.

6.8 Any Quality Control documentation relating to a batch record should be retained for one year after the expiry date of the batch and at least 5 years after the certification referred to in Article 51(3) of Directive 2001/83/EC.

6.9 For some kinds of data (e.g., analytical tests results, yields, environmental controls), it is recommended that records are kept in a manner permitting trend evaluation.

6.10 In addition to the information which is part of the batch record, other original data such as laboratory notebooks and/or records should be retained and readily available.

Sampling

6.11 The sample taking should be done in accordance with approved written procedures that describe

- the method of sampling;
- the equipment to be used;
- the amount of the sample to be taken;
- instructions for any required subdivision of the sample;
- the type and condition of the sample container to be used;
- the identification of containers sampled;
- any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
- the storage conditions; and
- instructions for the cleaning and storage of sampling equipment.

6.12 Reference samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g., beginning or end of a process).

6.13 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling, and the containers from which samples have been drawn.

6.14 Further guidance on reference and retention samples is given in Annex 19.

Testing

6.15 Analytical methods should be validated. All testing operations described in the Marketing Authorization should be carried out according to the approved methods.

6.16 The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be critically examined.

6.17 The tests performed should be recorded and the records should include at least the following data: (a) name of the material or product and, where applicable, dosage form; (b) batch number and, where appropriate, the manufacturer and/or supplier; (c) references to the relevant specifications and testing procedures; (d) test results, including observations and calculations, and reference to any certificates of analysis; (e) dates of testing; (f) initials of the persons who performed the testing; (g) initials of the persons who verified the testing and the calculations, where appropriate; and (h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

6.18 All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.

6.19 Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards, and culture media. They should be prepared in accordance with written procedures.

6.20 Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardization and the last current factor should be indicated.

6.21 Where necessary, the date of receipt of any substance used for testing operations (e.g., reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

6.22 Animals used for testing components, materials or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

Ongoing Stability Program

6.23 After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate program that will permit the detection of any stability issue (e.g., changes in levels of impurities or dissolution profile) associated with the formulation in the marketed package.

6.24 The purpose of the ongoing stability program is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labeled storage conditions.

6.25 This mainly applies to the medicinal product in the package in which it is sold, but consideration should also be given to the inclusion in the program of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing

site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an ongoing basis. However, when relevant, the stability of reconstituted product can also be monitored.

6.26 The ongoing stability program should be described in a written protocol following the general rules of Chapter 4 and results formalized as a report. The equipment used for the ongoing stability program (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 and Annex 15.

6.27 The protocol for an ongoing stability program should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:

- number of batch(es) per strength and different batch sizes, if applicable;
- relevant physical, chemical, microbiological and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container closure system(s);
- testing intervals (time points);
- description of the conditions of storage (standardized ICH conditions for long-term testing, consistent with the product labeling, should be used); and
- other applicable parameters specific to the medicinal product.

6.28 The protocol for the ongoing stability program can be different from that of the initial long-term stability study as submitted in the Marketing Authorization dossier provided that this is justified and documented in the protocol (e.g., the frequency of testing, or when updating to ICH recommendations).

6.29 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability program (unless none are produced during that year). For products where ongoing stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk-benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

6.30 In certain situations, additional batches should be included in the ongoing stability program. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing, or recovery operation should also be considered for inclusion.

6.31 Results of ongoing stability studies should be made available to key personnel and, in particular, to the Qualified Person(s). Where on-going stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of ongoing stability studies should be available at the site of manufacture for review by the competent authority.

6.32 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with Chapter 8 of the GMP guide and in consultation with the relevant competent authorities.

6.33. A summary of all the data generated, including any interim conclusions on the program, should be written and maintained. This summary should be subjected to periodic review.

Chapter 7: Contract Manufacture and Analysis

Principle

Contract manufacture and analysis must be correctly defined, agreed, and controlled in order to avoid misunderstandings, which could result in a product or work of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor, which clearly establishes the duties of each party. The contract must clearly state the way in which the Qualified Person releasing each batch of product for sale exercises his full responsibility.

Note: This Chapter deals with the responsibilities of manufacturers toward the competent authorities of the member states with respect to the granting of marketing and manufacturing authorizations. It is not intended in any way to affect the respective liability of contract acceptors and contract givers to consumers; this is governed by other provisions of Community and national law.

General

7.1 There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

7.2 All arrangements for contract manufacture and analysis including any proposed changes in technical or other arrangements should be in accordance with the Marketing Authorization for the product concerned.

The Contract Giver

7.3 The Contract Giver is responsible for assessing the competence of the Contract Acceptor to carry out successfully the work required and for ensuring by means of the contract that the principles and guidelines of GMP as interpreted in this guide are followed.

7.4 The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the Marketing Authorization and any other legal requirements. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work which might pose a hazard to his premises, equipment, personnel, other materials, or other products.

7.5 The Contract Giver should ensure that all processed products and materials delivered to him by the Contract Acceptor comply with their specifications or that the products have been released by a Qualified Person.

The Contract Acceptor

7.6 The Contract Acceptor must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver. Contract manufacture may be undertaken only by a manufacturer who is the holder of a manufacturing authorization.

7.7 The Contract Acceptor should ensure that all products or materials delivered to him are suitable for their intended purpose.

7.8 The Contract Acceptor should not pass to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original Contract Giver and Contract Acceptor.

7.9 The Contract Acceptor should refrain from any activity which may adversely affect the quality of the product manufactured and/or analyzed for the Contract Giver.

The Contract

7.10 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis, and Good Manufacturing Practice. All arrangements for manufacture and analysis must be in accordance with the Marketing Authorization and agreed by both parties.

7.11 The contract should specify the way in which the Qualified Person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of Marketing Authorization.

7.12 The contract should describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and Quality Controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the Contract Acceptor should take samples at the premises of the manufacturer.

7.13 Manufacturing, analytical and distribution records, and reference samples should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the Contract Giver.

7.14 The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.

7.15 In the case of contract analysis, the Contract Acceptor should understand that he is subject to Inspection by the competent Authorities.

Chapter 8: Complaints and Product Recall

Principle

All complaints and other information concerning potentially defective products must be reviewed carefully according to written procedures. In order to provide for all contingencies, and in accordance with Article 117 of Directive 2001/83/EC and Article 84 of Directive 2001/82/EC, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

Complaints

8.1 A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him. If this person is not the Qualified Person, the latter should be made aware of any complaint, investigation, or recall.

8.2 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

8.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control should normally be involved in the study of such problems.

8.4 If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.

8.5 All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

8.6 Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

8.7 Special attention should be given to establishing whether a complaint was caused because of counterfeiting.

8.8 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, detection of counterfeiting, or any other serious quality problems with a product

Recalls

8.9 A person should be designated as responsible for execution and coordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organization. If this person is not the Qualified Person, the latter should be made aware of any recall operation.

8.10 There should be established written procedures, regularly checked and updated when necessary, in order to organize any recall activity.

8.11 Recall operations should be capable of being initiated promptly and at any time.

8.12 All Competent Authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of being defective.

8.13 The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone and/or fax numbers inside and outside working hours, batches, and amounts delivered), including those for exported products and medical samples.

8.14 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.

8.15 The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.

8.16 The effectiveness of the arrangements for recalls should be evaluated regularly.

15

EDQM Certification

The European legislation does not require mandatory routine GMP inspections for active substance manufacturers. Responsibility for using only active substances that have been manufactured in accordance with good manufacturing practice is placed on the holders of a manufacturing authorization. Art. 111 Directive 2001/83/EC (Art. 80 Directive 2001/82/EC for veterinary medicinal products), however makes provision for GMP inspections of active substance manufacturing sites to be carried out at the request of the manufacturer itself. The request for the inspection should be made to the EEA competent authority where the site is located or, in case of sites located in third countries, to a competent authority where the active substance is used as a starting material in the manufacture of medicinal products. If this is not the case, any EEA authority can be approached. There is no guarantee that such a request will be fulfilled, as the competent authorities need to balance such requests with other priorities. It should also be borne in mind that an inspection does not replace the responsibility of the manufacturing authorization holder using the active substance in question as a starting material and will not be accepted alone as adequate assurance that the manufacturing authorization holder has fulfilled its responsibilities.

Manufacturing authorization holders sometimes confuse the role of inspectorates with their own obligations but nevertheless, when inspection reports or GMP certificates issued by EEA, MRA partners, or other recognized authorities are available; these can provide useful information to manufacturing authorization holders. However, these alone cannot fulfill the statutory obligations of the manufacturing authorization holder or the requirements of section 5.25 of the GMP Guide, but the results of inspections, may be used together with other supporting information in a risk-based approach by the manufacturer in establishing priorities for its own audit program of active substance suppliers.

A GMP certificate is a certificate issued, following a GMP inspection, by the competent authority responsible for carrying out the inspection, to confirm the GMP compliance status of the inspected site. GMP certificates are site specific, but can be restricted to particular activities depending on the scope of the inspection (e.g., manufacturing activities related to a specific product). Directives 2001/82/EC and 2001/83/EC, as amended state that after every GMP inspection, and within 90 days of the inspection, a GMP certificate shall be issued to a manufacturer, if the outcome of the inspection shows that the manufacturer complies with GMP.

CMPs are product specific certificates, issued by the competent authority that granted the marketing authorization (EMEA issues CMPs on behalf of the European Commission for centrally authorized products), in the context of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce, to confirm the marketing authorization status of the products. These certificates also confirm the GMP compliance status of the manufacturing site(s). CMPs are mainly used by companies to support applications to export their pharmaceutical products to countries with less developed regulatory systems.

CEPs are certificates issued by the European Directorate for the Quality of Medicines (EDQM) to confirm that a certain active substance is produced according to the requirements of the relevant monograph of the European Pharmacopoeia or of the monograph on TSE. CEPs can be used by companies when submitting an application for marketing authorization, and replaces much of the documentation required for the active substance in the marketing authorization dossier. GMP inspections of active substance manufacturers can be requested by EDQM in the context of the CEP certification scheme.

EMEA does not perform inspections; they are carried out on its behalf by the national competent authorities of the member states of the EEA, in connection with products under the centralized marketing authorization procedure. The competent authority responsible for carrying out the inspection issues the GMP certificate, or makes an entry of noncompliance into the EudraGMP Database.

The EDQM allows raw material manufacturers to submit and secure approval for their active pharmaceutical ingredients besides the approval of the finished products; such approvals are not available in the jurisdictions of the FDA. Given below is submission requirement that can be used by the manufacturers to audit for the quality of the API in those instances where such certificates and/or DMF are not available.

I. 2.3.S DRUG SUBSTANCE

A. 2.3.S.1 General Information

Use of the substance: *Route(s) of administration, maximum daily dose*.

Commercialization history: *Summarize the history based on the table in application form.*

Declarations: Summarize the declarations appended to the application form:

- *Manufacture of the substance in accordance with ICH Q7A GMP rules*
- *Commitment by the manufacturer to keep the proposed holder informed of any changes to the documentation*
- *If applicable: manufacturer's authorization for X to act as representative*
- *Willingness to be inspected (holder, manufacturers)*
- *Nonuse/use of materials of human or animal origin in the process*

1. 2.3.S.1.1 Nomenclature

(a) *Recommended International Nonproprietary name (INN)*
(b) *Chemical name(s)*
(c) *Company or laboratory code*
(d) *Other nonproprietary name(s) (e.g., national name, USAN, BAN)*
(e) *CAS No.: Molecular Formula MW*

2.3.S.1.2 General Properties

Give summarized data on

(a) *Physical description (e.g., appearance, color, physical state. . .)*
(b) *Physical form (e.g., polymorphic form, solvate, hydrate): to be commented especially if requested as grade*
(c) *Solubility and other properties as necessary*
(d) *Particle size: for example, nonmicronized, micronized, or any grade claimed as subtitle*

2.3.S.2 Manufacture

2.3.S.2.1 Manufacturer(s) (Name, Manufacturer) and Sites Involved in the Entire Process

Give the name, address, and responsibility of each manufacturer, including contractors and manufacturer and each proposed production site or facility involved in manufacture.

2.3.S.2.2 Description of Manufacturing Process and Process Controls

(a) *Give a brief narrative step-by-step description of the manufacturing process(es) and provide reference to detailed description in the documentation. Confirm the maximum batch size*
(b) *If applicable, summarize alternate processes and give a short explanation of their use*
(c) *Comment shortly on recovery of materials (solvents, reagents, and mother liquor) together with reprocessing steps and give a brief justification*

2.3.S.2.3 Control of Materials

(I) Starting material(s)
  (a) *Give summarized specifications (including impurities profile) including their justification based on studies of carry-over.*
  NB: If starting material is obtained by fermentation or is from herbal origin, summarize the information related to the nature of this material.

(II) Reagents and solvents
Summarize the quality and controls of the materials (e.g., raw materials, solvents pure, and/or recovered, reagents, catalysts) used in the manufacture of the drug substance.

2.3.S.2.4 Controls of Critical Steps and Intermediates

Summary of the controls performed at critical steps of the manufacturing process and on intermediates, compare analytical procedures used for intermediates and final substance.

2.3.S.2.5 Process Validation and/or Evaluation

For aseptic processing and sterilization, only give the summary of process validation and/or evaluation studies.

2.3.S.3 Characterization

2.3.S.3.1 Impurities

(I) Related substances
  (a) *Fill in the following table identifying related substances, their origin, and distinguishing between potential and actual impurities and comparing with impurity section of the monograph*
  (b) Justify these specifications based on *data observed for impurities in relevant batches*
  (c) *Discuss briefly about the* suitability of the monograph *to control the potential impurities present in the substance (residual starting materials, reactants, and reagents etc.)*
  (d) Specific discussion on possible genotoxic impurities: *Give a brief discussion on impurities with potential genotoxicity based on the requirements of the guideline*

(II) Residual solvent(s)/reagent(s)/catalyst(s)
  (a) *Fill in the following table*
  (b) Discuss briefly the basis for setting the specification

2.3.S.4 Control of the Drug Substance

2.3.S.4.1 Specification

Give a table summarizing the proposed specifications.

2.3.S.4.2 Analytical Procedures

(a) *Summarize of the analytical procedures*

2.3.S.4.3 Validation of Analytical Procedures

Give the summary of the validation information for any in-house tests and compare shortly with the method(s) described in the monograph (cross-validation).

2.3.S.4.4 Batch Analyses

(a) *Give a short description of the batches: batch number, batch size date, and site of production*
(b) *Summarize the results for relevant batches (according to specifications and showing equivalence of any alternative supplier, process etc.)*

2.3.S.4.5 Justification of Specification

Justify the drug substance specification

2.3.S.5 Reference Standards or Materials

(a) *Give the source of primary reference standards or reference materials (e.g., Ph.Eur.) for final substance and its impurities where relevant*
(b) *Summarize characterization and evaluation of in-house standards*

Chemical Name	Ph.Eur. Impurity	Applicant's Specifications	Ph.Eur. Specifications	Origin	Levels Found	LOD of the Method	LOQ of the Method

Solvent/Reagent/Catalyst	Used in Step X/Y	Applicant's Limit	ICH Class/Limit	Levels (PPM)	LOD of the Method	LOQ of the Method

2.3.S.6 Container Closure System

(a) *Describe shortly the container closure system(s) for the storage and shipment of the drug substance, as it has to be mentioned on the CEP in case a retest period is requested (i.e.. in a clear and understandable manner)*
(b) *Summarize the specifications (description + identification)*

2.3.S.7 Stability

State retest period claimed for the substance and storage recommendations, if any.

2.3.S.7.1 Stability Summary and Conclusions

(a) *Summarize accelerated* and *long-term testing (e.g., studies conducted, protocols used, results obtained)*
(b) *Justify of the retest period claimed based on data available*

2.3.S.7.2 Postapproval Stability Protocol and Stability Commitment

Give the stability protocol for commitment batches.

16

Impurities: Guideline for Residual Solvents

I. INTRODUCTION

The objective of this guideline is to recommend acceptable amounts for residual solvents in pharmaceuticals for the safety of the patient. The guideline recommends use of less toxic solvents and describes levels considered to be toxicologically acceptable for some residual solvents.

Residual solvents in pharmaceuticals are defined here as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of drug substance may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical parameter in the synthetic process. This guideline does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Since there is no therapeutic benefit from residual solvents, all residual solvents should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Some solvents that are known to cause unacceptable toxicities (Class 1, Table 16.1) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Some solvents associated with less severe toxicity (Class 2, Table 16.2) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, Table 16.3) should be used where practical. The complete list of solvents included in this guideline is given in Appendix 1.

The lists are not exhaustive and other solvents can be used and later added to the lists. Recommended limits of Class 1 and 2 solvents or classification of solvents may change as new safety data becomes available. Supporting safety data in a marketing application for a new drug product containing a new solvent may be based on concepts in this guideline or the concept of qualification of impurities as expressed in the guideline for drug substance (Q3A, *Impurities in New Drug Substances*) or drug product (Q3B, *Impurities in New Drug Products*), or all three guidelines.

II. SCOPE OF THE GUIDELINE

Residual solvents in drug substances, excipients, and in drug products are within the scope of this guideline. Therefore, testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. It is only necessary to test for solvents that are used or produced in the manufacture or purification of drug substances, excipients, or drug product. Although manufacturers may choose to test the drug product, a cumulative method may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product. If the calculation results in a level equal to or below that recommended in this guideline, no testing of the drug product for residual solvents need be considered. If, however, the calculated level is above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. Drug product should also be tested if a solvent is used during its manufacture.

This guideline does not apply to potential new drug substances, excipients, or drug products used during the clinical research stages of development, nor does it apply to existing marketed drug products.

The guideline applies to all dosage forms and routes of administration. Higher levels of residual solvents may be acceptable in certain cases such as short term (30 days or less) or topical application. Justification for these levels should be made on a case-by-case basis.

See Appendix 2 for additional background information related to residual solvents.

III. GENERAL PRINCIPLES

A. Classification of Residual Solvents by Risk Assessment

The term "tolerable daily intake" (TDI) is used by the International Programme on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals and "acceptable daily intake" (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The new term "permitted daily exposure" (PDE) is defined in the present guideline as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADIs of the same substance.

Residual solvents assessed in this guideline are listed in Appendix 1 by common names and structures. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

Class 1 solvents: solvents to be avoided: Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

Class 2 solvents: solvents to be limited: Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity. Solvents suspected of other significant but reversible toxicities.

Class 3 solvents: solvents with low toxic potential: Solvents with low toxic potential to man; no health-based exposure limit is needed. Class 3 solvents have PDEs of 50 mg or more per day.

Table 16.1 Class 1 Solvents in Pharmaceutical Products (Solvents That Should Be Avoided)

Solvent	Concentration limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

Table 16.2 Class 2 Solvents in Pharmaceutical Products

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,*N*-Dimethylacetamide	10.9	1090
N,*N*-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	6.2	620
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1180
N-Methylpyrrolidone	48.4	4840
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene[a]	21.7	2170

[a]Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

Table 16.3 Class 3 Solvents Which Should Be Limited by GMP or Other Quality-Based Requirements

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Cumene	2-Methyl-1-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	Tetrahydrofuran

B. Methods for Establishing Exposure Limits

The method used to establish permitted daily exposures for residual solvents is presented in Appendix 3. Summaries of the toxicity data that were used to establish limits are published in *Pharmeuropa*, Vol. 9, No. 1, Supplement, April 1997.

C. Options for Describing Limits of Class 2 Solvents

Two options are available when setting limits for Class 2 solvents.

Option 1: The concentration limits in ppm stated in Table 16.2 can be used. They were calculated using equation (1) below by assuming a product mass of 10 g administered daily.

$$\text{Concentration (ppm)} = \frac{1000 \times \text{PDE}}{\text{dose}} \qquad (1)$$

Here, PDE is given in terms of mg/day and dose is given in g/day.

These limits are considered acceptable for all substances, excipients, or products. Therefore this option may be applied if the daily dose is not known or fixed. If all excipients and drug substances in a formulation meet the limits given in Option 1, then these components may be used in any proportion. No further calculation is necessary provided the daily dose does not exceed 10 g. Products that are administered in doses greater than 10 g/day should be considered under Option 2.

Option 2: It is not considered necessary for each component of the drug product to comply with the limits given in Option 1. The PDE in terms of mg/day as stated in Table 16.2 can be used with the known maximum daily dose and equation (1) above to determine the concentration of residual solvent allowed in drug product. Such limits are considered acceptable provided that it has been demonstrated that the residual solvent has been reduced to the practical minimum. The limits should be realistic in relation to analytical precision, manufacturing capability, reasonable variation in the manufacturing process, and the limits should reflect contemporary manufacturing standards.

Option 2 may be applied by adding the amounts of a residual solvent present in each of the components of the drug product. The sum of the amounts of solvent per day should be less than that given by the PDE.

Consider an example of the use of Option 1 and Option 2 applied to acetonitrile in a drug product. The permitted daily exposure to acetonitrile is 4.1 mg/day; thus, the Option 1 limit is 410 ppm. The maximum administered daily mass of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

Component	Amount in formulation	Acetonitrile content	Daily exposure
Drug substance	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	400 ppm	0.36 mg
Excipient 2	3.8 g	800 ppm	3.04 mg
Drug product	5.0 g	728 ppm	3.64 mg

Excipient 1 meets the Option 1 limit, but the drug substance, excipient 2, and drug product do not meet the Option 1 limit. Nevertheless, the product meets the Option 2 limit of 4.1 mg/day and thus conforms to the recommendations in this guideline.

Consider another example using acetonitrile as residual solvent. The maximum administered daily mass of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile is given in the following table.

Component	Amount in formulation	Acetonitrile content	Daily exposure
Drug substance	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	2000 ppm	1.80 mg
Excipient 2	3.8 g	800 ppm	3.04 mg
Drug Product	5.0 g	1016 ppm	5.08 mg

In this example, the product meets neither the Option 1 nor the Option 2 limit according to this summation. The manufacturer could test the drug product to determine if the formulation process reduced the level of acetonitrile. If the level of acetonitrile was not reduced during formulation to the allowed limit, then the manufacturer of the drug product should take other steps to reduce the amount of acetonitrile in the drug product. If all of these steps fail to reduce the level of residual solvent, in exceptional cases the manufacturer could provide a summary of efforts made to reduce the solvent level to meet the guideline value, and provide a risk-benefit analysis to support allowing the product to be used with residual solvent at a higher level.

D. Analytical Procedures

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. Any harmonized procedures for determining levels of residual solvents as described in the pharmacopoeias should be used, if feasible. Otherwise, manufacturers would be free to select the most appropriate validated analytical procedure for a particular application. If only Class 3 solvents are present, a nonspecific method such as loss on drying may be used.

Validation of methods for residual solvents should conform to ICH guidelines Text on Validation of Analytical Procedures and Extension of the ICH Text on Validation of Analytical Procedures.

E. Reporting Levels of Residual Solvents

Manufacturers of pharmaceutical products need certain information about the content of residual solvents in excipients or drug substances in order to meet the criteria of this guideline. The following statements are given as acceptable examples of the information that could be provided from a supplier of excipients or drug substances to a pharmaceutical manufacturer. The supplier might choose one of the following as appropriate:

- Only Class 3 solvents are likely to be present. Loss on drying is less than 0.5%.
- Only Class 2 solvents X, Y, . . . are likely to be present. All are below the Option 1 limit. (Here the supplier would name the Class 2 solvents represented by X, Y, . . .).
- Only Class 2 solvents X, Y, . . . and Class 3 solvents are likely to be present. Residual Class 2 solvents are below the Option 1 limit and residual Class 3 solvents are below 0.5%.

If Class 1 solvents are likely to be present, they should be identified and quantified.

"Likely to be present" refers to the solvent used in the final manufacturing step and to solvents that are used in earlier manufacturing steps and not removed consistently by a validated process.

If solvents of Class 2 or Class 3 are present at greater than their Option 1 limits or 0.5%, respectively, they should be identified and quantified.

Table 16.4 Solvents for Which No Adequate Toxicological Data Was Found

1,1-Diethoxypropane	Methylisopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Petroleum ether
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

IV. LIMITS OF RESIDUAL SOLVENTS

A. Solvents to Be Avoided

Solvents in Class 1 should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 16.1, unless otherwise justified. 1,1,1-Trichloroethane is included in Table 16.1 because it is an environmental hazard. The stated limit of 1500 ppm is based on a review of the safety data.

B. Solvents to Be Limited

Solvents in Table 16.2 should be limited in pharmaceutical products because of their inherent toxicity. PDEs are given to the nearest 0.1 mg/day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of the validation of the method.

C. Solvents with Low Toxic Potential

Solvents in Class 3 (shown in Table 16.3) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg/day or less (corresponding to 5000 ppm or 0.5% under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice.

D. Solvents for Which No Adequate Toxicological Data Was Found

The following solvents (Table 16.4) may also be of interest to manufacturers of excipients, drug substances, or drug products. However, no adequate toxicological data on which to base a PDE was found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

GLOSSARY

Genotoxic Carcinogens—Carcinogens which produce cancer by affecting genes or chromosomes.

LOEL—Abbreviation for lowest-observed effect level.

Lowest-Observed Effect Level—The lowest dose of substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

Modifying Factor—A factor determined by professional judgment of a toxicologist and applied to bioassay data to relate that data safely to humans.

Neurotoxicity—The ability of a substance to cause adverse effects on the nervous system.

NOEL—Abbreviation for no-observed-effect level.

No-Observed-Effect Level—The highest dose of substance at which there are no biologically significant increases in frequency or severity of any effects in the exposed humans or animals.

PDE—Abbreviation for permitted daily exposure.

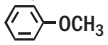
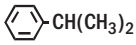
Permitted Daily Exposure—The maximum acceptable intake per day of residual solvent in pharmaceutical products.

Reversible Toxicity—The occurrence of harmful effects that are caused by a substance and which disappear after exposure to the substance ends.

Strongly Suspected Human Carcinogen—A substance for which there is no epidemiological evidence of carcinogenesis but there are positive genotoxicity data and clear evidence of carcinogenesis in rodents.

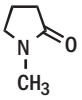
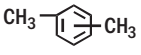
Teratogenicity—The occurrence of structural malformations in a developing fetus when a substance is administered during pregnancy.

Appendix 1. List of Solvents Included in the Guideline

Solvent	Other names	Structure	Class
Acetic acid	Ethanoic acid	CH_3COOH	Class 3
Acetone	2-Propanone Propan-2-one	CH_3COCH_3	Class 3
Acetonitrile		CH_3CN	Class 2
Anisole	Methoxybenzene		Class 3
Benzene	Benzol		Class 1
1-Butanol	*n*-Butyl alcohol Butan-1-ol	$CH_3(CH_2)_3OH$	Class 3
2-Butanol	*sec*-Butyl alcohol Butan-2-ol	$CH_3CH_2CH(OH)CH_3$	Class 3
Butyl acetate	Acetic acid butyl ester	$CH_3COO(CH_2)_3CH_3$	Class 3
tert-Butylmethyl ether	2-Methoxy-2-methyl- propane	$(CH_3)_3COCH_3$	Class 3
Carbon tetrachloride	Tetrachloromethane	CCl_4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	$CHCl_3$	Class 2
Cumene	Isopropylbenzene (1-Methyl) ethylbenzene		Class 3
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	*sym*-Dichloroethane Ethylene dichloride Ethylene chloride	CH_2ClCH_2Cl	Class 1
1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	$H_2C = CCl_2$	Class 1
1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	$ClHC = CHCl$	Class 2
Dichloromethane	Methylene chloride	CH_2Cl_2	Class 2
1,2-Dimethoxyethane	Ethyleneglycol dimethyl ether Monoglyme Dimethyl Cellosolve	$H_3COCH_2CH_2OCH_3$	Class 2
N,*N*-Dimethylacetamide	DMA	$CH_3CON(CH_3)_2$	Class 2
N,*N*-Dimethylformamide	DMF	$HCON(CH_3)_2$	Class 2
Dimethyl sulfoxide	Methylsulfinylmethane Methyl sulfoxide DMSO	$(CH_3)_2SO$	Class 3
1,4-Dioxane	*p*-Dioxane [1,4]Dioxane		Class 2
Ethanol	Ethyl alcohol	CH_3CH_2OH	Class 3
2-Ethoxyethanol	Cellosolve	$CH_3CH_2OCH_2CH_2OH$	Class 2
Ethyl acetate	Acetic acid ethyl ester	$CH_3COOCH_2CH_3$	Class 3
Ethyleneglycol	1,2-Dihydroxyethane 1,2-Ethanediol	$HOCH_2CH_2OH$	Class 2

(*continued*)

Appendix 1. List of Solvents Included in the Guideline *(Continued)*

Solvent	Other names	Structure	Class
Ethyl ether	Diethyl ether Ethoxyethane 1,1'-Oxybisethane	$CH_3CH_2OCH_2CH_3$	Class 3
Ethyl formate	Formic acid ethyl ester	$HCOOCH_2CH_3$	Class 3
Formamide	Methanamide	$HCONH_2$	Class 2
Formic acid		$HCOOH$	Class 3
Heptane	*n*-Heptane	$CH_3(CH_2)_5CH_3$	Class 3
Hexane	*n*-Hexane	$CH_3(CH_2)_4CH_3$	Class 2
Isobutyl acetate	Acetic acid isobutyl ester	$CH_3COOCH_2CH(CH_3)_2$	Class 3
Isopropyl acetate	Acetic acid isopropyl ester	$CH_3COOCH(CH_3)_2$	Class 3
Methanol	Methyl alcohol	CH_3OH	Class 2
2-Methoxyethanol	Methyl Cellosolve	$CH_3OCH_2CH_2OH$	Class 2
Methyl acetate	Acetic acid methyl ester	CH_3COOCH_3	Class 3
3-Methyl-1-butanol	Isoamyl alcohol Isopentyl alcohol 3-Methylbutan-1-ol	$(CH_3)_2CHCH_2CH_2OH$	Class 3
Methylbutyl ketone	2-Hexanone Hexan-2-one	$CH_3(CH_2)_3COCH_3$	Class 2
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylethyl ketone	2-Butanone MEK Butan-2-one	$CH_3CH_2COCH_3$	Class 3
Methylisobutyl ketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	$CH_3COCH_2CH(CH_3)_2$	Class 3
2-Methyl-1-propanol	Isobutyl alcohol 2-Methylpropan-1-ol	$(CH_3)_2CHCH_2OH$	Class 3
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
Nitromethane		CH_3NO_2	Class 2
Pentane	*n*-Pentane	$CH_3(CH_2)_3CH_3$	Class 3
1-Pentanol	Amyl alcohol Pentan-1-ol Pentyl alcohol	$CH_3(CH_2)_3CH_2OH$	Class 3
1-Propanol	Propan-1-ol Propyl alcohol	$CH_3CH_2CH_2OH$	Class 3
2-Propanol	Propan-2-ol Isopropyl alcohol	$(CH_3)_2CHOH$	Class 3
Propyl acetate	Acetic acid propyl ester	$CH_3COOCH_2CH_2CH_3$	Class 3
Pyridine			Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide		Class 2
Tetrahydrofuran	Tetramethylene oxide Oxacyclopentane		Class 3
Tetralin	1,2,3,4-Tetrahydro-naphthalene		Class 2
Toluene	Methylbenzene		Class 2
1,1,1-Trichloroethane	Methylchloroform	CH_3CCl_3	Class 1
1,1,2-Trichloroethene	Trichloroethene	$HClC=CCl_2$	Class 2
Xylene[a]	Dimethybenzene Xylol		Class 2

[a]Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

Appendix 2. Additional Background

A2.1 Environmental Regulation of Organic Volatile Solvents

Several of the residual solvents frequently used in the production of pharmaceuticals are listed as toxic chemicals in Environmental Health Criteria (EHC) monographs and the Integrated Risk Information System (IRIS). The objectives of such groups as the International Programme on Chemical Safety (IPCS), the United States Environmental Protection Agency (USEPA), and the United States Food and Drug Administration (USFDA) include the determination of acceptable exposure levels. The goal is the protection of human health and maintenance of environmental integrity against the possible deleterious effects of chemicals resulting from long-term environmental exposure. The methods involved in the estimation of maximum safe exposure limits are usually based on long-term studies. When long-term study data are unavailable, shorter-term study data can be used with modification of the approach such as use of larger safety factors. The approach described therein relates primarily to long-term or *lifetime exposure of the general population* in the ambient environment, that is, ambient air, food, drinking water, and other media.

A2.2 Residual Solvents in Pharmaceuticals

Exposure limits in this guideline are established by referring to methodologies and toxicity data described in EHC and IRIS monographs. However, some specific assumptions about residual solvents to be used in the synthesis and formulation of pharmaceutical products should be taken into account in establishing exposure limits. They are as follows:

(1) Patients (not the general population) use pharmaceuticals to treat their diseases or for prophylaxis to prevent infection or disease.
(2) The assumption of lifetime patient exposure is not necessary for most pharmaceutical products but may be appropriate as a working hypothesis to reduce risk to human health.
(3) Residual solvents are unavoidable components in pharmaceutical production and will often be a part of drug products.
(4) Residual solvents should not exceed recommended levels except in exceptional circumstances.
(5) Data from toxicological studies that are used to determine acceptable levels for residual solvents should have been generated using appropriate protocols such as those described, for example, by OECD, EPA, and the FDA *Red Book*.

Appendix 3. Methods for Establishing Exposure Limits

The Gaylor–Kodell method of risk assessment (Gaylor DW, Kodell RL (1980). Linear interpolation algorithm for low dose assessment of toxic substance. J Environ Pathol 4:305.) is appropriate for Class 1 carcinogenic solvents. Only in cases where reliable carcinogenicity data are available should extrapolation by the use of mathematical models be applied to setting exposure limits. Exposure limits for Class 1 solvents could be determined with the use of a large safety factor (i.e., 10,000 to 100,000) with respect to the no-observed-effect level (NOEL). Detection and quantitation of these solvents should be by state-of-the-art analytical techniques.

Acceptable exposure levels in this guideline for Class 2 solvents were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals (*Pharmacopeial Forum*, Nov–Dec 1989), and the method adopted by IPCS for Assessing Human Health Risk of Chemicals (Environmental Health Criteria 170, WHO, 1994). These methods are similar to those used by the USEPA (IRIS) and the USFDA (*Red Book*) and others. The method is outlined here to give a better understanding of the origin of the PDE values. It is not necessary to perform these calculations in order to use the PDE values tabulated in section IV of this document.

PDE is derived from the no-observed-effect level (NOEL) or the lowest-observed-effect level (LOEL) in the most relevant animal study as follows:

$$\text{PDE} = \frac{\text{NOEL} \times \text{Weight Adjustment}}{\text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}} \quad (1)$$

The PDE is derived preferably from a NOEL. If no NOEL is obtained, the LOEL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of "uncertainty factors" used in EHC (Environmental Health Criteria 170, World Health Organization, Geneva, 1994), and "modifying factors" or "safety factors" in *Pharmacopeial Forum*. The assumption of 100% systemic exposure is used in all calculations regardless of route of administration.

The modifying factors are as follows:

F1 = A factor to account for extrapolation between species
F1 = 5 for extrapolation from rats to humans
F1 = 12 for extrapolation from mice to humans
F1 = 2 for extrapolation from dogs to humans
F1 = 2.5 for extrapolation from rabbits to humans
F1 = 3 for extrapolation from monkeys to humans
F1 = 10 for extrapolation from other animals to humans

F1 takes into account the comparative surface area:body weight ratios for the species concerned and for man. Surface area (S) is calculated as:

$$S = kM^{0.67} \quad (2)$$

in which M = body mass, and the constant k has been taken to be 10. The body weights used in the equation are those shown below in Table A3.1.

F2 = A factor of 10 to account for variability between individuals

A factor of 10 is generally given for all organic solvents, and 10 is used consistently in this guideline.

F3 = A variable factor to account for toxicity studies of short-term exposure
F3 = 1 for studies that last at least one half lifetime (1 year for rodents or rabbits; 7 years for cats, dogs, and monkeys)
F3 = 1 for reproductive studies in which the whole period of organogenesis is covered
F3 = 2 for a 6-month study in rodents or a 3.5-year study in nonrodents
F3 = 5 for a 3-month study in rodents or a 2-year study in nonrodents
F3 = 10 for studies of a shorter duration

In all cases, the higher factor has been used for study durations between the time points, for example, a factor of 2 for a 9-month rodent study.

Table A3.1 Values Used in the Calculations in This Document

Rat body weight	425 g	Mouse respiratory volume	43 L/day
Pregnant rat body weight	330 g	Rabbit respiratory volume	1440 L/day
Mouse body weight	28 g	Guinea pig respiratory volume	430 L/day
Pregnant mouse body weight	30 g	Human respiratory volume	28,800 L/day
Guinea pig body weight	500 g	Dog respiratory volume	9000 L/day
Rhesus monkey body weight	2.5 kg	Monkey respiratory volume	1150 L/day
Rabbit body weight (pregnant or not)	4 kg	Mouse water consumption	5 mL/day
Beagle dog body weight	11.5 kg	Rat water consumption	30 mL/day
Rat respiratory volume	290 L/day	Rat food consumption	30 g/day

F4 = A factor that may be applied in cases of severe toxicity, for example, nongenotoxic carcinogenicity, neurotoxicity, or teratogenicity. In studies of reproductive toxicity, the following factors are used:
F4 = 1 for fetal toxicity associated with maternal toxicity
F4 = 5 for fetal toxicity without maternal toxicity
F4 = 5 for a teratogenic effect with maternal toxicity
F4 = 10 for a teratogenic effect without maternal toxicity
F5 = A variable factor that may be applied if the no-effect level was not established

When only an LOEL is available, a factor of up to 10 could be used depending on the severity of the toxicity.

The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kg. This relatively low weight provides an additional safety factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculation. It is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE. If the solvent was present in a formulation specifically intended for pediatric use, an adjustment for a lower body weight would be appropriate.

As an example of the application of this equation, consider a toxicity study of acetonitrile in mice that is summarized in *Pharmeuropa*, Vol. 9, No. 1, Supplement, April 1997, page S24. The NOEL is calculated to be 50.7 mg/kg/day. The PDE for acetonitrile in this study is calculated as follows:

$$\text{PDE} = \frac{50.7 \text{ mg kg}^{-1} \text{ day}^{-1} \times 50 \text{ kg}}{12 \times 10 \times 5 \times 1 \times 1} = 4.22 \text{ mg day}^{-1}$$

In this example,

F1 = 12 to account for the extrapolation from mice to humans
F2 = 10 to account for differences between individual humans
F3 = 5 because the duration of the study was only 13 weeks
F4 = 1 because no severe toxicity was encountered
F5 = 1 because the no-effect level was determined

The equation for an ideal gas, $PV = nRT$, is used to convert concentrations of gases used in inhalation studies from units of ppm to units of mg/L or mg/m^3. Consider as an example the rat reproductive toxicity study by inhalation of carbon tetrachloride (molecular weight 153.84) that is summarized in *Pharmeuropa*, Vol. 9, No. 1, Supplement, April 1997, page S9.

$$\frac{n}{V} = \frac{P}{RT} = \frac{300 \times 10^{-6} \text{ atm} \times 153840 \text{ mg mol}^{-1}}{0.082 \text{ L atm K}^{-1} \text{ mol}^{-1} \times 298 \text{ K}} = \frac{46.15 \text{ mg}}{24.45 \text{ L}} = 1.89 \text{ mg/L}$$

The relationship 1000 L = 1 m^3 is used to convert to mg/m3.

17

Electronic Records and Signatures (CFR 21 Part 11 Compliance)

The regulations in 21 CFR part 11 set forth the criteria under which the agency (FDA) considers electronic records, electronic signatures, and handwritten signatures executed to electronic records to be trustworthy, reliable, and generally equivalent to paper records and handwritten signatures executed on paper. This chapter discusses the current revisions as of April 2008 on these compliance issues.

This part applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted, under any records requirements set forth in agency regulations. This part also applies to electronic records submitted to the agency under requirements of the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, even if such records are not specifically identified in agency regulations. However, this part does not apply to paper records that are, or have been, transmitted by electronic means.

Where electronic signatures and their associated electronic records meet the requirements of this part, the agency will consider the electronic signatures to be equivalent to full handwritten signatures, initials, and other general signings as required by agency regulations, unless specifically excepted by regulation(s) effective on or after August 20, 1997.

Electronic records that meet the requirements of this part may be used in lieu of paper records, in accordance with 11.2, unless paper records are specifically required.

Computer systems (including hardware and software), controls, and attendant documentation maintained under this part shall be readily available for, and subject to, FDA inspection.

This part does not apply to records required to be established or maintained by 1.326 through 1.368 of this chapter. Records that satisfy the requirements of part 1, subpart J of this chapter, but that also are required under other applicable statutory provisions or regulations, remain subject to this part.

For records required to be maintained but not submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that the requirements of this part are met.

For records submitted to the agency, persons may use electronic records in lieu of paper records or electronic signatures in lieu of traditional signatures, in whole or in part, provided that the requirements of this part are met and the document or parts of a document to be submitted have been identified in public docket No. 92S-0251 as being the type of submission the agency accepts in electronic form. This docket will identify specifically what types of documents or parts of documents are acceptable for submission in electronic form without paper records and the agency receiving unit(s) (e.g., specific center, office, division, branch) to which such submissions may be made. Documents to agency receiving unit(s) not specified in the public docket will not be considered as official if they are submitted in electronic form; paper forms of such documents will be considered as official and must accompany any electronic records. Persons are expected to consult with the intended agency receiving unit for details on how (e.g., method of transmission, media, file formats, and technical protocols) and whether to proceed with the electronic submission.

I. DEFINITIONS

The following definitions of terms also apply to this part:

- Act means the Federal Food, Drug, and Cosmetic Act [secs. 201–903 (21 USC 321–393)].
- Agency means the Food and Drug Administration.
- Biometrics means a method of verifying an individual's identity based on measurement of the individual's physical feature(s) or repeatable action(s) where those features and/or actions are both unique to that individual and measurable.
- Closed system means an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.
- Digital signature means an electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.
- Electronic record means any combination of text, graphics, data, audio, pictorial, or other information representation in digital form that is created, modified, maintained, archived, retrieved, or distributed by a computer system.
- Electronic signature means a computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.
- Handwritten signature means the scripted name or legal mark of an individual handwritten by that individual and executed or adopted with the present intention to authenticate a writing in a permanent form. The act of signing with a writing or marking instrument such as a pen or stylus is preserved. The scripted name or legal mark, while conventionally applied to paper, may also be applied to other devices that capture the name or mark.
- Open system means an environment in which system access is not controlled by persons who are responsible for the content of electronic records that are on the system.

II. ELECTRONIC RECORDS—CONTROLS FOR CLOSED SYSTEMS

Persons who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and

controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records, and to ensure that the signer cannot readily repudiate the signed record as not genuine. Such procedures and controls shall include the following:

- Validation of systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records.
- The ability to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the agency. Persons should contact the agency if there are any questions regarding the ability of the agency to perform such review and copying of the electronic records.
- Protection of records to enable their accurate and ready retrieval throughout the records retention period.
- Limiting system access to authorized individuals.
- Use of secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Record changes shall not obscure previously recorded information. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying.
- Use of operational system checks to enforce permitted sequencing of steps and events, as appropriate.
- Use of authority checks to ensure that only authorized individuals can use the system, electronically sign a record, access the operation or computer system input or output device, alter a record, or perform the operation at hand.
- Use of device (e.g., terminal) checks to determine, as appropriate, the validity of the source of data input or operational instruction.
- Determination that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks.
- The establishment of, and adherence to, written policies that hold individuals accountable and responsible for actions initiated under their electronic signatures, in order to deter record and signature falsification.
- Use of appropriate controls over systems documentation including
  - adequate controls over the distribution of, access to, and use of documentation for system operation and maintenance and
  - revision and change control procedures to maintain an audit trail that documents time-sequenced development and modification of systems documentation.

III. CONTROLS FOR OPEN SYSTEMS

Persons who use open systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, as appropriate, the confidentiality of electronic records from the point of their creation to the point of their receipt. Such procedures and controls shall include those identified above, as appropriate, and additional measures such as document encryption and use of appropriate digital signature standards to ensure, as necessary under the circumstances, record authenticity, integrity, and confidentiality.

A. Signature Manifestations

- Signed electronic records shall contain information associated with the signing that clearly indicates all of the following:
  - The printed name of the signer;
  - The date and time when the signature was executed; and
  - The meaning (such as review, approval, responsibility, or authorship) associated with the signature.
- The items identified in paragraphs above this section shall be subject to the same controls as for electronic records and shall be included as part of any human readable form of the electronic record (such as electronic display or printout).

B. Signature/Record Linking

Electronic signatures and handwritten signatures executed to electronic records shall be linked to their respective electronic records to ensure that the signatures cannot be excised, copied, or otherwise transferred to falsify an electronic record by ordinary means.

C. Electronic Signatures

- Each electronic signature shall be unique to one individual and shall not be reused by, or reassigned to, anyone else.
- Before an organization establishes, assigns, certifies, or otherwise sanctions an individual's electronic signature, or any element of such electronic signature, the organization shall verify the identity of the individual.
- Persons using electronic signatures shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.
  - The certification shall be submitted in paper form and signed with a traditional handwritten signature, to the Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857.
  - Persons using electronic signatures shall, upon agency request, provide additional certification or testimony that a specific electronic signature is the legally binding equivalent of the signer's handwritten signature.

IV. ELECTRONIC SIGNATURE COMPONENTS AND CONTROLS

- Electronic signatures that are not based upon biometrics shall:
  - employ at least two distinct identification components such as an identification code and password.
- When an individual executes a series of signings during a single, continuous period of controlled system access, the first signing shall be executed using all electronic signature components; subsequent signings shall be executed using at least one electronic signature component that is only executable by, and designed to be used only by, the individual.
- When an individual executes one or more signings not performed during a single, continuous period of controlled system access, each signing shall be executed using all of the electronic signature components.
  - Be used only by their genuine owners; and
  - Be administered and executed to ensure that attempted use of an individual's electronic signature by anyone

other than its genuine owner requires collaboration of two or more individuals.
- Electronic signatures based upon biometrics shall be designed to ensure that they cannot be used by anyone other than their genuine owners.

V. CONTROLS FOR IDENTIFICATION CODES/PASSWORDS

Persons who use electronic signatures based upon use of identification codes in combination with passwords shall employ controls to ensure their security and integrity. Such controls shall include:

- Maintaining the uniqueness of each combined identification code and password, such that no two individuals have the same combination of identification code and password.
- Ensuring that identification code and password issuances are periodically checked, recalled, or revised (e.g., to cover such events as password aging).
- Following loss management procedures to electronically deauthorize lost, stolen, missing, or otherwise potentially compromised tokens, cards, and other devices that bear or generate identification code or password information, and to issue temporary or permanent replacements using suitable, rigorous controls.
- Use of transaction safeguards to prevent unauthorized use of passwords and/or identification codes, and to detect and report in an immediate and urgent manner any attempts at their unauthorized use to the system security unit, and, as appropriate, to organizational management.
- Initial and periodic testing of devices, such as tokens or cards, that bear or generate identification code or password information to ensure that they function properly and have not been altered in an unauthorized manner.

VI. EXPLICATORY NOTES ABOUT 21 CFR PART 11 COMPLIANCE

The guidance described above is intended to describe the Food and Drug Administration's (FDA's) current thinking (as of April 2008) regarding the scope and application of part 11 of Title 21 of the Code of Federal Regulations; Electronic Records; Electronic Signatures (21 CFR part 11).

Given below is a discussion on how to implement systems that would fulfill the requirements in the above guidance. This pertains mostly to persons who maintain records or submit information to FDA and have chosen to maintain the records or submit designated information electronically and, as a result, have become subject to part 11. Part 11 applies to records in electronic form that are created, modified, maintained, archived, retrieved, or transmitted under any records requirements set forth in Agency regulations. Part 11 also applies to electronic records submitted to the Agency under the Federal Food, Drug, and Cosmetic Act (the Act) and the Public Health Service Act (the PHS Act), even if such records are not specifically identified in Agency regulations (§ 11.1). The underlying requirements set forth in the Act, PHS Act, and FDA regulations (other than part 11) are referred to in this guidance document as predicate rules.

As an outgrowth of its current good manufacturing practice (CGMP) initiative for human and animal drugs and biologics, FDA continuously reexamines how part 11 applies to all FDA regulated products. In making rules based on the guidance, FDA interprets the scope of part 11 rather narrowly. The FDA does not currently exercise enforcement discretion with respect to certain part 11 requirements to enforce compliance with the validation, audit trail, record retention, and record copying requirements of part 11. However, records must still be maintained or submitted in accordance with the underlying predicate rules, and the Agency can take regulatory action for noncompliance with such predicate rules.

The FDA does not intend to take (or recommend) action to enforce any part 11 requirements with regard to systems that were operational before August 20, 1997, the effective date of part 11 (commonly known as legacy systems).

A. Overall Approach to Part 11 Requirements

As described in more detail below, the approach outlined in this guidance is based on three main elements:

- Part 11 will be interpreted narrowly and FDA offers clarification on which record are considered subject to part 11.
- For those records that remain subject to part 11, FDA exercises enforcement discretion with regard to part 11 requirements for validation, audit trails, record retention, and record copying in the manner described in this guidance and with regard to all part 11 requirements for systems that were operational before the effective date of part 11 (also known as legacy systems).
- FDA will enforce all predicate rule requirements, including predicate rule record and record-keeping requirements.

It is important to note that FDA's exercise of enforcement discretion as described in this guidance is limited to specified part 11 requirements (setting aside legacy systems, as to which the extent of enforcement discretion, under certain circumstances, will be more broad). FDA enforces all other provisions of part 11 including, but not limited to, certain controls for closed systems in § 11.10. For example, we intend to enforce provisions related to the following controls and requirements:

- limiting system access to authorized individuals
- use of operational system checks
- use of authority checks
- use of device checks
- determination that persons who develop, maintain, or use electronic systems have the education, training, and experience to perform their assigned tasks
- establishment of and adherence to written policies that hold individuals accountable for actions initiated under their electronic signatures
- appropriate controls over systems documentation
- controls for open systems corresponding to controls for closed systems bulleted above (§ 11.30)
- requirements related to electronic signatures (e.g., §§ 11.50, 11.70, 11.100, 11.200, and 11.300)

The FDA expects compliance with these provisions, and enforces them. Furthermore, persons must comply with applicable predicate rules, and records that are required to be maintained or submitted must remain secure and reliable in accordance with the predicate rules.

B. Details of Approach—Scope of Part 11

The FDA interprets part 11 rather narrowly since broad interpretations could lead to unnecessary controls and costs and could discourage innovation and technological advances without providing added benefit to the public health. Under the narrow interpretation of the scope of part 11, with respect to records required to be maintained under predicate rules

or submitted to FDA, when persons choose to use records in electronic format in place of paper format, part 11 would apply. On the other hand, when persons use computers to generate paper printouts of electronic records, and those paper records meet all the requirements of the applicable predicate rules and persons rely on the paper records to perform their regulated activities, FDA would generally not consider persons to be "using electronic records in lieu of paper records" under §§ 11.2(a) and 11.2(b). In these instances, the use of computer systems in the generation of paper records would not trigger part 11.

C. Definition of Part 11 Records

Under this narrow interpretation, FDA considers part 11 to be applicable to the following records or signatures in electronic format (part 11 records or signatures):

- Records that are required to be maintained under predicate rule requirements and that are maintained in electronic format in place of paper format. On the other hand, records (and any associated signatures) that are not required to be retained under predicate rules, but that are nonetheless maintained in electronic format, are not part 11 records. It is recommended that firms determine, based on the predicate rules, whether specific records are part 11 records and document such decisions.
- Records that are required to be maintained under predicate rules, that are maintained in electronic format in addition to paper format, and that are relied on to perform regulated activities. In some cases, actual business practices may dictate whether firms are using electronic records instead of paper records under § 11.2(a). For example, if a record is required to be maintained under a predicate rule and you use a computer to generate a paper printout of the electronic records, but the firm nonetheless relies on the electronic record to perform regulated activities, the Agency may consider you to be using the electronic record instead of the paper record. That is, the Agency may take your business practices into account in determining whether part 11 applies. Accordingly, FDA recommends that for each record required to be maintained under predicate rules, you determine in advance whether you plan to rely on the electronic record or paper record to perform regulated activities. We recommend that you document this decision [e.g., in a standard operating procedure (SOP), or specification document].
- Records submitted to FDA, under predicate rules (even if such records are not specifically identified in Agency regulations) in electronic format (assuming the records have been identified in docket number 92S-0251 as the types of submissions the Agency accepts in electronic format). However, a record that is not itself submitted, but is used in generating a submission, is not a part 11 record unless it is otherwise required to be maintained under a predicate rule and it is maintained in electronic format.
- Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules. Part 11 signatures include electronic signatures that are used, for example, to document the fact that certain events or actions occurred in accordance with the predicate rule (e.g., approved, reviewed, and verified).

D. Approach to Specific Part 11 Requirements

1. Validation: The Agency exercises enforcement discretion regarding specific part 11 requirements for validation of computerized systems [§ 11.10(a) and corresponding requirements in § 11.30]. Although persons must still comply with all applicable predicate rule requirements for validation [e.g., 21 CFR 820.70(i)], this guidance should not be read to impose any additional requirements for validation. It is suggested that a firm's decision to validate computerized systems, and the extent of the validation, take into account the impact the systems have on its ability to meet predicate rule requirements. Firms should also consider the impact those systems might have on the accuracy, reliability, integrity, availability, and authenticity of required records and signatures. Even if there is no predicate rule requirement to validate a system, in some instances it may still be important to validate the system. It is also recommended that firms base their approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity. For instance, validation would not be important for a word processor used only to generate SOPs.
2. Audit Trail: The Agency exercises enforcement discretion regarding specific part 11 requirements related to computer-generated, time-stamped audit trails [§ 11.10 (e), (k)(2) and any corresponding requirement in § 11.30]. Persons must still comply with all applicable predicate rule requirements related to documentation of, for example, date [e.g., § 58.130(e)], time, or sequencing of events, as well as any requirements for ensuring that changes to records do not obscure previous entries. Even if there are no predicate rule requirements to document, for example, date, time, or sequence of events in a particular instance, it may nonetheless be important to have audit trails or other physical, logical, or procedural security measures in place to ensure the trustworthiness and reliability of the records. It is recommended that firms base their decision on whether to apply audit trails, or other appropriate measures, on the need to comply with predicate rule requirements, a justified and documented risk assessment, and a determination of the potential effect on product quality and safety and record integrity. It is also recommended that firms apply appropriate controls based on such an assessment. Audit trails can be particularly appropriate when users are expected to create, modify, or delete regulated records during normal operation.
3. Legacy Systems: The Agency exercises enforcement discretion with respect to all part 11 requirements for systems that otherwise were operational prior to August 20, 1997, the effective date of part 11, under the circumstances specified below. This means that the Agency does not intend to take enforcement action to enforce compliance with any part 11 requirements if all the following criteria are met for a specific system:
   a. The system was operational before the effective date.
   b. The system met all applicable predicate rule requirements before the effective date.
   c. The system currently meets all applicable predicate rule requirements.
   d. Firm has documented evidence and justification that the system is fit for its intended use (including having an acceptable level of record security and integrity, if applicable).
   e. If a system has been changed since August 20, 1997, and if the changes would prevent the system from meeting predicate rule requirements, part 11 controls should be applied to part 11 records and signatures pursuant to the enforcement policy expressed in this guidance.

E. Copies of Records

The Agency exercises enforcement discretion with regard to specific part 11 requirements for generating copies of records [§ 11.10 (b) and any corresponding requirement in § 11.30]. Firms should provide an investigator with reasonable and useful access to records during an inspection. All records held by firms are subject to inspection in accordance with predicate rules [e.g., §§ 211.180(c), (d), and 108.35(c)(3)(ii)].

It is recommend that firms supply copies of electronic records by

- producing copies of records held in common portable formats when records are maintained in these formats;
- Using established automated conversion or export methods, where available, to make copies in a more common format (examples of such formats include, but are not limited to, PDF, XML, or SGML).

In each case, it is recommended that the copying process used produces copies that preserve the content and meaning of the record. If you have the ability to search, sort, or trend part 11 records, copies given to the Agency should provide the same capability if it is reasonable and technically feasible. You should allow inspection, review, and copying of records in a human readable form at your site using your hardware and following your established procedures and techniques for accessing records.

F. Record Retention

The Agency exercises enforcement discretion with regard to the part 11 requirements for the protection of records to enable their accurate and ready retrieval throughout the records retention period [§ 11.10 (c) and any corresponding requirement in § 11.30]. Persons must still comply with all applicable predicate rule requirements for record retention and availability [e.g., §§ 211.180(c),(d), 108.25(g), and 108.35(h)]. It is suggested that firm's decision on how to maintain records be based on predicate rule requirements and that the firm bases its decision on a justified and documented risk assessment and a determination of the value of the records over time.

FDA does not object if firms decide to archive required records in electronic format to nonelectronic media such as microfilm, microfiche, and paper, or to a standard electronic file format (examples of such formats include, but are not limited to, PDF, XML, or SGML). Persons must still comply with all predicate rule requirements, and the records themselves and any copies of the required records should preserve their content and meaning. As long as predicate rule requirements are fully satisfied and the content and meaning of the records are preserved and archived, you can delete the electronic version of the records. In addition, paper and electronic record and signature components can coexist (i.e., a hybrid situation) as long as predicate rule requirements are met and the content and meaning of those records are preserved.

VII. ESTABLISHING A COMPLIANCE PLAN

A large number of vendors are available to assist companies in identifying the level of compliance, building software control systems and auditing facilities to assure continued compliance. However, it is not possible for any vendor to offer a "turnkey" solution since compliance requires both procedural controls (i.e., notification, training, SOPs, administration) and administrative controls to be put in place by the user in addition to the technical controls that the vendor can offer. Vendors should be relied only for supply of application containing the required technical requirements of a compliant system.

In keeping records, question often arises on the type of media used to store data, particularly the type that is alterable such as flash memory or memory buffer. Generally, this is not the main concern how the data are stored, the important thing for the FDA to consider is whether the operator can manipulate the data before they are printed. The real problem is that most of this equipment does not have functions as required by part 11.

Often firms use a hybrid system who have not yet developed confidence in electronic database management. A "Hybrid System" is defined as an environment consisting of both Electronic and Paper-based Records (Frequently Characterized by Handwritten Signatures Executed on Paper). A very common example of a Hybrid System is one in which the system user generates an electronic record using a computer-based system (e-batch records, analytical instruments, etc.) and then is require to sign that record as per the Predicate Rules (GLP, GMP. GCP). However, the system does not have an electronic signature option, so the user has to print out the report and sign the paper copy. Now he has an electronic record and a paper/handwritten signature. The "system" has an electronic and a paper component, hence the term, hybrid. Since part 11 does not require that electronic records be signed using electronic signatures, e-records may be signed with handwritten signatures that are applied to electronic records or handwritten signatures that are applied to a piece of paper. If the handwritten signature is applied to a piece of paper, it must link to the electronic record. The FDA will publish guidance on how to achieve this link in the future, but for now it is suggested that firms include in the paper as much information as possible to accurately identify the unique electronic record (e.g., at least file name, size in bytes, creation date, and a hash or checksum value.) Hoverer, the master record is still the electronic record. Thus, signing a printout of an electronic record does not exempt the electronic record from part 11 compliance. There is no deadline for converting to electronic signatures. Having handwritten signatures on paper is acceptable if signature are linked to electronic records so signers cannot repudiate records.

Audio recordings of regulated patient information or experimental observations are infrequent, but sometimes acquired. Also, audio conferences discussing projects, reports, data are common in the pharma industry. If the data therein is required to be maintained by predicate rules, and the audio file is saved to durable media, part 11 would apply.

An audit trail initiation requirements differ for data versus textual materials. For data: if you are generating, retaining, importing, or exporting any electronic data, the Audit Trail begins from the instant the data hits the durable media. For textual documents: if the document is subject to approval and review, the Audit Trail begins upon approval and release of the document. The execution of a signature is also part of audit trail. When using e-mails as recorded data, then the e-mails have to be managed in a compliant way.

The restrictions regarding login are specific and enforceable. A single restricted login does not suffice as an electronic signature. The operator has to indicate intent when signing something, and he has to reenter the user ID/password (shows awareness that he is executing a signature) and give the meaning for the e-sig. To support this, part 11 § 11.50, states that signed e-records shall contain information associated with the signing that indicates the printed name of the signer, the date/time, and the meaning, and that

these items shall be included in any human readable form of the record. The predicate rules mandate when a regulated document needs to be signed. It is however not necessary for a firm to certify that every associate's electronic signature is legally binding. The required one-time e-sig certification is for an organization as a whole. Its intent is to certify that a company recognizes that its e-signatures are equivalent to their handwritten signatures.

The Agency has recently reconsidered its position on local date and time stamp requirements. The draft guidance document reflects their current thinking, and supersedes the position with respect to the time zone that should be recorded. The document states, "You should implement time stamps with a clear understanding of what time zone reference you use. Systems documentation should explain time zone references as well as zone acronyms or other naming conventions."

According to the Rule, the definition of closed system is "an environment in which system access is controlled by persons who are responsible for the content of electronic records that are on the system.'' The agency agrees that the most important factor in classifying a system as closed or open is whether the persons responsible for the content of the electronic records control access to the system containing those records. A system is closed if persons responsible for the content of the records control access. If those persons do not control such access, then the system is open because the records may be read, modified, or compromised by others to the possible detriment of the persons responsible for record content. Hence, those responsible for the records would need to take appropriate additional measures in an open system to protect those records from being read, modified, destroyed, or otherwise compromised by unauthorized and potentially unknown parties.

Part 11 sec. 11.70 states that electronic signatures and handwritten signatures executed to electronic records must be linked (i.e., verifiably bound) to their respective records to ensure that signatures could not be excised, copied, or otherwise transferred to falsify another electronic record. The agency does not, however, intend to mandate use of any particular "linking" technology. FDA recognizes that, because it is relatively easy to copy an electronic signature to another electronic record and thus compromise or falsify that record, a technology-based link is necessary. The agency does not believe that procedural or administrative controls alone are sufficient to ensure that objective because such controls could be more easily circumvented than a straightforward technology-based approach.

A predicate rule is any requirements set forth in the Act (Federal Food, Drug and Cosmetic Act), the PHS Act (Public Health Service Act), or any FDA regulation (GxP: GLP, GMP, GCP, etc.). The predicate rules mandate what records must be maintained; the content of records; whether signatures are required; how long records must be maintained, etc. If there is no FDA requirement that a particular record be created or retained, then 21 CFR part 11 most likely does not apply to the record.

To make sure that e-records are still readable throughout the retention period (with focus on the formats), there are several possible solutions being considered include data migration, data emulation, and system "Time Capsules". As of today, there are no set standards, or widely accepted procedures to ensure long-term data viability.

Meta data is defined as "data about data". In practical terms, the types of metadata that can be associated with an electronic record may include the following: details of the record's creation, author, creation date, ownership, searchable keywords that can be used to classify the document, details of the type of data found in the document, and the relationships between different data components. Metadata must be stored as an integral part of the electronic document it describes.

The use of Electronic Signatures implies that your system is an Electronic Record system and, therefore, must be in compliance with all provisions of 21 CFR part 11. For the exact wording for the e-sig certification, please consult the FDA website at www.fda.gov. One can also find wording for the certification in the preamble of the final Rule. The response to comment #120 is "... The final rule instructs persons to send certifications to FDA's Office of Regional Operations (HFC-100), 5600 Fishers Lane, Rockville, MD 20857. Persons outside the United States may send their certifications to the same office. The agency offers, as guidance, an example of an acceptable sec. 11.100(c) certification: Pursuant to section 11.100 of title 21 of the Code of Federal Regulations, this is to certify that (name of organization) intends that all electronic signatures executed by our employees, agents, or representatives, located anywhere in the world, are the legally binding equivalent of traditional handwritten signatures."

In an effort to remain technologically neutral, the FDA does not specify the kind of media that one must use for archiving. There are studies currently underway from independent sources that are trying to test the "lifetime" of such media as CD-ROM, although there is no set standard lifetime for such media. Some companies are doing their own tests on media lifetime.

Whether part 11 applies to instruments that are not connected to computers but that have microprocessors within depends whether such a system generates electronic records according to the definition of e-records in part 11 (data starting its life written to durable media), and/or these e-records are not subject to the GxP regulations, then part 11 does not apply.

The "Predicate Rules" (GxP) regulations determine what records must be signed, not part 11. Not all e-records need to be signed. Check your predicate rules for what records must be signed, when and by whom.

In order for a system to comply with part 11, both the hardware and the software should be under controlled access. This is necessary to monitor who is signing the documents.

Although it is not specified in part 11, most software programs that execute e-sigs and that have notification capabilities report attempts via an e-mail notice to a database administrator for any forgery attempts.

The audit trail for Excel should capture changes to both the data and to formulas. Things like formatting changes (alignment/font) to cells do not have to be audit trailed.

Hashing can be used for accessing data or for data security. A hash is a number generated from a string of text. The hash is substantially smaller than the text itself and is generated by a formula in such a way that it is unlikely that some other text will produce the same hash value. Hashes play a role in security systems where they are used to ensure that transmitted messages have not been tampered with. The sender generates a hash of the message, encrypts it, and sends it with the message itself. The recipient then decrypts both the message and the hash, produces another hash from the received message, and compares the two hashes. If they are the same, there is a very high probability that the message was transmitted intact.

In part 11.300, controls for identification codes/passwords usage is listed under.

The controls for password/user ID usage apply across the board for ERES systems. They apply to the proper management of electronic records in addition to executing compliant electronic signatures.

For part 11, data integrity is related to the trustworthiness of the electronic records generated/managed by critical systems. The FDA is most concerned about systems that are involved with drug distribution, drug approval, manufacturing, and quality assurance because these systems pose the most risk in terms of product quality and/or public safety.

What type of "reporting" capability on audit trail data should be supported?

According to part 11 § 11.10 (e) audit trails must be secure, computer-generated and time-stamped to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. Such audit trail documentation shall be retained for a period at least as long as that required for the subject electronic records and shall be available for agency review and copying. Audit trails should say "who did what to your records and when (why for GLP)". Part 11 does not specify the format for audit trials. This should be discussed in a forthcoming FDA guidance document for part 11 audit trails.

A digital signature is computed using a set of rules and a mathematical algorithm such that the identity of the signatory and integrity of the data can be verified. Signature generation makes use of a private key to generate a digital signature. Signature verification makes use of a public key that corresponds to, but is not the same as, the private key. Each user possesses a private and public key pair. Public keys are obviously known to the public, while private keys are never shared. Anyone can verify the signature of a user by employing that user's public key. Only the possessor of the user's private key can perform signature generation. A hash function is used in the signature generation process to obtain a condensed version of data, called a message digest. The message digest is then incorporated into the mathematical algorithm to generate the digital signature. The digital signature is sent to the intended verifier along with the signed message. The verifier of the message and signature verifies the signature by using the sender's public key. The same hash function must also be used in the verification process. The hash function is specified in a separate standard.

For an analytical instrument, any information that is captured by a computerized workstation is considered either data or metadata. (Metadata is described as data-about-data. It is what puts the real data into logical context.) The second that any information hits the "durable media" it then becomes an electronic record. Parameters that are typically captured by an HPLC system (i.e., flow rate, sample lot #, etc.) are considered metadata. This information should be saved and protected as part of the official electronic record.

VIII. SOFTWARE AND SYSTEMS SUPPORT

The Food and Drug Administration (FDA) in the United States designed part 11 of title 21 of the Code of Federal Regulations (21 CFR part 11) to help ensure that life sciences companies can use electronic records and signatures that are equivalent to those based on paper and ink. However, initiating and maintaining part 11 compliance can be complex and costly. Many excellent fully validated software systems are available for all levels of investment. Most notably, SAP and Oracle systems now provide full integration of all recommendations made in part 11. On the other end of the cost of deployment, the 2007 Microsoft Office system simplifies compliance with support for the complete document lifecycle. In fact, much of the functionality necessary for part 11 compliance is built into the Office system, including workflow, audit trails, digital signatures, and full versioning support.

The life sciences industry is challenged with increasingly stringent regulations, requiring enormous volumes of documentation. Electronic document management has helped to streamline these documentation processes. However, in the life sciences industry, the way in which this documentation is managed comes with its own specific regulations, known as 21 CFR part 11.

These FDA regulations establish criteria under which electronic records and signatures can be considered equivalent to paper-based records and handwritten signatures. Without a part 11-compliant document management environment, life sciences companies that fail to meet compliance regulations are subject to substantial fines or the shutdown of operations. Technology requirements pertaining to part 11 compliance include the following:

- Security controls to prevent unauthorized access to documents
- Time and date-stamped audit trails recording changes to records
- Electronic signatures on documents with name, date, and purpose of signature
- Policies that hold users accountable for documents

Although many systems exist that claim to be part 11-compliant, they are often too complex to be effective. Common complaints include the following:

- The inability to collaborate efficiently on documentation while maintaining competitive speed-to-market
- Difficulty locating files across multiple databases and applications
- Lack of understanding and use of compliant enterprise content management systems
- Bottlenecks resulting from having only one "expert" appointed to post documents into a repository

The 2007 Microsoft Office system provides easy-to-use document management tools that can help life science companies of all sizes achieve part 11 compliance quickly and cost-effectively. Following are the key features that address specific part 11 requirements:

- Document security. Apply restrictions to individual documents and across entire libraries in order to more easily control who can open, copy, print, or forward information. A records vault prevents direct tampering of documents and helps ensure the protection of original versions. Portal access is password-protected, and access to specific content can be restricted based on role.
- Detailed auditing. Powerful document tracking functionality provides a detailed, time-stamped audit trail of document management activity.
- Digital signatures. The applications of the 2007 Microsoft Office system automatically assess the authenticity of digital signatures and signed documents and alert the administrator if there are any discrepancies.
- Automated workflow and policies. Managers can easily configure templates so that all the elements required for compliance (such as specific content fields, digital signature fields, and policy requirements) can be built directly

into a Microsoft Office Word 2007 or Microsoft Office Excel 2007 file. This helps support compliant practices and helps ensure that documents are automatically assigned to the right people for review and approval.

By adopting a 21 CFR part 11 solution based on the 2007 Microsoft Office system, life sciences companies can

- dramatically simplify the document management processes required for compliance;
- reduce errors by using predefined templates;
- encourage compliant document management practices through familiar, easy-to-use Microsoft technologies;
- minimize compliance-related headcount;
- reduce compliance and infrastructure costs by leveraging investments in Microsoft products; and
- implement a solution quickly without disrupting the organization.

To rapidly address 21 CFR part 11 challenges, the 2007 Microsoft Office system is the ideal choice. New technologies built into the 2007 Microsoft Office system can help in the following ways:

- Simplify the management of complex compliance process
- Users can easily initiate a wide range of automated workflows directly from Microsoft Office Word 2007 or Microsoft Office Excel 2007, including reviews, approvals, edits, requests for digital signatures, and feedback
- Administrators can track each workflow and monitor how it performs overall, as well as drill down into specific instances of a workflow
- Content types allow administrators and compliance managers to predefine templates so that all new documents of a given type are automatically assigned the appropriate policies, such as workflow, resulting actions, and expiration
- Perform detailed audit analysis
- Microsoft Office SharePoint Server 2007 allows administrators to audit key events within document libraries and monitor global events on a site (such as search, user changes, and changes in content types and columns), which creates evidence of who accessed which resources at what time
- A central administration site makes it easy to configure various settings for auditing, such as selecting specific events to audit
- Auditing functionality can be extended using a Web service or by using the audit log service object model, so other applications can provide a full audit when their files are stored on a SharePoint site
- Protect data with more powerful security features
- Users of the portal are authenticated automatically based on their role and user information from Active Directory
- Information Rights Management (IRM) policies can be applied to both individual documents and entire libraries, making it easier to get consistent use of IRM across a set of documents without creating extra work for individual users
- The applications of the 2007 Microsoft Office system automatically assess the authenticity of digital signatures and signed documents, and alert the administrator if there are any discrepancies
- A records repository facilitates security-enhanced document management processes, including content collection, consistent policy enforcement, item retention and holds in response to external events, and content expiration
- Reduce administrative costs with new tools and formats
- New, XML-based file formats for Microsoft Office Word 2007, Microsoft Office Excel 2007, and Microsoft Office PowerPoint 2007 can allow these documents to easily integrate with existing and future line-of-business systems
- Office Open XML Formats use ZIP compression technology, so documents take up far less space than the previous formats, which means shorter transmission times and a smaller impact on storage
- The Office Customization Tool simplifies customization simple and efficient by replacing the many wizards that were necessary in previous releases of the Microsoft Office
- Leverage deployed Microsoft technologies
- Roll out a 21 CFR part 11 solution quickly, with minimal training, leveraging the familiar Microsoft products you have already installed
- Maintain a low total cost of ownership by extending investments in Microsoft products
- Take advantage of a rich network of technology partners who are well-versed in Microsoft Office technologies and 21 CFR part 11 implementations

The 2007 Microsoft Office system is an integrated set of products, technologies, and services that enable customers to increase their organizational, team, and personal productivity. A 21 CFR part 11-compliant solution often uses these products and technologies:

Microsoft Office SharePoint Server 2007
Microsoft Office Word 2007
Microsoft Office Excel 2007
Microsoft Office InfoPath 2007

In addition to Microsoft products, many companies have partnered with Microsoft to offer very affordable solutions to part 11 compliance. Some of these include the following:

- NextDocs Corporation: NextDocs Document Management. NextDocs DM is an enterprise document and records management solution.
- QualityDocs is end-to-end quality management system that enables management of quality documents and processes.
- EmployeeDocs is a robust tracking and employee record management system.
- ProjectDocs provides turnkey project level document management.
- ThoughtBridge, LLC: Engineering Change Orders (ECOs). ThoughtBridge has created an automated, systematic approach to driving the ECO process—and customized it for the life sciences industry using the 2007 Microsoft Office System. ECOs help companies monitor and track activities associated with any changes to its products.
- Zorch Software: Zorch DM/Zorch Submission Manager. Zorch Software provides comprehensive Microsoft-based document management and submission management solutions.
- Clusterseven Ltd: Enterprise Spreadsheet Management Software is a complete solution to support the use of Excel spreadsheets as operational applications in business-critical processes. It delivers auditability, regulatory compliance (e.g., SOX), reduced risk, change management and transparency of data and activity. It does all this without reducing the flexibility and familiarity that makes Excel so powerful at delivering fast, competitive and cost-effective solutions to changing business needs.
- Perficient: Collaborative Document Generation and Workflow. The Collaborative Document Generation and

Workflow solution is a comprehensive Document Creation application that automatically generates word documents for very complex documents with a high degree of business rules and processing.

- Newtech Global Solutions LLC: NGS's SPLGen. A quality process that lighten the need for companies to undertake significant internal review prior to submission in preparing and validating the SPL XML data. The ability to keep labeling documents within Microsoft Share Point Electronic Document Management System, so it meets document compliance and record management requirements. SPLGen has an option to import SPL compliant XML data files from other systems like DailyMed.
- Strategic Thought Group PLC: Active Risk Manager. Providing compliance, project, operational and corporate risk, control, opportunity, and issue management. Fully integrated to the MS Project Server family of products and MS SharePoint. Delivers value streams for projects, assets, processes, organization, key performance indicators and financial accounts.
- Workshare USA: Workshare Professional. Workshare Professional is an Outbound Content Security and Document Integrity solution that eliminates the risk of content leaks and inaccuracies, enabling the safe, compliant and high speed information exchange needed in today's competitive business environment.
- Workshare, an information security company, delivers Secure Content Compliance solutions ensuring safe information exchange without business disruption. SourceCode – K2.net Workflow: K2.net BlackPearl (K2.net 2007).

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		Compliance 1 2 3[a]	Remarks	EU Guide
1	**PERSONNEL**			
1.1	Qualified personnel available?	☐ ☐ ☐		2.1
1.2	Organization charts available?	☐ ☐ ☐		2.2
1.3	Job descriptions available?	☐ ☐ ☐		2.2
1.4	Responsibilities clearly defined?	☐ ☐ ☐		2.2
	Key personnel			
	Responsible persons designated for			
1.5	• production?	☐ ☐ ☐		2.5
1.6	• quality control?	☐ ☐ ☐		2.6
1.7	Are they independent from each other?	☐ ☐ ☐		2.3
1.8	Are joint functions clearly defined?	☐ ☐ ☐		2.7
1.9	Are the responsible persons working full time?	☐ ☐ ☐		2.3
1.10	Do the responsible persons have the appropriate formation, knowledge, and experience?	☐ ☐ ☐		2.1/2.2
1.11	Do the relevant departments have enough personnel?	☐ ☐ ☐		2.1
	Training			
1.12	Continuous training programs for the production and QC staff?	☐ ☐ ☐		2.8
1.13	Initial job training for all employees?	☐ ☐ ☐		2.9
1.14	Teaching aids (videos, slides, and brochures) available?	☐ ☐ ☐		2.9
1.15	External training courses for the staff?	☐ ☐ ☐		2.9
1.16	Training records?	☐ ☐ ☐		2.9
1.17	Special training in sensitive areas? (sterile prod. and toxic subs.)	☐ ☐ ☐		2.10
1.18	Information for visitors to the manufacturing area?	☐ ☐ ☐		2.11
2	**HYGIENE**			
	Personnel hygiene			
	Detailed written hygiene programs for			
2.1	• clothing?	☐ ☐ ☐		2.13
2.2	• use of washrooms?	☐ ☐ ☐		2.13
2.3	• behavior in production areas?	☐ ☐ ☐		2.13
2.4	Precautions against sick or personnel with open wounds in production?	☐ ☐ ☐		2.14
	Medical examination:			
2.5	• on recruitment?	☐ ☐ ☐		2.15
2.6	• regular reexaminations?	☐ ☐ ☐		2.15

		Compliance 1 2 3[a]	Remarks	EU Guide
	Duty of notification after:			
2.7	• trips to tropical countries?	☐ ☐ ☐		2.15
2.8	• cases of contagious illness in the family?	☐ ☐ ☐		2.15
2.9	Instructions for appropriate working clothes?	☐ ☐ ☐		2.16
2.10	Absence of food and drinks (chewing gum!) in the working area?	☐ ☐ ☐		2.17
2.11	Measures against contact with open product (gloves etc.)?	☐ ☐ ☐		2.18
2.12	Instructions for hand washing in production?	☐ ☐ ☐		2.19
2.13	Change of clothes when entering and leaving the production area?	☐ ☐ ☐		5.19
2.14	Change rooms and toilets easily within reach?	☐ ☐ ☐		3.31
2.15	Toilets and restrooms sufficiently separated from production areas?	☐ ☐ ☐		3.30/3.31
2.16	Workshops separate from production areas?	☐ ☐ ☐		3.32
2.17	Laboratory animal rooms totally segregated from production rooms?	☐ ☐ ☐		3.33
3	**WAREHOUSE**			
	Rooms, general			
3.1	Suitable for the intended use?	☐ ☐ ☐		3
3.2	• adequate size?	☐ ☐ ☐		3
3.3	• clean?	☐ ☐ ☐		3
3.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
3.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
3.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
3.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
3.8	Recording of temperature and humidity?	☐ ☐ ☐		
3.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
3.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
	Type of warehousing:			
3.11	Separation of goods sufficient?	☐ ☐ ☐		3.18
3.12	Provision for different storage temperatures?	☐ ☐ ☐		3.19
3.13	Goods receiving zone weather protected?	☐ ☐ ☐		3.20
3.14	Cleaning zone for incoming goods?	☐ ☐ ☐		3.20
3.15	Separate quarantine area with controlled access?	☐ ☐ ☐		3.21
3.16	Separate, protected sampling area?	☐ ☐ ☐		3.22
	Separate and safe storage of			
3.17	• returned goods?	☐ ☐ ☐		3.23
3.18	• rejected goods?	☐ ☐ ☐		3.23
3.19	Separate and safe storage of highly active, toxic, or dangerous substances?	☐ ☐ ☐		3.24
3.20	Safe storage of narcotics?	☐ ☐ ☐		3.24
3.21	Safe storage of printed packaging materials?	☐ ☐ ☐		3.25
3.22	Security measurements against theft?	☐ ☐ ☐		3.25
3.23	Smoke detectors?	☐ ☐ ☐		3.25
3.24	Fire extinguishing system?	☐ ☐ ☐		3.25

			Compliance 1 2 3[a]	Remarks	EU Guide
	Operations				
3.25	Reception, sampling, and labeling according to written procedures?		☐ ☐ ☐		5.2
3.26	Is a sampling plan available?		☐ ☐ ☐		Suppl. 4
3.27	Cleaning of incoming containers?		☐ ☐ ☐		5.3
3.28	Investigation and recording of damaged deliveries?		☐ ☐ ☐		5.4
3.29	FIFO principle?		☐ ☐ ☐		5.7
3.30	Inventory system?		☐ ☐ ☐		5.8
3.31	The location of materials can be detected at all times?		☐ ☐ ☐		
3.32	Incoming goods: containers and seals intact?		☐ ☐ ☐		5.27
3.33	Incoming goods: conformity with bill of delivery?		☐ ☐ ☐		5.27
	Labeling of incoming containers with				
3.34	• internal name and code?		☐ ☐ ☐		5.29
3.35	• allocated batch number?		☐ ☐ ☐		5.29
3.36	• quarantine status?		☐ ☐ ☐		5.29
3.37	• expiry date or reanalysis date?		☐ ☐ ☐		5.29
3.38	Identity test for each incoming container?		☐ ☐ ☐		5.29
3.39	Are the sampled containers marked?		☐ ☐ ☐		5.30
3.40	Are reference samples taken?		☐ ☐ ☐		5.30
3.41	Safe storage of printed packaging materials?		☐ ☐ ☐		5.41
3.42	Lot tracing of all packaging materials possible?		☐ ☐ ☐		5.42
3.43	Are excessive packaging materials destroyed?		☐ ☐ ☐		5.43
	Release of starting materials by				
	Physical/inventory checks on raw materials, packaging materials, and finished goods:				
	Item:	Stocks: Physical:	Stocks: Inventory:	Storage conditions:	
4	**DISPENSING/ASSEMBLING**				
	Rooms, general				
4.1	Suitable for the intended use?		☐ ☐ ☐		3
4.2	• adequate size?		☐ ☐ ☐		3
4.3	• clean?		☐ ☐ ☐		3
4.4	Located and designed to exclude external contamination?		☐ ☐ ☐		3.1
4.5	Appropriate level of maintenance?		☐ ☐ ☐		3.2
4.6	Maintenance works possible without contamination risk?		☐ ☐ ☐		3.2

		Compliance 1 2 3[a]	Remarks	EU Guide
4.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
4.8	Recording of temperature and humidity?	☐ ☐ ☐		
4.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
4.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
4.11	Segregated from production and warehouse?	☐ ☐ ☐		3.13
4.12	Separate weighing cabins?	☐ ☐ ☐		3.13
4.13	Separate AHU for each cabin?	☐ ☐ ☐		3.12
	Air pressure gradient from weighing cabin → corridor:			3.3
4.14	Dust extraction systems available?	☐ ☐ ☐		5.11
	Operations			
4.15	Balances regularly calibrated?	☐ ☐ ☐		3.41
4.16	Only pharmaceutical raw materials in this area?	☐ ☐ ☐		5.17
4.17	Check on remains from previous materials before entering of new materials into a weighing cabin?	☐ ☐ ☐		5.9/5.35
4.18	Only one material in one cabin?	☐ ☐ ☐		5.9
4.19	Are dispensed materials correct labeled?	☐ ☐ ☐		5.29
4.20	Only released products in the dispensing?	☐ ☐ ☐		5.31
4.21	Cleaning SOP's for the dispensing?	☐ ☐ ☐		4.28
4.22	Previously dispensed material recorded on weighing protocol?	☐ ☐ ☐		4.8
4.23	Safety measures against mix-ups during assembling (e.g., cage pallets)?	☐ ☐ ☐		5.32/5.34
5	**SOLIDS MANUFACTURING**			
	Field of activity:			
	• granulation	☐		
	• compression	☐		
	• encapsulation	☐		
	• film and sugar coating	☐		
	• visual inspection (capsules, tablets, etc.)	☐		
	• premix (human)	☐		
	Rooms, general			
5.1	Suitable for the intended use?	☐ ☐ ☐		3
5.2	• adequate size?	☐ ☐ ☐		3
5.3	• clean?	☐ ☐ ☐		3
5.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
5.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
5.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
5.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
5.8	Recording of temperature and humidity?	☐ ☐ ☐		
5.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
5.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
5.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6

		Compliance 1 2 3[a]	Remarks	EU Guide
5.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
5.13	Logical flow of materials?	☐ ☐ ☐		3.7
5.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
5.15	Easy cleaning possible?	☐ ☐ ☐		3.10
5.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
5.17	Appropriate air-handling system?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
5.18	Appropriate dust extraction system?	☐ ☐ ☐		3.14
5.19	Appropriate lighting?	☐ ☐ ☐		3.16
5.20	Separate rest rooms?	☐ ☐ ☐		3.30
5.21	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
5.22	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
5.23	Suitable for the intended use?	☐ ☐ ☐		3.34
5.24	Well maintained?	☐ ☐ ☐		3.34
5.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
5.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
5.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
5.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
5.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
5.30	Calibration records available?	☐ ☐ ☐		3.41
5.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
5.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
5.33	Not functioning equipment in the production area (if yes: clearly marked)?	Y N ☐ ☐ ☐		3.44
5.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
5.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
5.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
5.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
5.38	Check of each single container of the starting materials (contents, weight, and identity)?	☐ ☐ ☐		5.3
5.39	Limits for yields?	☐ ☐ ☐		5.8
5.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
5.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
5.42	Appropriate measures against generation of dust (e.g. closed systems)?	☐ ☐ ☐		5.11
	Correct labeling of containers, materials, equipment, and rooms with			5.12

		Compliance 1 2 3[a]	Remarks		EU Guide
5.43	• product name and batch no.	☐ ☐ ☐			5.12
5.44	• quarantine status?	☐ ☐ ☐			5.12
5.45	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐			5.14
5.46	Special procedures for the production of antibiotics, hormones, etc.?	☐ ☐ ☐			5.19
5.47	• Campaign production?	☐ ☐ ☐			5.19
5.48	• Special monitoring?	☐ ☐ ☐			5.19
5.49	• Validated decontamination procedure?	☐ ☐ ☐			5.19
5.50	Double check on weight?	☐ ☐ ☐			5.34
5.51	Line clearance before start of production?	☐ ☐ ☐			5.35
5.52	Investigation of deviations in yields?	☐ ☐ ☐			5.39
5.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐			5.62
5.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐			5.63
5.55	Special release procedure (QA) for those batches?	☐ ☐ ☐			5.64
5.56	Use of protective clothing (hair cover, shoes, masks, and gloves)?	☐ ☐ ☐			2.16
5.57	Clothing regulation for visitors?	☐ ☐ ☐			2.11
	IPC				5.38
	Who performs IPC?				
5.58	Are IPC methods approved by QC?	☐ ☐ ☐			6.18
	Performance of IPCs:	During Start-up? Yes No	Frequency	Automatic data recording? Yes No	
	Tablets/kernels				
5.59	Individual weights	☐ ☐		☐ ☐	
5.60	Disintegration	☐ ☐		☐ ☐	
5.61	Thickness	☐ ☐		☐ ☐	
5.62	Hardness	☐ ☐		☐ ☐	
5.63	Friability/Abrasion	☐ ☐		☐ ☐	
	Sugar-/film-coated tablets				
5.64	Weights	☐ ☐		☐ ☐	
5.65	Disintegration	☐ ☐		☐ ☐	
5.66	Residual absolute humidity (IR or)	☐ ☐		☐ ☐	
	Capsules				
5.67	Individual weights	☐ ☐		☐ ☐	
5.68	Disintegration	☐ ☐		☐ ☐	
	Validation				
5.69	Validation according to fixed procedures?	☐ ☐ ☐			5.21
5.70	New procedures released only after validation?	☐ ☐ ☐			5.22
	Validation of changes of				
5.71	• processes?	☐ ☐ ☐			5.23
5.72	• starting materials?	☐ ☐ ☐			5.23
5.73	• equipment?	☐ ☐ ☐			5.23

		Compliance 1 2 3[a]	Remarks	EU Guide
5.74	Revalidation in fixed intervals?	☐ ☐ ☐		5.24
5.75	Procedures for the retrospective validation of old procedures?	☐ ☐ ☐		
6	**LIQUIDS MANUFACTURING**			
	Operations carried out:			
	• Dispensing (if different from solid)	☐ ☐ ☐		
	• Syrups and suspensions	☐ ☐ ☐		
	• Drops	☐ ☐ ☐		
	• Ointment manufacture	☐ ☐ ☐		
	• Ointment filling	☐ ☐ ☐		
	• Ampoule solution manufacture	☐ ☐ ☐		
	• Sterile or aseptic ampoule filling	☐ ☐ ☐		
	• Sterile freeze drying	☐ ☐ ☐		
	• Sterile powder filling	☐ ☐ ☐		
	Rooms, general			
6.1	Suitable for the intended use?	☐ ☐ ☐		3
6.2	• adequate size?	☐ ☐ ☐		3
6.3	• clean?	☐ ☐ ☐		3
6.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
6.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
6.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
6.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
6.8	Recording of temperature and humidity?	☐ ☐ ☐		
6.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
6.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
6.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6
6.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
6.13	Logical flow of materials?	☐ ☐ ☐		3.7
6.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
6.15	Easy cleaning possible?	☐ ☐ ☐		3.10
6.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
6.17	Appropriate air-handling system with filtered air where open products are exposed to the environment?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
6.18	Appropriate lighting?	☐ ☐ ☐		3.16
6.19	Separate rest rooms?	☐ ☐ ☐		3.30
6.20	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
6.21	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
6.22	Suitable for the intended use?	☐ ☐ ☐		3.34
6.23	Well maintained?	☐ ☐ ☐		3.34
6.24	Tanks, containers, pipework, and pumps designed for easy cleaning and sanitation (dead legs!)?	☐ ☐ ☐		Suppl. 2

		Compliance 1 2 3[a]	Remarks	EU Guide
6.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
6.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
6.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
6.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
6.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
6.30	Calibration records available?	☐ ☐ ☐		3.41
6.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
6.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
6.33	Not functioning equipment in the production area (if yes: clearly marked)?	Y N ☐ ☐ ☐		3.44
6.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
6.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
6.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
6.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
6.38	Check of each single container of the starting materials (contents, weight, and identity)?	☐ ☐ ☐		5.3
6.39	Limits for yields?	☐ ☐ ☐		5.8
6.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
6.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
	Correct labeling of containers, materials, equipment, and rooms with			5.12
6.42	• product name and batch no.	☐ ☐ ☐		5.12
6.43	• quarantine status?	☐ ☐ ☐		5.12
6.44	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐		5.14
6.45	Special procedures for the production of antibiotics, hormones, etc.?	☐ ☐ ☐		5.19
6.46	• Campaign production?	☐ ☐ ☐		5.19
6.47	• Special monitoring?	☐ ☐ ☐		5.19
6.48	• Validated decontamination procedure?	☐ ☐ ☐		5.19
6.49	Double check on weight?	☐ ☐ ☐		5.34
6.50	Line clearance before start of production?	☐ ☐ ☐		5.35
6.51	Investigation of deviations in yields?	☐ ☐ ☐		5.39
6.52	Specification of max. storage time and storage conditions if products are not immediately filled or packaged?	☐ ☐ ☐		Suppl. 9
6.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐		5.62
6.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐		5.63
6.55	Special release procedure (QA) for those batches?	☐ ☐ ☐		5.64
6.56	Use of protective clothing (hair cover, shoes, masks, and gloves)?	☐ ☐ ☐		2.16
6.57	Clothing regulation for visitors?	☐ ☐ ☐		2.11

		Compliance 1 2 3[a]	Remarks	EU Guide
	Water			
6.58	Loop system for purified water?	☐ ☐ ☐		Suppl. 4
6.59	Antimicrobial treatment of purified water?	☐ ☐ ☐		Suppl. 4
6.60	Loop system for water for injection?	☐ ☐ ☐		Suppl. 4
	Storage temperature of water for injection:			Suppl. 4
6.61	Loop system constructed to avoid deadlegs?	☐ ☐ ☐		Suppl. 4
6.62	Regular microbiological monitoring?	☐ ☐ ☐		Suppl. 4
6.63	Regular endotoxin control?	☐ ☐ ☐		Suppl. 4
	Special requirements for sterile and aseptic products			**Suppl.**
	Rooms and equipment			
6.64	Access of staff and materials to clean areas *only* through air locks?	☐ ☐ ☐		1
6.66	Rooms classified according EC guide?	☐ ☐ ☐		3
	Classification for products to be sterilized:			
6.67	• Solution preparation (EC: class C, with special precautions class D):	Class:		5
6.68	• Filling (EC: under LF in class C):	Class:		5
	Classification for aseptic products:			
6.69	• Handling of starting materials that can be sterile filtered (EC: class C):	Class:		6
6.70	• Handling of starting materials that cannot be sterile filtered (EC: class A in class B):	Class:		6
6.71	• Handling and filling of bulk (EC: class A in Class B):	Class:		6
6.72	All rooms easy to clean disinfect?	☐ ☐ ☐		17
6.73	Doors, windows, frames, lighting, etc. without edges?	☐ ☐ ☐		18
6.74	Suspended ceilings (if yes: sealed?)?	☐ ☐ ☐		19
6.75	Traps constructed to avoid microb. contamination?	☐ ☐ ☐		21
6.76	Appropriate constructed changing rooms?	☐ ☐ ☐		22
6.77	Measures against opening of both doors of air locks?	☐ ☐ ☐		23
6.78	Overpressure gradient from cleanest areas to others?	☐ ☐ ☐		24
6.79	AHU validated and regularly revalidated?	☐ ☐ ☐		25
6.80	Control instruments for pressure gradient?	☐ ☐ ☐		26
6.81	Warning system for errors in air supply?	☐ ☐ ☐		26
6.82	Recording of pressure gradients?	☐ ☐ ☐		26
6.83	Do conveyor belts leave sterile areas?	☐ ☐ ☐		28
6.84	Maintenance works outside from clean areas possible?	☐ ☐ ☐		28
6.85	Cleaning and disinfection procedure after maintenance works?	☐ ☐ ☐		29
6.86	Regular revalidation of all equipment and systems?	☐ ☐ ☐		30
6.87	Water prepared, circulated, and stored to exclude microb. contamination?	☐ ☐ ☐		31
6.88	Cleaning and disinfection of rooms according to validated SOPs rooms?	☐ ☐ ☐		32
	• Disinfection methods?			
6.89	Microb. monitoring of cleaning and disinfection agents?	☐ ☐ ☐		33

		Compliance 1 2 3[a]	Remarks	EU Guide
6.90	Microb. monitoring program of production areas?	☐ ☐ ☐		35
6.91	Results recorded and considered for the release?	☐ ☐ ☐		35
	Personnel and hygiene			
6.92	Minimal no. of personnel in clean areas?	☐ ☐ ☐		7
6.93	Special and regular training?	☐ ☐ ☐		8
6.94	Regular medical examinations?	☐ ☐ ☐		10
6.95	Appropriate clean room clothes (material, design)?	☐ ☐ ☐		12
6.96	Protective clothes worn correctly?	☐ ☐ ☐		12
6.97	Prohibition of cosmetics, jewellery, and watches?	☐ ☐ ☐		13
6.98	New clean room clothes for each working cycle?	☐ ☐ ☐		15
6.99	Appropriate washing and sterilization of clothes?	☐ ☐ ☐		16
	Operations			
6.100	Validation (media filling) in regular intervals?	☐ ☐ ☐		38
	Monitoring of water preparation system, frequency:			
6.101	• microbiological:			40
6.102	• chemical:			40
6.103	• particles:			40
6.104	• endotoxins:			40
6.105	Microbiological monitoring of starting materials?	☐ ☐ ☐		42
6.106	Max. storage times defined for sterilized equipment?	☐ ☐ ☐		45
6.107	Max. storage time defined between solution preparation and filtration?	☐ ☐ ☐		46
6.108	Material transfer to clean areas through double door autoclaves?	☐ ☐ ☐		48
	Sterilization processes			
6.109	All processes validated?	☐ ☐ ☐		50
6.110	Sterilized and nonsterilized materials clearly separated?	☐ ☐ ☐		54
	Trays and boxes clearly labeled with			
6.111	• product name and code	☐ ☐ ☐		54
6.112	• batch no.	☐ ☐ ☐		54
6.113	• status: sterilized or not sterilized	☐ ☐ ☐		54
	Sterilizers:			
6.114	• Recording of temp., pressure, and time?	☐ ☐ ☐		55
6.115	• Coldest point determined?	☐ ☐ ☐		55
6.116	• Independent counter check probe?	☐ ☐ ☐		55
6.117	• Heat-up time for each product determined?	☐ ☐ ☐		56
6.118	• Sterile cooling media?	☐ ☐ ☐		57
6.119	• Tightness tests for vacuum autoclaves?	☐ ☐ ☐		58
6.120	• Clean steam for steam autoclaves?	☐ ☐ ☐		58
6.121	• Circulated air with overpressure?	☐ ☐ ☐		61
6.122	• Recirculated air: sterile filtered?	☐ ☐ ☐		61
6.123	• Ethylene oxide autoclaves: humidity, temp., and time recorded?	☐ ☐ ☐		69
6.124	• Ethylene oxide autoclaves: use of bioindicators?	☐ ☐ ☐		70

		Compliance 1 2 3[a]	Remarks	EU Guide
	Filtration			
6.125	Double filtration?	☐ ☐ ☐		75
6.126	Integrity testing of filters immediately after use?	☐ ☐ ☐		77
6.127	Are results part of the batch protocol?	☐ ☐ ☐		77
6.128	Optical control of each single container of ampoules, vials, and infusions?	☐ ☐ ☐		82
	IPC			
6.129	Written IPC procedures and SOPs?	☐ ☐ ☐		
	Particle testing of			
6.130	• rooms	☐ ☐ ☐		
6.131	• primary packaging materials	☐ ☐ ☐		
6.132	• system of warning and action limits?	☐ ☐ ☐		
	Microbiological monitoring of:			
6.133	• rooms			
6.134	• personnel			
6.135	• equipment			
6.136	Residual O_2 of ampoules, infusions, and syrups?	☐ ☐ ☐		
6.137	Endotoxin testing of water and packaging materials?	☐ ☐ ☐		
6.138	Calibration of equipment?	☐ ☐ ☐		
6.139	Regular revalidation of equipment?	☐ ☐ ☐		
7	**PACKAGING**			
	Operations carried out: • Blistering • Foil–packaging • Filling into tablet glasses • Effervescent packaging • Powder filling • Syrup/drops filling • Ointment filling	 ☐ ☐ ☐ ☐ ☐ ☐ ☐		
	Rooms			
7.1	Suitable for the intended use?	☐ ☐ ☐		3
7.2	• adequate size?	☐ ☐ ☐		3
7.3	• clean?	☐ ☐ ☐		3
7.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
7.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
7.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
7.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
7.8	Recording of temperature and humidity?	☐ ☐ ☐		
7.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
7.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
7.11	Adequate separation of the packaging lines?	☐ ☐ ☐		3.15
	Operations			
7.12	Only *one* product per line?	☐ ☐ ☐		5.44

		Compliance 1 2 3[a]	Remarks	EU Guide
7.13	Check list for clearance before processing a new product/new batch?	☐ ☐ ☐		5.45
7.14	Adequate labeling of the lines (product name and code)?	☐ ☐ ☐		5.46
7.15	Check of all materials delivered to the line (quantity, identity, and conformity with order)?	☐ ☐ ☐		5.47
7.16	Cleaning of primary packaging materials?	☐ ☐ ☐		5.48
7.17	Immediate labeling after filling?	☐ ☐ ☐		5.49
7.18	Careful check of all printing processes (code and expiry date)?	☐ ☐ ☐		5.50
7.19	Special safety measures for off-line printing?	☐ ☐ ☐		5.51
7.20	Regular checks of all control devices (code reader, counter, etc.)?	☐ ☐ ☐		5.52
7.21	Printings clear and durable?	☐ ☐ ☐		5.53
7.22	Balancing of printed packaging materials and bulk?	☐ ☐ ☐		5.56
7.23	Destruction of excessive coded packaging material after completion of an order?	☐ ☐ ☐		5.57
7.24	Are the finished products kept in quarantine until final release?	☐ ☐ ☐		5.58
7.25	Appropriate storage after release?	☐ ☐ ☐		5.60
	IPC			
7.26	Checks on identity of bulk and packaging materials?	☐ ☐ ☐		5.47
	Regular line checks on:			
7.27	• aspect of the packages	☐ ☐ ☐		5.54a
7.28	• completeness	☐ ☐ ☐		5.54b
7.29	• conformity of quantity and quality of materials with packaging order	☐ ☐ ☐		5.54c
7.30	• correct imprint	☐ ☐ ☐		5.54d
7.31	• correct function of control devices	☐ ☐ ☐		5.54d
	Are the following IPC checks performed?			
7.32	• Leaking	☐ ☐ ☐		
7.33	• Release torque of screw caps	☐ ☐ ☐		
7.34	• pH, density, drop weight, viscosity, and sedimentation	☐ ☐ ☐		
8	**DOCUMENTATION**			
	Specifications			
8.1	Specifications for raw/packaging materials available?	☐ ☐ ☐		4.10
	Do they include			
8.2	• internal name and code	☐ ☐ ☐		4.11
8.3	• name of supplier and/or manufacturer?	☐ ☐ ☐		4.11
8.4	• reference sample (printed pack.mat.)?	☐ ☐ ☐		4.11
8.5	• sampling procedure?	☐ ☐ ☐		4.11
8.6	• qualitative/quantitative specifications with limits?	☐ ☐ ☐		4.11
8.7	• storage conditions?	☐ ☐ ☐		4.11
8.8	• maximum storage period?	☐ ☐ ☐		4.11
	Goods receiving?			
8.9	Written procedures for the reception of deliveries?	☐ ☐ ☐		4.19

		Compliance 1 2 3[a]	Remarks	EU Guide
	Do records receipt include			
8.10	• product name on labels and delivery note?	☐ ☐ ☐		4.20
8.11	• internal name and code?	☐ ☐ ☐		4.20
8.12	• receiving date?	☐ ☐ ☐		4.20
8.13	• name of supplier and/or manufacturer?	☐ ☐ ☐		4.20
8.14	• batch number of supplier?	☐ ☐ ☐		4.20
8.15	• total quantity and number of containers?	☐ ☐ ☐		4.20
8.16	• allocated internal batch number?	☐ ☐ ☐		4.20
8.17	SOPs for labeling, quarantine, and storage conditions of all incoming goods available?	☐ ☐ ☐		4.21
	Sampling procedures (SOPs) include:			
8.18	• authorized sampling personnel?	☐ ☐ ☐		4.22
8.19	• methods, equipment, and quantities?	☐ ☐ ☐		4.22
8.20	• safety measures?	☐ ☐ ☐		4.22
	Master formulae			
8.21	Are master formulae for each product and batch size available?	☐ ☐ ☐		4.3
8.22	Is the master formula approved and signed by the authorized persons?	☐ ☐ ☐		4.3
	The master formula includes			
8.23	• product name and code?	☐ ☐ ☐		4.14a
8.24	• description of galenical form, dosage, and batch size?	☐ ☐ ☐		4.14b
8.25	• all active ingredients with name, code, and weight?	☐ ☐ ☐		4.14c
8.26	• all excipients used during manufacture with name, code, and weight?	☐ ☐ ☐		4.14c
8.27	• yields with limits?	☐ ☐ ☐		4.14d
	Does the working procedure include			
8.28	• the production line?	☐ ☐ ☐		4.15a
8.29	• equipment to be used?	☐ ☐ ☐		4.15a
8.30	• reference to methods for cleaning, assembling, and calibration of machines?	☐ ☐ ☐		4.15b
8.31	• detailed stepwise manufacturing prescription?	☐ ☐ ☐		4.15c
8.32	• IPCs to be performed with limits?	☐ ☐ ☐		4.15d
8.33	• precautions to be followed?	☐ ☐ ☐		4.15e
8.34	Are batch records kept for each batch processed?	☐ ☐ ☐		4.17
	Do batch records include			
8.35	• protocol of line clearance?	☐ ☐ ☐		4.17
8.36	• name of the product and batch no.?	☐ ☐ ☐		4.17a
8.37	• date and time of start and end of production?	☐ ☐ ☐		4.17b
8.38	• name and initials of responsible workers for each step?	☐ ☐ ☐		4.17c, d
8.39	• batch and analytical no. and actual weight of all starting materials?	☐ ☐ ☐		4.17e
8.40	• equipment used?	☐ ☐ ☐		4.17f
8.41	• results of IPCs with initials of person who carries them out?	☐ ☐ ☐		4.17g
8.42	• yields of the relevant manufacturing steps?	☐ ☐ ☐		4.17h
8.43	• detailed notes on problems and process deviations?	☐ ☐ ☐		4.17i

		Compliance 1 2 3[a]	Remarks	EU Guide
8.44	Records on reprocessing of batches?	☐ ☐ ☐		
	Packaging instructions			
8.45	Packaging instructions for each product, package size, and presentation?	☐ ☐ ☐		4.16
	Do they include			
8.46	• product name?	☐ ☐ ☐		4.16a
8.47	• description of galenical form and strength?	☐ ☐ ☐		4.16b
8.48	• package size?	☐ ☐ ☐		4.17c
8.49	• list of all packaging materials with code for a standard batch size?	☐ ☐ ☐		4.17d
8.50	• samples of printed packaging materials?	☐ ☐ ☐		4.17e
8.51	• special precautions?	☐ ☐ ☐		4.17f
8.52	• description of the process and equipment?	☐ ☐ ☐		4.17g
8.53	• IPCs to be performed with sampling instruction?	☐ ☐ ☐		4.17h
8.54	Are packaging batch records kept for each batch or part batch?	☐ ☐ ☐		4.18
	Do the packaging batch records include			
8.55	• protocol of line clearance?	☐ ☐ ☐		4.18
8.56	• name of the product?	☐ ☐ ☐		4.18a
8.57	• date and time when operations have been performed?	☐ ☐ ☐		4.18b
8.58	• name of the responsible person?	☐ ☐ ☐		4.18c
8.59	• initials of workers carrying out operations?	☐ ☐ ☐		4.18d
8.60	• notes on identity checks and conformity with packaging instructions?	☐ ☐ ☐		4.18e
8.61	• results of IPCs	☐ ☐ ☐		4.18e
8.62	• details of operations and equipment used?	☐ ☐ ☐		4.18f
8.63	• samples of printed packaging materials with codes (MFD, EXP, Batch no., etc.)?	☐ ☐ ☐		4.18g
8.64	• record of problems and process deviations?	☐ ☐ ☐		4.18h
8.65	• quantities of packaging materials delivered, used, destroyed, or returned?	☐ ☐ ☐		4.18i
8.66	• no. of packs consumed?	☐ ☐ ☐		4.18j
	Testing			
	Do the written testing procedures include			
8.67	• test methods?	☐ ☐ ☐		4.23
8.68	• equipment for testing?	☐ ☐ ☐		4.23
8.69	Tests documented?	☐ ☐ ☐		4.23
	Others			
8.70	Procedures for release and rejection of materials and finished products?	☐ ☐ ☐		4.24
8.71	Final release by authorized person?	☐ ☐ ☐		4.24
8.72	Records about distribution of each batch?	☐ ☐ ☐		4.25
	Procedures and protocols about			
8.73	• validation?	☐ ☐ ☐		4.26

		Compliance 1 2 3[a]	Remarks	EU Guide
8.74	• set up and calibration of equipment?	☐ ☐ ☐		4.26
8.75	• maintenance, cleaning, and disinfection?	☐ ☐ ☐		4.26
8.76	• training records?	☐ ☐ ☐		4.26
8.77	• environmental monitoring of production areas?	☐ ☐ ☐		4.26
8.78	• pest control?	☐ ☐ ☐		4.26
8.79	• complaints?	☐ ☐ ☐		4.26
8.80	• recalls?	☐ ☐ ☐		4.26
8.81	• returned goods?	☐ ☐ ☐		4.26
8.82	Instructions for use of manufacturing and testing equipment?	☐ ☐ ☐		4.27
	Logbooks for major equipment incl. date and name of persons who performed			
8.83	• validation?	☐ ☐ ☐		4.28
8.84	• calibration?	☐ ☐ ☐		4.28
8.85	• maintenance, cleaning, and repair works?	☐ ☐ ☐		4.28
8.86	Chronological records of use of major equipment and manufacturing areas?	☐ ☐ ☐		4.29
9	**QUALITY CONTROL**			**6**
	General requirements			
9.1	Independent QC department available?	☐ ☐ ☐		6.1
9.2	Head of QC well qualified and sufficiently experienced?	☐ ☐ ☐		6.1
9.3	Qualified personnel available?	☐ ☐ ☐		2.1
9.4	Organization charts available?	☐ ☐ ☐		2.2
9.5	Job descriptions available?	☐ ☐ ☐		2.2
9.6	Responsibilities clearly defined?	☐ ☐ ☐		2.2
9.7	Continuous training programs for QC staff?	☐ ☐ ☐		2.2
9.8	Initial job training for all employees?	☐ ☐ ☐		2.9
9.9	Training records?	☐ ☐ ☐		
9.10	QC personnel admitted to the production rooms for sampling etc.?	☐ ☐ ☐		
	QC Laboratories			
9.11	Suitable for the intended use?	☐ ☐ ☐		3.26
9.12	Laboratories of adequate size?	☐ ☐ ☐		3.26
9.13	Appropriate level of maintenance?	☐ ☐ ☐		3.1
9.14	Adequate separation from the production area?	☐ ☐ ☐		3.26
9.15	Controlled access of authorized personnel only?	☐ ☐ ☐		3.5
9.16	Special laboratory to handle biological samples available?	☐ ☐ ☐		3.29
9.17	Special laboratory to handle radioactive material available?	☐ ☐ ☐		3.29
9.18	Separate recreation rooms for the personnel available?	☐ ☐ ☐		3.30
9.19	Animal laboratories present?	☐ ☐ ☐		3.33
9.20	Animal laboratories separated from other areas?	☐ ☐ ☐		3.33
9.21	Animal laboratories equipped with a separate air-handling system?	☐ ☐ ☐		3.33

		Compliance 1 2 3[a]	Remarks	EU Guide
	QC Documentation			
9.22	Do procedures exist for			
	self inspection?	☐ ☐ ☐		
	release or rejection of products or raw material?	☐ ☐ ☐		
	product complaints?	☐ ☐ ☐		
	product recalls?	☐ ☐ ☐		
	local stability testing?	☐ ☐ ☐		
	storage of reference samples?	☐ ☐ ☐		
	validation of analytical procedures?	☐ ☐ ☐		
9.23	Specifications available for	☐ ☐ ☐		6.7
	raw materials?	☐ ☐ ☐		
	bulk products?	☐ ☐ ☐		
	packaging materials?	☐ ☐ ☐		
9.24	Analytical procedures for every product?	☐ ☐ ☐		
9.25	Are Basel methods followed?	☐ ☐ ☐		
9.26	Validation of locally developed test methods?	☐ ☐ ☐		
9.27	Sampling procedures available for			6.7
	raw materials?	☐ ☐ ☐		
	bulk products?	☐ ☐ ☐		
	packaging materials?	☐ ☐ ☐		
9.28	Suppliers certificates available?	☐ ☐ ☐		6.7
9.29	Calibration program for analytical instruments installed?	☐ ☐ ☐		6.7
9.30	Maintenance program for analytical instruments?	☐ ☐ ☐		6.7
9.31	Retention system for QC records?	☐ ☐ ☐		6.8
9.32	Batch documents stored for expiry + 1 year or 5 years (EEC 75/319, article 22) minimum?	☐ ☐ ☐		6.8
9.33	Are original data like notebooks stored in addition to the batch documents?	☐ ☐ ☐		6.10
9.34	Can the original data be traced back easily and quickly from the analytical report number or batch number?	☐ ☐ ☐		6.10
9.35	Are trend analyses being performed for			6.9
	analytical results?	☐ ☐ ☐		
	yields?	☐ ☐ ☐		
	environmental monitoring data?	☐ ☐ ☐		
	Sampling			
9.36	Written procedures for taking samples?	☐ ☐ ☐		6.11
9.37	Do procedures define			
	method of sampling?	☐ ☐ ☐		
	necessary equipment?	☐ ☐ ☐		
	quantity of the sample?	☐ ☐ ☐		
	subdivision of the sample?	☐ ☐ ☐		
	sample container?	☐ ☐ ☐		
	labeling of samples?	☐ ☐ ☐		
	storage conditions?	☐ ☐ ☐		
	cleaning and storage of sampling equipment?	☐ ☐ ☐		
	identification of containers sampled	☐ ☐ ☐		
9.38	Are samples representative for the batch they are taken from? (sampling plan)	☐ ☐ ☐		6.12
9.39	Are critical steps being surveilled and validated by additional sampling (e.g., beginning or end of a process)?	☐ ☐ ☐		6.12

		Compliance 1 2 3[a]	Remarks	EU Guide
9.40	Sample containers labeled with			6.13
	name of the content	☐ ☐ ☐		
	batch number	☐ ☐ ☐		
	date of sampling	☐ ☐ ☐		
	batch containers sampled	☐ ☐ ☐		
9.41	Are samples taken by QC/QA?	☐ ☐ ☐		
9.42	Reference samples retained for validity plus 1 year?	☐ ☐ ☐		6.14
9.43	Storage of reference samples under the recommended storage conditions?	☐ ☐ ☐		6.14
9.44	Finished products stored in the final packaging?	☐ ☐ ☐		6.14
9.45	Quantity of the reference sample makes 1 (better 2) complete reanalysis possible?	☐ ☐ ☐		6.14
9.46	Sample room secure?	☐ ☐ ☐		
9.47	Sample room neatly organized and not overcrowded?	☐ ☐ ☐		
	Testing			
9.48	Are the applied analytical methods validated?	☐ ☐ ☐		6.15
9.49	Analytical methods in compliance with the registration?	☐ ☐ ☐		6.16
9.50	Are all results recorded and checked for correctness?	☐ ☐ ☐		6.16
9.51	Are all calculations checked?	☐ ☐ ☐		6.16
9.52	Do the testing protocols contain			6.17
	name and galenical form of material?	☐ ☐ ☐		
	batch number?	☐ ☐ ☐		
	supplier if applicable?	☐ ☐ ☐		
	specification reference?	☐ ☐ ☐		
	method reference?	☐ ☐ ☐		
	analytical results?	☐ ☐ ☐		
	reference to analytical certificates?	☐ ☐ ☐		
	date of the analysis?	☐ ☐ ☐		
	name of the analyst?	☐ ☐ ☐		
	name of the person verifying the data?	☐ ☐ ☐		
	statement of release or rejection?	☐ ☐ ☐		
	date and sign of the release person?	☐ ☐ ☐		
9.53	Are all IPC methods in production approved by QC?	☐ ☐ ☐		6.18
9.54	Are written methods available for the preparation of reagents and volumetric solutions?	☐ ☐ ☐		6.19
9.55	Is a record maintained of standardization of volumetric solutions?	☐ ☐ ☐		6.2
9.56	Are reagents for prolonged use labeled with			6.20
	date of the preparation?	☐ ☐ ☐		
	sign of the preparator?	☐ ☐ ☐		
9.57	Are unstable reagents labeled with;			6.20
	expiry date?	☐ ☐ ☐		
	storage conditions?	☐ ☐ ☐		
9.58	Are volumetric solutions labeled with			6.20
	the last date of standardization?	☐ ☐ ☐		
	last current factor?	☐ ☐ ☐		
9.59	Are reference standards labeled with			6.21
	name and potency	☐ ☐ ☐		
	suppliers reference	☐ ☐ ☐		
	date of receipt	☐ ☐ ☐		
	date of expiry	☐ ☐ ☐		

		Compliance 1 2 3[a]	Remarks	EU Guide
9.60	Are reference standards stored properly and under the control of a designated person?	☐ ☐ ☐		
9.61	Are animals used for testing of components, materials, or products; quarantined before use? checked for suitability? Are records maintained showing the history of their use?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		
10	**COMPLAINTS AND PRODUCT RECALLS**			**8**
	Complaints			8.1
10.1	Does a written complaint procedure exist?	☐ ☐ ☐		8.2
10.2	Are product complaints carefully reviewed?	☐ ☐ ☐		8.1
10.3	Is a person designated to handle complaints and to decide on measures to be taken?	☐ ☐ ☐		8.1
10.4	Is each complaint concerning a product recorded with all original details?	☐ ☐ ☐		8.3
10.5	Are product complaints thoroughly investigated?	☐ ☐ ☐		8.3
10.6	Is a responsible person of QC involved in the study?	☐ ☐ ☐		8.3
10.7	Is it considered that other batches might be concerned as well?	☐ ☐ ☐		8.4
10.8	Are decisions and measures as a result recorded?	☐ ☐ ☐		8.5
10.9	Is this record added to the corresponding batch documents?	☐ ☐ ☐		8.5
10.10	Are the complaint records regularly revised with respect to specific or recurring problems?	☐ ☐ ☐		8.6
10.11	Are the authorities informed of serious quality problems with a product?	☐ ☐ ☐		8.7
	Recalls			8.8
10.12	Does a written recall procedure exist?	☐ ☐ ☐		8.9
10.13	Is a person nominated responsible for the execution and coordination of a recall?	☐ ☐ ☐		8.8
10.14	Responsible person independent of the marketing and sales organization?	☐ ☐ ☐		8.8
10.15	Are the competent authorities informed of an imminent recall?	☐ ☐ ☐		8.11
10.16	Does the person responsible for a recall have access to the distribution records?	☐ ☐ ☐		8.12
10.17	Do the distribution records contain sufficient information on customers with addresses? Phone numbers inside or outside working hours? Batches and amounts delivered? Medical samples?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		8.12
10.18	Are recalled products stored separately in a secure area?	☐ ☐ ☐		8.13
10.19	Is a final record made including a reconciliation between the delivered and recovered quantities?	☐ ☐ ☐		8.14
10.20	Is the effectiveness of the arrangements for recalls checked critically from time to time?	☐ ☐ ☐		8.15
11	**SELF-INSPECTION**			**9**
11.1	Does a self-inspection procedure exist which defines frequency and program?	☐ ☐ ☐		9.1
11.2	Are self-inspections carried out to check compliance with GMP rules?	☐ ☐ ☐		9.1

		Compliance 1 2 3[a]	Remarks	EU Guide
11.3	Are self-inspections conducted in an independent and detailed way? by designated competent persons from the company or external experts?	☐ ☐ ☐ ☐ ☐ ☐		9.2
11.4	Are self-inspections recorded?	☐ ☐ ☐		9.3
11.5	Do reports contain the observations made during a self-inspection? proposals for corrective measures?	☐ ☐ ☐ ☐ ☐ ☐		9.3
11.6	Are actions subsequently taken recorded?	☐ ☐ ☐		9.3
12	**CONTRACT MANUFACTURE AND ANALYSIS**			**7**
12.1	Written contract between contract giver and contract acceptor available?	☐ ☐ ☐		7.1
12.2	Are responsibilities and duties clearly defined?	☐ ☐ ☐		7
12.3	All arrangements in accordance with the marketing authorization of the product concerned?	☐ ☐ ☐		7.2
	The contract giver			
12.4	Competence of the acceptor to carry out the work successful and according to GMP assessed?	☐ ☐ ☐		7.3
12.5	Acceptor provided with all the informations necessary to carry out the contract work?	☐ ☐ ☐		7.4
12.6	Acceptor informed of safety aspects?	☐ ☐ ☐		7.4
12.7	Conformance of products supplied by the acceptor ensured?	☐ ☐ ☐		7.5
12.8	Product released by a qualified person on the acceptor's side?	☐ ☐ ☐		7.5
	The contract acceptor			
12.9	Does the acceptor have adequate premises and equipment? Knowledge and experience? Competent personnel? A manufacturing authorization?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.6
12.10	Does the acceptor ensure that all products or materials delivered to him are suitable?	☐ ☐ ☐		7.7
12.11	There must be no work passed to a third party without the permission of the giver.	☐ ☐ ☐		7.8
12.12	If a third party is involved, it must have the necessary manufacturing and analytical information.	☐ ☐ ☐		7.8
	The contract			
12.13	Does the written contract specify the responsibilities?	☐ ☐ ☐		7.10
12.14	Have technical aspects been drawn up by competent persons?	☐ ☐ ☐		7.10
12.15	Release of material and check for compliance with the marketing authorization defined?	☐ ☐ ☐		7.11
12.16	Is it defined who is responsible for purchasing of materials? IPC controls Testing and release of materials? Manufacturing and quality control? Sampling? Storage of batch documentation?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.12
12.17	Are manufacturing, analytical, and distribution records available to the contract giver?	☐ ☐ ☐		7.13
12.18	Contract permits the giver to visit the facilities of the acceptor?	☐ ☐ ☐		7.14

		Compliance 1 2 3[a]	Remarks	EU Guide
12.19	In the case of contract analysis: Does the contract acceptor understand that he is subject to inspection by the competent authorities?	☐ ☐ ☐		7.15
13	**AUDIT OF SUPPLIERS**			**2.7**
13.1	Supplier audits performed for excipients? Active substances? Packaging material?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		

[a] 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (or Drug Substance)—Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Air lock—An enclosed space with two or more doors, which is interposed between two or more rooms, for example, of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An air lock is designed for use either by people or for goods and/or equipment.

API Starting Material—A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

Authorized Person—The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested, and approved for release in compliance with the laws and regulations in force in that country.

Batch (or Lot)—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Batch Number (or Lot Number)—A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

Batch Records—All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bioburden—The level and type (e.g., objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates, or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Bulk Product—Any product that has completed all processing stages up to, but not including, final packaging.

Calibration—The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Clean Area—An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Computer System—A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions. A process or operation integrated with a computer system.

Consignment (or delivery)—The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Contamination—The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, and storage or transport.

Contract Manufacturer—A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical—Describes a process step, process condition, test requirement, or other relevant parameter or item that

must be controlled within predetermined criteria to ensure that the API meets its specification.

Critical Operation—An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Cross-Contamination—Contamination of a material or product with another material or product. Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Deviation—Departure from an approved instruction or established standard.

Drug (Medicinal) Product—The dosage form in the final immediate packaging intended for marketing. (Reference Q1A).

Drug Substance—See Active Pharmaceutical Ingredient.

Expiry Date (or Expiration Date)—The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf-life specifications if stored under defined conditions, and after which it should not be used.

Finished Product—A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.

Impurity—Any component present in the intermediate or API that is not the desired entity.

Impurity Profile—A description of the identified and unidentified impurities present in an API.

In-Process Control (or Process Control)—Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

In-Process Control—Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate—A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Large-Volume Parenterals—Sterile solutions intended for parenteral application with a volume of 100 mL or more in one container of the finished dosage form.

Lot—See Batch

Lot Number—See Batch Number

Manufacture—All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Manufacturer—A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of pharmaceuticals.

Marketing Authorization (Product License, Registration Certificate)—A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling, and shelf life.

Master Formula—A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master Record—A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Material—A general term used to denote raw materials (starting materials, reagents, and solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother Liquor—The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It may be used for further processing.

Packaging—All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized would not normally be regarded as part of packaging.

Packaging Material—Any material intended to protect an intermediate or API during storage and transport. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical Product—Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Procedure—A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids—Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon).

Process Control—See In-Process Control.

Production—All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, and labeling and relabeling, to completion of the finished product.

Qualification—Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)—The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)—Checking or testing that specifications are met.

Quality Unit(s)—An organizational unit independent of production, which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine—The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Quarantine—The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Raw Material—A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reconciliation—A comparison between the theoretical quantity and the actual quantity.

Recovery—The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

Reference Standard, Primary—A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity.

Reference Standard, Secondary—A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing—Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate), or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and preapproved as part of the marketing authorization.

Retest Date—The date when a material should be reexamined to ensure that it is still suitable for use.

Reworking—Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

Reworking—Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not preapproved as part of the marketing authorization.

Self-Contained Area—Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well-established procedures, controls, and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

Signature (Signed)—See definition for signed.

Signed (Signature)—The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent—An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification—A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Specification—A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Standard Operating Procedure (SOP)—An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g., equipment operation, maintenance, and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting Material—Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Validation—A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity, or system actually leads to the expected results (see also qualification).

Validation Protocol—A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected—The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical—The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

19

Bioequivalence Testing Protocols

To receive approval for an ANDA, applicants generally must demonstrate, among other things, that their product has the same active ingredient, dosage form, strength, route of administration and conditions of use as the listed drug, and that the proposed drug product is BE to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. BE drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 USC 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320.

The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-specific BE studies, the U.S. FDA will be issuing product-specific BE recommendations (www.fda.gov/cder/ogd/index.htm). Given below are the current recommendations for the products of relevance to this specific volume of the book:

Amoxicillin; Clavulanate Potassium Suspension/Oral. *Recommended studies*: Three studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 600 mg/EQ 42.9 mg (base)/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 600 mg/EQ 42.9 mg (base)/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (3) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 400 mg/EQ 57 mg (base)/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Amoxicillin and clavulanate potassium in plasma. *Bioequivalence based on (90% CI)*: Amoxicillin and clavulanate potassium. *Waiver request of in vivo testing*: 200 mg/EQ 28.5 mg (base)/5 mL based on (i) acceptable bioequivalence studies on the 400 mg/EQ 57 mg (base)/5-mL strength, (ii) proportional similarity of the 200 mg/EQ 28.5 mg (base)/5 mL and 400 mg/EQ 57 mg (base)/5-mL strengths, and (iii) acceptable in vitro dissolution testing of the 200 mg/EQ 28.5 mg (base)/5 mL and 400 mg/EQ 57 mg (base)/5-mL strengths.

Carbamazepine Suspension/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 100 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 100 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Carbamazepine in plasma. *Bioequivalence based on (90% CI)*: Carbamazepine. *Waiver request of in vivo testing*: Not applicable.

Cefixime Suspension/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 200 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. (2) *Type of Study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 200 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluid)*: Cefixime in plasma. *Bioequivalence based on (90% CI)*: Cefixime. *Waiver request of in vivo testing*: 100 mg/5 mL based on (i) acceptable bioequivalence studies on the 200-mg strength /5-mL strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. A dosage unit for a suspension is the labeled strength (5 mL). A total of 12 units from 12 different bottles should be used.

Clarithromycin Granules for Suspension/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 250 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 250 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Clarithromycin in plasma. *Bioequivalence based on (90% CI)*: Clarithromycin. *Waiver request of in vivo testing*: 125 mg/5 mL based on (i) acceptable bioequivalence studies on the 250-mg strength/5-mL strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Deferasirox Tablets for Oral Suspension. *Recommended studies*: One study. *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 500 mg. *Subjects*: Normal healthy males and females, general population. *Additional comments*: The following passage is reproduced from the Dosage and Administration section of the labeling: Tablets should be completely dispersed by stirring in water, orange juice, or apple juice until a fine suspension is obtained. Doses of <1 g should be dispersed in 3.5 oz of liquid and doses of >1 g in 7.0 oz of liquid. After swallowing the suspension, any residue should be resuspended in a small volume of liquid and swallowed. Tablets should not be chewed or swallowed whole. *Analytes to measure (in appropriate biological fluid)*: Deferasirox in plasma. *Bioequivalence based on (90% CI)*: Deferasirox. *Waiver request of in vivo testing*: 250- and 125-mg tablets based on (i) acceptable bioequivalence studies on the 500-mg strength, (ii) proportionally similar across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.

Dextromethorphan Polistirex Extended-Release Oral Suspension/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way

crossover in vivo. *Strength*: 30 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 30 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Dextromethorphan and its metabolite. Dextrorphan in plasma. *Bioequivalence based on (90% CI)*: Dextromethorphan. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax. *Waiver request of in vivo testing*: Not applicable. A dosage unit for a suspension is the labeled strength (5 mL). A total of 12 units from 12 different bottles should be used. In addition to the method above, for modified-release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP apparatus I at 100 rpm and/or apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5, and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased, if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation.

Felbamate Oral Suspension/Oral. *Recommended studies*: One study. *Type of study*: Fasting. *Design*: Multiple-dose, two-way steady-state crossover in vivo. *Strength*: 600 mg/5 mL. *Subjects*: Male and nonpregnant female epilepsy patients. *Additional comments*: Please also consider the following additional safety monitoring: (a) If any evidence of bone marrow (hematologic) depression occurs, felbamate treatment should be discontinued and a hematologist consulted to ensure appropriate medical care. (b) Additional criteria for exclusion from the study relative to baseline be practiced including (i) twofold increase in the highest, 2-day prestudy seizure frequency, (ii) single, generalized, tonic–clonic seizure if none occurred during pretreatment screening, and/or, (iii). significant prolongation of generalized, tonic–clonic seizures. *Analytes to measure*: Felbamate in plasma. (1) Measurements of felbamate are requested on at least two consecutive days immediately prior to PK-analysis, days 7 and 14 to confirm steady-state concentrations of felbamate (i.e., additional consecutive measures on days 5, 6 and 12, 13). (2) Because felbamate is rapidly absorbed and reaches a peak plasma concentration within 1 to 3 hours post consumption, please also include blood sampling at 0.25 hours after drug dosing to accurately measure the absorption/distribution phases of the felbamate PK profile. (3) Patients who receive multiples of 600 mg of felbamate per day (1200–4800 mg/day) would be eligible for the study by continuing their established maintenance dose. Because patients will be administered different dosing regimens, the dose needs to be included in the analysis of variance (ANOVA) statistical model. Dose normalization is not advised. (4) No washout period is necessary between treatment periods. (5) You are encouraged to submit protocols for the in vivo bioequivalence studies to be conducted at steady state in patients already taking the RLD at a therapeutic dose for review prior to initiating the studies. *Bioequivalence based on (90% CI)*: Felbamate. *Waiver request of in vivo testing*: Not applicable of all strengths of the test and reference products. A dosage unit for a suspension is the labeled strength (5 mL). A total of 12 units from 12 different bottles should be used.

Fosamprenavir Calcium Suspension/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: EQ 50 mg Base/mL (Dose = 28 mL corresponding to a dose of 1400 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. Bottle should be shaken well before drug administration. (2) *Type of Study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: EQ 50 mg Base/mL (Dose = 28 mL corresponding to a dose of 1400 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluid)*: Amprenavir, the active metabolite of fosamprenavir, in plasma. *Bioequivalence based on (90% CI)*: Amprenavir. *Waiver request of in vivo testing*: Not applicable.

Ibuprofen and Pseudoephedrine Hydrochloride Suspension/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 100 mg/5 mL and 15 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 100 mg/5 mL and 15 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Ibuprofen and pseudoephedrine in plasma. *Bioequivalence based on (90% CI)*: Ibuprofen and pseudoephedrine. *Waiver request of in vivo testing*: Not applicable of all strengths of the test and reference products. A dosage unit for a suspension is the labeled strength (5 mL). A total of 12 units from 12 different bottles should be used.

Meloxicam Suspension/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo dose and suspension. *Strength*: 5 mL of 7.5 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females should not be pregnant, and if applicable, should practice abstinence or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo dose and suspension. *Strength*: 5 mL of 7.5 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluid)*: Meloxicam in plasma. *Bioequivalence based on (90% CI)*: Meloxicam. *Waiver request of in vivo testing*: Not applicable.

Nelfinavir Mesylate Suspension/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 50 mg/scoopful. *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 50 mg/scoopful. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Nelfinavir in plasma. *Bioequivalence based on (90% CI)*: Nelfinavir. *Waiver request of in vivo testing*: Not applicable.

Nevirapine Suspension/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, one-period parallel in vivo. *Strength*: 50 mg/5 mL. *Subjects*:

Normal healthy males and females, general population. *Additional comments*: Because of safety concerns of sever life-threatening skin reactions and hepatotoxicity, single-dose parallel study designs in normal healthy subjects are recommended. (2) *Type of study*: Fed. *Design*: Single-dose, one-period parallel in vivo. *Strength*: 50 mg/5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comments above. *Analytes to measure (in appropriate biological fluid)*: Nevirapine in plasma. *Bioequivalence based on (90% CI)*: Nevirapine. *Waiver request of in vivo testing*: Not applicable.

Omeprazole Powder for Suspension/Oral. *Recommended studies*: One study. *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 40 mg/packet. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure*: Omeprazole in plasma. *Bioequivalence based on (90% CI)*: Omeprazole. *Waiver request of in vivo testing*: 20 mg/packet based on (i) acceptable bioequivalence study on the 40-mg strength, (ii) proportional similarity of the formulations across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths. Since omperazole powder for oral suspension, 20 mg/packet and 40 mg/packet, are subject to two separate New Drug Applications, two separate Abbreviated New Drug Application must be submitted. A waiver of in vivo bioequivalence testing is available.

Oxcarbazepine Suspension/Oral. *Recommended studies*: Two studies. 1. *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 300 mg/5 mL (600-mg dose). *Subjects*: Normal healthy males and females, general population. *Additional comments*: (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 300 mg/5 mL (600-mg dose). *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Oxcarbazepine and its 10-hydroxy metabolite (monohydroxy derivative, MHD) in plasma using an achiral assay. *Bioequivalence based on (90% CI)*: Oxcarbazepine. Please submit the metabolite data as supportive evidence of comparable therapeutic outcome. For the metabolite, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax. *Waiver request of in vivo testing*: Not applicable product at this Web site. Please note that a dosage unit for a suspension is the labeled strength (5 mL). A total of 12 units from 12 different bottles should be used.

Phenytoin Suspension/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 125 mg/5 mg (dose of 300 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Washout period of at least 14 days. The single-dose studies for fasting and fed can be conducted as single dose, two-treatment, four periods, replicated design. The strength(s) designated in the Orange Book as the RLD should be used in the studies. (2) *Type of study*: Fed. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 125 mg/5 mg (dose of 300 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comments above. *Analytes to measure*: Phenytoin in plasma. *Bioequivalence based on (90% CI)*: Phenytoin. *Waiver request of in vivo testing*: Not applicable. Please conduct comparative dissolution testing on 12 dosage units of all strengths of the test and reference products using the USP method. A dosage unit for a suspension is the labeled strength (5 mL). A total of 12 units from 12 different bottles should be used.

Posaconazole Suspension/Oral. *Recommended studies*: Two studies. (1) *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 40 mg/mL (dose of 400 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Females must have a negative baseline pregnancy test within 24 hours prior to receiving the drug. Females should not be pregnant or lactating, and if applicable, should practice abstention or contraception during the study. (2) *Type of study*: Fed. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 40 mg/mL (dose of 400 mg). *Subjects*: Normal healthy males and females, general population. *Additional comments*: Please see comment above. *Analytes to measure (in appropriate biological fluid)*: Posaconazole in plasma. *Bioequivalence based on (90% CI)*: Posaconazole. *Waiver request of in vivo testing*: Not applicable product at this Web site. Please note that a dosage unit for a suspension is the labeled strength (mL). A total of 12 units from 12 different bottles should be used. Specifications

Sulfamethoxazole; Trimethoprim Suspension/Oral. *Recommended studies*: One study. *Type of study*: Fasting. *Design*: Single-dose, two-treatment, two-period crossover in vivo. *Strength*: 200 mg/40 mg per 5 mL. *Subjects*: Normal healthy males and females, general population. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Sulfamethoxazole and trimethoprim in plasma. *Bioequivalence based on (90% CI)*: Sulfamethoxazole and trimethoprim. *Waiver request of in vivo testing*: Not applicable.

Voriconazole Suspension/Oral. *Recommended studies*: One study. *Type of study*: Fasting. *Design*: Single-dose, two-way crossover in vivo. *Strength*: 200 mg/5 mL. *Subjects*: Normal healthy males and females, general population. Females should not be pregnant, and if applicable, should practice abstention or contraception during the study. *Additional comments*: *Analytes to measure (in appropriate biological fluid)*: Voriconazole in plasma. *Bioequivalence based on (90% CI)*: Voriconazole. *Waiver request of in vivo testing*: Not applicable.

Dissolution Testing of Liquid Dosage Forms

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Acyclovir	Suspension	II (Paddle)	50	0.1 N HCl	900	10, 20, 30, 45, and 60	02/20/2004
Amoxicillin/clavulanate potassium	Suspension	II (Paddle)	75	Water (deaerated)	900	5, 10, 15, and 30	01/14/2004
Carbamazepine	Suspension	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, 45, and 60	01/20/2004
Cefadroxil	Suspension	II (Paddle)	25	Water	900	5, 10, 15, 30, and 45	07/25/2007
Cefdinir	Suspension	II (Paddle)	50	0.05 M phosphate buffer, pH 6.8	900	10, 20, 30, and 45	04/09/2007
Cefixime	Suspension	II (Paddle)	50	0.05 M phosphate buffer, pH 7.2	900	10, 20, 30, and 45	04/09/2007
Cefpodoxime proxetil	Suspension	II (Paddle)	50	0.04 M glycine buffer, pH 3.0	900	10, 20, 30, and 45	12/20/2005
Cefprozil monohydrate	Suspension	II (Paddle)	25	Water (deaerated)	900	5, 10, 15, and 30	01/21/2004
Ceftibuten dihydrate	Suspension	II (Paddle)	50	0.05 M phosphate buffer, pH 7.0	1000	10, 20, 30, and 45	01/21/2004
Cephalexin	Suspension	II (Paddle)	25	Water	900	5, 10, 20, and 30	07/25/2007
Clarithromycin	Suspension	II (Paddle)	50	0.05 M phosphate buffer, pH 6.8	900	10, 20, 30, 45, and 60	01/23/2004
Dextromethorphan polistirex	Suspension	II (Paddle)	50	0.1 N HCl	500	30, 60, 90, and 180	03/04/2006
Erythromycin ethylsuccinate	Suspension	II (Paddle)	75	Monobasic sodium phosphate, pH 6.8 buffer with 1% SLS buffer w/1% SLS	900	10, 20, 30, 45, and 60	01/27/2004
Felbamate	Suspension	II (Paddle)	50	Water (deaerated)	900	5, 10, 15, and 30	01/28/2004
Fluconazole (200 mg/5 mL)	Suspension	II (Paddle)	50	Water (deaerated)	900	10, 20, 30, and 45	01/30/2004
Fluconazole (50 mg/5 mL)	Suspension	II (Paddle)	50	Water (deaerated)	500	10, 20, 30, and 45	01/30/2004
Griseofulvin	Suspension	II (Paddle)	50	0.54% SLS	1000	10, 20, 30, and 45	04/09/2007
Ibuprofen/pseudoephedrine HCl	Suspension	II (Paddle)	50	0.05 M phosphate buffer, pH 7.2	900	5, 10, 15, and 30	02/04/2004
Linezolid	Suspension	II (Paddle)	50	0.05 M phosphate buffer, pH 6.8	900	10, 20, 30, and 45	01/14/2008
Meloxicam	Suspension	II (Paddle)	25	Phosphate buffer at pH 7.5	900	5, 10, 15, and 30	01/26/2006

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Mycophenolate mofetil	Suspension	II (Paddle)	40	0.1 N HCl	900	5, 10, 20, and 30	02/10/2004
Nevirapine	Suspension	II (Paddle)	25	0.1 N HCl	900	10, 20, 30, 45, and 60	02/11/2004
Oxcarbazepine	Suspension	II (Paddle)	75	1% SDS in water	900	10, 20, 30, and 45	02/12/2004
Paroxetine HCl	Suspension	II (Paddle)	100	SGF without enzyme	900	10, 20, 30, and 45	02/13/2004
Phenytoin	Suspension			Refer to USP			06/18/2007
Sucralfate	Suspension	II (Paddle)	75	0.1 N HCl/0.067 M KCl, pH 1.0	900	10, 20, 30, and 45	03/04/2006
Sulfamethoxazole/trimethoprim	Suspension	II (Paddle)	50	1 mL of 0.2 N HCl in water	900	10, 20, 30, 45, 60, and 90	02/25/2004
Voriconazole	Suspension	II (Paddle)	50	0.1 N HCl	900	10, 20, 30, and 45	01/03/2007
Azithromycin	Suspension oral	II (Paddle)	50	Phosphate buffer, pH 6.0	900	10, 20, 30, and 45	08/17/2006
Fosamprenavir calcium	Suspension oral	II (Paddle)	25	10 mM HCl	900	5, 10,15, and 20	12/03/2007
Posaconazole	Suspension oral	II (Paddle)	25	0.3% SLS	900	10, 20, 30, and 45	12/03/2007
Sulfisoxazole acetyl	Suspension oral (pediatric)	II (Paddle)	30	1% SLS in 0.1 N HCl	900	15, 30, 45, 60, and 90	08/17/2006
Ampicillin/ampicillin trihydrate	Suspension oral, powder	II (Paddle)	25	Water (deaerated)	900	5, 10, 15, 20	01/03/2007
Mesalamine enema	Suspension, enema	II (Paddle)	50	Phosphate buffer, pH 7.2	900	5, 10, 15, and 30	06/18/2007

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Approved Excipients in Liquid Forms

Ingredient	Dosage Form	Qty	Unit
1-*o*-tolylbiguanide	Topical; solution	0.0125	%
Acesulfame potassium	Oral; suspension, liquid	0.15	%
Acesulfame potassium	Oral; solution	0.5	%
Acetic acid	Topical; suspension	0.04	%
Acetic acid, glacial	Oral; solution, syrup	0.1	%
Acetic acid, glacial	Oral; solution, elixir	0.1067	%
Acetone	Topical; solution	12.69	%
Acetone	Topical; shampoo	13	%
Acetylated monoglycerides	Oral; solution	24	%
Alcohol	Rectal; suspension	0.35	%
Alcohol	Oral; suspension	7.25	%
Alcohol	Topical; shampoo	10	%
Alcohol	Oral; solution, liquid, concentrate, oral	15.068	%
Alcohol	Topical; emulsion, aerosol foam	58.21	%
Alcohol	Oral; solution	66	%
Alcohol	Oral; concentrate	71.6	%
Alcohol	Oral; syrup	75	%
Alcohol	Topical; solution	91.07	%
Alcohol	Oral; solution, elixir	94.7	%
Alcohol, dehydrated	Oral; aerosol, metered	0.4716	%
Alcohol, dehydrated	Topical; swab	0.695	ML
Alcohol, dehydrated	Sublingual; spray, metered	0.95	%
Alcohol, dehydrated	Oral; suspension	1.75	%
Alcohol, dehydrated	Rectal; gel	11.224	%
Alcohol, dehydrated	Oral; solution, elixir	20	%
Alcohol, dehydrated	Topical; solution, liquid	25	%
Alcohol, dehydrated	Oral; syrup	29	%
Alcohol, dehydrated	Oral; solution	35.63	%
Alcohol, dehydrated	Topical; aerosol	60.39	%
Alcohol, dehydrated	Topical; emulsion, aerosol foam	60.43	%
Alcohol, dehydrated	Topical; solution	96.67	%
Alcohol, denatured	Oral; syrup	7	%
Alcohol, denatured	Topical; solution	60.16	%
Alcohol, denatured	Topical; aerosol	68	%
Alcohol, denatured	Topical; swab	75	ML
Alcohol, diluted	Oral; syrup	1.5	%

Ingredient	Dosage Form	Qty	Unit
Alcohol, diluted	Oral; solution, elixir	20	%
Alcohol, diluted	Topical; aerosol	68.5	%
Alkyl aryl sodium sulfonate	Topical; shampoo, suspension	2.5	%
Aluminum acetate	Topical; shampoo	0.1	%
Amerchol C	Topical; emulsion	0.1	%
Ammonia solution	Oral; suspension	0.015	%
Ammonium chloride	Oral; syrup	7	%
Ammonium glycyrrhizate	Oral; solution	0.8	%
Ammonium lauryl sulfate	Topical; emulsion	39.75	%
Ammonyx	Topical; aerosol, metered	3	%
Ammonyx	Topical; solution	3.5	%
Amphoteric-2	Topical; shampoo, suspension	5	%
Anethole	Oral; solution, elixir	0.003	%
Anethole	Oral; syrup	0.046	%
Anise	Oral; solution, elixir	0.009	%
Anise extract	Oral; solution, elixir	0.015	%
Anise oil	Oral; suspension	0.05	%
Anise oil	Oral; solution	0.14	%
Anise oil	Rectal; solution	0.14	%
Anise oil	Oral; solution, elixir	15	%
Arlacel	Topical; emulsion	5.5	%
Ascorbic acid	Topical; solution	0.044	%
Ascorbic acid	Oral; suspension	0.2	%
Ascorbic acid	Oral; concentrate	0.6	%
Ascorbic acid	Oral; syrup	1.25	%
Ascorbyl palmitate	Topical; solution	0.0044	%
Aspartame	Oral; syrup	0.0125	%
Aspartame	Oral; suspension	40.244	%
Beheneth-10	Topical; solution	1.5	%
Bentonite	Oral; suspension	1.3	%
Bentonite	Topical; shampoo, suspension	4	%
Benzaldehyde	Oral; suspension	0.06	%
Benzalkonium chloride	Topical; solution	0.005	%
Benzalkonium chloride	Topical; solution, drops	0.0075	%
Benzalkonium chloride	Topical; suspension	0.01	%
Benzalkonium chloride	Topical; shampoo	0.2	%
Benzoic acid	Oral; suspension	0.1	%
Benzoic acid	Rectal; suspension	0.1	%
Benzoic acid	Topical; solution	0.1	%
Benzoic acid	Rectal; gel	0.14	%
Benzoic acid	Oral; solution	0.5	%
Benzoic acid	Oral; solution, elixir	0.5	%
Benzoic acid	Oral; syrup	0.753	%

Ingredient	Dosage Form	Qty	Unit
Benzoic acid	Oral; concentrate	1.25	%
Benzyl alcohol	Oral; suspension	1	%
Benzyl alcohol	Topical; suspension	1	%
Benzyl alcohol	Rectal; gel	1.55	%
Benzyl alcohol	Topical; solution	2	%
Benzyl alcohol	Oral; solution	5	%
Boric acid	Topical; solution, drops	0.12	%
Boric acid	Topical; suspension	0.6	%
Boric acid	Topical; emulsion	1.3	%
Boric acid	Topical; shampoo	2	%
Butane	Sublingual; aerosol, metered	2.1998	%
Butyl alcohol	Topical; solution	0.0786	%
Butyl ester of PVM/MA copolymer	Topical; solution	30	%
Butylated hydroxyanisole	Oral; concentrate	0.0075	%
Butylated hydroxyanisole	Oral; solution	0.0189	%
Butylated hydroxyanisole	Oral; suspension	0.05	%
Butylated hydroxytoluene	Oral; solution, liquid, concentrate, oral	0.01	%
Butylated hydroxytoluene	Oral; solution	0.0189	%
Butylated hydroxytoluene	Topical; solution	0.088	%
Butylated hydroxytoluene	Topical; emulsion, aerosol foam	0.1	%
Butylated hydroxytoluene	Topical; shampoo	0.1	%
Butylparaben	Oral; syrup	0.0075	%
Butylparaben	Oral; drops	0.1	%
Butylparaben	Oral; solution	0.5	%
Butylparaben	Rectal; solution	0.5	%
Butylparaben	Oral; suspension	0.8	%
C20–40 pareth-24	Topical; solution	0.25	%
Calcium chloride	Oral; concentrate	0.008	%
Calcium chloride	Oral; suspension	0.05	%
Calcium phosphate, dibasic	Topical; shampoo	54.8	%
Calcium salicylate	Oral; solution, elixir	0.2487	%
Caprylic/capric triglyceride	Oral; solution	2.62	%
Caprylic/capric triglyceride	Topical; solution	50	%
Caprylic/capric/succinic triglyceride	Sublingual; aerosol, metered	1.0359	%
Capsicum oleoresin	Oral; syrup	0.0011	%
Captan	Topical; shampoo, suspension	1	%
Caramel	Oral; solution	0.008	%
Caramel	Oral; syrup	2.4	%
Caramel	Oral; suspension	11.112	%
Carbomer 934	Topical; solution	0.15	%
Carbomer 934	Oral; suspension	1	%
Carbomer 934	Rectal; enema	14.4	%
Carbomer 934P	Rectal; enema	0.075	%

Ingredient	Dosage Form	Qty	Unit
Carbomer 934P	Topical; solution	0.18	%
Carbomer 934P	Oral; suspension	1.4	%
Carbomer 940	Topical; emulsion	0.6	%
Carboxymethylcellulose	Oral; suspension	6.4	%
Carboxymethylcellulose sodium	Oral; suspension, drops	0.1	%
Carboxymethylcellulose sodium	Oral; drops	0.514	%
Carboxymethylcellulose sodium	Oral; syrup	2.65	%
Carboxymethylcellulose sodium	Oral; solution	3.5	%
Carboxymethylcellulose sodium	Oral; suspension	3.75	%
Cardamom	Oral; solution, elixir	0.25	%
Carmine	Oral; suspension	1.008	%
Cedar leaf oil	Topical; shampoo	30	%
Cellulose microcrystalline/carboxymethylcellulose sodium	Oral; suspension, drops	0.76	%
Cellulose microcrystalline/carboxymethylcellulose sodium	Oral; suspension	3	%
Cellulose microcrystalline/carboxymethylcellulose sodium	Oral; suspension, liquid	3	%
Cellulose, microcrystalline	Oral; suspension	1.45	%
Cellulose, microcrystalline	Oral; mucilage	63	MG
Cellulose, microcrystalline	Oral; dispersible tablet	253.2	MG
Cetearyl alcohol	Topical; suspension	2.5	%
Ceteth-20	Topical; solution	2	%
Ceteth-20	Topical; solution, liquid	2	%
Cetyl alcohol	Rectal; aerosol, metered	0.162	%
Cetyl alcohol	Topical; aerosol	1.16	%
Cetyl alcohol	Topical; suspension	2.013	%
Cetyl alcohol	Topical; emulsion, aerosol foam	3.226	%
Cetyl alcohol	Topical; aerosol, metered	10	%
Cetyl palmitate	Topical; solution	0.05	%
Chlorobutanol	Topical; solution	0.3	%
Choleth-24	Topical; emulsion	5	%
Cinnamaldehyde	Oral; suspension	0.01	%
Cinnamon	Oral; solution, elixir	1.05	%
Cinnamon oil	Oral; syrup	0.005	%
Cinnamon oil	Oral; suspension	0.0204	%
Cinnamon oil	Oral; solution, elixir	55	%
Citrate	Oral; syrup	1.2	%
Citric acid	Oral; suspension, for inhalation	0.028	%
Citric acid	Topical; aerosol	0.08	%
Citric acid	Topical; emulsion	0.11	%
Citric acid	Topical; emulsion, aerosol foam	0.11	%
Citric acid	Oral; drops	0.18	%
Citric acid	Oral; suspension, liquid	0.18	%

Ingredient	Dosage Form	Qty	Unit
Citric acid	Oral; suspension, drops	0.24	%
Citric acid	Oral; suspension, sustained action	0.5	%
Citric acid	Oral; solution, liquid	0.7	%
Citric acid	Oral; solution	0.8	%
Citric acid	Topical; shampoo, suspension	1	%
Citric acid	Oral; liquid	1.35	%
Citric acid	Oral; suspension	1.4065	%
Citric acid	Oral; concentrate	1.85	%
Citric acid	Oral; solution, elixir	2	%
Citric acid	Topical; shampoo	2.3	%
Citric acid	Topical; solution	40	%
Citric acid	Topical; swab	40	MG
Citric acid	Oral; syrup	72.2	%
Citric acid monohydrate	Topical; solution	0.188	%
Citric acid monohydrate	Topical; shampoo	0.24	%
Citric acid monohydrate	Oral; suspension	0.3	%
Citric acid monohydrate	Oral; solution	0.5	%
Citric acid monohydrate	Oral; syrup	0.96	%
Citric acid monohydrate	Oral; suspension, sustained action	14.08	%
Citric acid, hydrous	Oral; syrup	0.26	%
Citric acid, hydrous	Oral; suspension	0.75	%
Clove oil	Oral; suspension	0.01	%
Clove oil	Oral; solution, elixir	40	%
Cocamide diethanolamine	Topical; aerosol, metered	3	%
Cocamide diethanolamine	Topical; shampoo	3.5	%
Cocamide diethanolamine	Topical; solution	4	%
Cocamide diethanolamine	Topical; suspension	4	%
Cocamide ether sulfate	Topical; shampoo	5	%
Cocamine oxide	Topical; shampoo	2	%
Coco betaine	Topical; shampoo	6	%
Cocoa bean	Oral; suspension	24.666	%
Coconut oil	Topical; solution	15.5	%
Coriander oil	Oral; solution, elixir	15	%
Corn glycerides	Oral; solution	31.885	%
Corn oil	Oral; suspension	50	%
Corn syrup	Oral; solution	15	%
Corn syrup	Oral; solution, elixir	30.4	%
Corn syrup	Oral; suspension	34.2	%
Corn syrup	Oral; syrup	65.78	%
Crospovidone	Oral; suspension	0.05	%
Crospovidone	Topical; emulsion	1	%
Crospovidone	Oral; mucilage	9	MG
Crospovidone	Oral; suspension, sustained action	18.68	%

Ingredient	Dosage Form	Qty	Unit
Crospovidone	Oral; dispersible tablet	340	MG
Cyclomethicone	Topical; emulsion, aerosol foam	5.26	%
D&C Red No. 19	Topical; emulsion	0.0007	%
D&C Red No. 28	Topical; aerosol	0.0007	%
D&C Red No. 28	Oral; suspension	0.05	%
D&C Red No. 33	Oral; solution, elixir	0.0007	%
D&C Red No. 33	Oral; suspension, liquid	0.0013	%
D&C Red No. 33	Topical; shampoo	0.002	%
D&C Red No. 33	Oral; concentrate	0.0022	%
D&C Red No. 33	Oral; suspension	0.0025	%
D&C Red No. 33	Oral; solution	0.005	%
D&C Red No. 33	Oral; syrup	0.006	%
D&C Red No. 33	Oral; suspension, sustained action	0.4	%
D&C Yellow No. 10	Rectal; solution	0.0007	%
D&C Yellow No. 10	Oral; solution, liquid	0.0008	%
D&C Yellow No. 10	Oral; suspension, liquid	0.0008	%
D&C Yellow No. 10	Topical; shampoo	0.001	%
D&C Yellow No. 10	Oral; concentrate	0.0025	%
D&C Yellow No. 10	Topical; shampoo, suspension	0.005	%
D&C Yellow No. 10	Oral; solution, elixir	0.03	%
D&C Yellow No. 10	Oral; syrup	0.05	%
D&C Yellow No. 10	Oral; suspension	2	%
D&C Yellow No. 10	Oral; solution	5	%
D&C Yellow No. 6 Lake	Oral; solution	0.005	%
Denatonium benzoate	Topical; solution	0.0003	%
Dextrin	Topical; shampoo	5	%
Dextrose	Oral; syrup	27	%
Dichlorodifluoromethane	Topical; emulsion, aerosol foam	8	%
Dichlorodifluoromethane	Rectal; aerosol, metered	13.5	%
Dichlorofluoromethane	Oral; aerosol, metered	35	%
Dichlorotetrafluoroethane	Rectal; aerosol, metered	9	%
Diethyl sebacate	Topical; solution	24	%
Diisopropyl adipate	Topical; solution	17	%
Diisopropyl dimerate	Topical; solution	1	%
Dimethicone 350	Topical; solution	0.5	%
Disodium edisylate	Oral; solution	0.02	%
Disodium laureth sulfosuccinate	Topical; shampoo	15	%
Disodium lauryl sulfosuccinate	Topical; shampoo	15	%
Docosanol	Topical; solution	1.1	%
Docusate sodium	Oral; suspension, sustained action	0.077	%
Docusate sodium	Oral; suspension	0.115	%
Docusate sodium	Topical; shampoo	2	%
Dye blue 1	Oral; solution	0.0753	%

Ingredient	Dosage Form	Qty	Unit
Dye caramel 105	Oral; syrup	0.0052	%
Dye caramel acid proof 100	Oral; solution, elixir	0.005	%
Dye caramel acid proof 100	Oral; syrup	0.048	%
Dye FDC blue 10	Oral; syrup	0.0001	%
Dye wild cherry 7598	Oral; syrup	0.0035	%
Dye yellow 10	Oral; solution	0.006	%
Edamine	Oral; solution	0.37	%
Edetate calcium disodium	Oral; concentrate	0.025	%
Edetate calcium disodium	Oral; solution, elixir	0.1	%
Edetate disodium	Oral; suspension, for inhalation	0.01	%
Edetate disodium	Topical; solution	0.01	%
Edetate disodium	Topical; suspension	0.01	%
Edetate disodium	Oral; suspension, drops	0.04	%
Edetate disodium	Rectal; solution	0.04	%
Edetate disodium	Oral; liquid	0.05	%
Edetate disodium	Rectal; enema	0.1	%
Edetate disodium	Topical; emulsion	0.1107	%
Edetate disodium	Oral; suspension	0.2497	%
Edetate disodium	Oral; concentrate	0.3	%
Edetate disodium	Oral; solution	0.5	%
Edetate disodium	Oral; syrup	0.5	%
Edetic acid	Topical; suspension	0.0633	%
Edetic acid	Topical; shampoo	0.2	%
Edetic acid	Topical; solution	0.5	%
Epilactose	Oral; solution	1.3333	%
Epilactose	Rectal; solution	1.3333	%
Essence fritzbro orange	Oral; suspension	2.01	%
Essence lemon	Oral; syrup	0.25	%
Essence orange	Oral; syrup	1	%
Ethyl acetate	Topical; solution	31	%
Ethyl hexanediol	Topical; solution	0.25	%
Ethyl maltol	Oral; solution	0.05	%
Ethyl maltol	Oral; solution, elixir	0.06	%
Ethyl maltol	Oral; syrup	3.05	%
Ethyl vanillin	Oral; suspension	0.008	%
Ethylene glycol	Topical; shampoo, suspension	1	%
Eucalyptus oil	Oral; syrup	0.014	%
Fatty acid glycerides	Sublingual; spray, metered	0.096	%
Fatty acids	Topical; solution	13.58	%
FD&C Blue No. 1	Oral; solution, elixir	0.0005	%
FD&C Blue No. 1	Oral; suspension, liquid	0.0007	%
fd&c Blue No. 1	Oral; suspension	0.0015	%
fd&c Blue No. 1	Topical; shampoo	0.0036	%

Ingredient	Dosage Form	Qty	Unit
FD&C Blue No. 1	Oral; syrup	0.004	%
FD&C Blue No. 1	Oral; solution	0.0753	%
FD&C Blue No. 1	Rectal; solution	0.0753	%
FD&C Blue No. 1–Aluminum Lake	Oral; syrup	0.0013	%
FD&C Green No. 3	Oral; syrup	0.075	%
FD&C Red No. 3	Oral; solution, elixir	0.0008	%
FD&C Red No. 3	Oral; drops	0.005	%
FD&C Red No. 3	Oral; syrup	0.015	%
FD&C Red No. 3	Oral; suspension	0.02	%
FD&C Red No. 33	Oral; solution	0.0011	%
FD&C Red No. 33	Oral; syrup	0.002	%
FD&C Red No. 33	Oral; solution, elixir	2.75	%
FD&C Red No. 3–Aluminum Lake	Topical; solution	0.006	%
FD&C Red No. 4	Topical; solution	0.0005	%
FD&C Red No. 40	Oral; drops	0.001	%
FD&C Red No. 40	Oral; concentrate	0.0035	%
FD&C Red No. 40	Topical; shampoo	0.004	%
FD&C Red No. 40	Oral; suspension, liquid	0.005	%
FD&C Red No. 40	Oral; suspension, drops	0.016	%
FD&C Red No. 40	Oral; solution	0.04	%
FD&C Red No. 40	Oral; syrup	2	%
FD&C Red No. 40	Oral; suspension	10	%
FD&C Red No. 40	Oral; solution, elixir	12.5	%
FD&C Red No. 40–Aluminum Lake	Oral; solution	0.007	%
FD&C Red No. 40–Aluminum Lake	Oral; suspension	0.04	%
FD&C Yellow No. 10	Oral; suspension	0.01	%
FD&C Yellow No. 10	Oral; syrup	0.025	%
FD&C Yellow No. 5	Oral; syrup	0.0015	%
FD&C Yellow No. 5	Oral; solution, elixir	0.002	%
FD&C Yellow No. 5	Topical; solution	0.0055	%
FD&C Yellow No. 5	Oral; solution	0.1	%
FD&C Yellow No. 6	Oral; concentrate	0.003	%
FD&C Yellow No. 6	Oral; suspension, liquid	0.01	%
FD&C Yellow No. 6	Oral; suspension, sustained action	0.0115	%
FD&C Yellow No. 6	Oral; suspension	0.1	%
FD&C Yellow No. 6	Oral; syrup	0.4	%
FD&C Yellow No. 6	Oral; solution, elixir	4	%
FD&C Yellow No. 6	Oral; solution	20	%
FD&C Yellow No. 6	Rectal; solution	20	%
Ferric oxide red	Oral; suspension, sustained action	0.27	%
Flavor anise 29653	Oral; solution	0.0186	%
Flavor apple watermelon PFC 9887	Oral; syrup	0.51	%
Flavor apricot 23067	Oral; suspension	0.0963	%

Ingredient	Dosage Form	Qty	Unit
Flavor apricot 24829	Oral; solution	0.2	%
Flavor apricot peach	Oral; syrup	0.52	%
Flavor banana 74546	Oral; suspension	0.21	%
Flavor BBA-47769	Oral; drops	0.23	%
Flavor berry citrus blend 8409	Oral; concentrate	0.8	%
Flavor berry citrus blend 8409	Oral; solution	5	%
Flavor berry citrus blend 9621	Oral; solution	5.125	%
Flavor bitter mask 9885	Oral; solution	0.5	%
Flavor bitterness modifier 36734	Oral; syrup	0.1	%
Flavor bitterness modifier 367343	Oral; syrup	0.5	%
Flavor blood orange SA	Oral; syrup	0.021	%
Flavor bubble gum 15864	Oral; syrup	0.1	%
Flavor bubble gum 175303	Oral; solution	0.1234	%
Flavor bubble gum 3266P	Oral; syrup	0.05	%
Flavor bubble gum mc-4938	Oral; suspension	0.36	%
Flavor butterscotch F-1785	Oral; syrup	35	%
Flavor C&K mixed fruit A13688	Oral; solution	2.5	%
Flavor candied sugar 510155U	Oral; syrup	0.7223	%
Flavor cheri beri PCD-5580	Oral; syrup	5	%
Flavor cheri beri PFC-8580	Oral; solution	0.05	%
Flavor cheri beri PFC-8580	Oral; syrup	5	%
Flavor cherry 104613	Oral; syrup	0.0002	%
Flavor cherry 107026	Oral; syrup	0.1	%
Flavor cherry 1566	Oral; solution	0.15	%
Flavor cherry 213	Oral; syrup	0.07	%
Flavor cherry 3321	Oral; syrup	0.15	%
Flavor cherry 349	Oral; solution	1.645	%
Flavor cherry 500910U	Oral; suspension	0.04	%
Flavor cherry 57.679/A	Oral; suspension	5	%
Flavor cherry 590271A	Oral; suspension	0.0061	%
Flavor cherry 598384	Oral; syrup	0.14	%
Flavor cherry 825.476WC	Oral; solution	0.3	%
Flavor cherry 842	Oral; syrup	0.5	%
Flavor cherry 8513	Oral; syrup	0.022	%
Flavor cherry berry F-1194	Oral; suspension, liquid	0.4	%
Flavor cherry burgundy 11650	Oral; solution	0.3	%
Flavor cherry cream 14850	Oral; suspension	0.0715	%
Flavor cherry DP300684	Oral; syrup	0.35	%
Flavor cherry E.P.modified 151	Oral; concentrate	0.1	%
Flavor cherry F-232	Oral; concentrate	0.1	%
Flavor cherry F-232	Oral; suspension	0.1	%
Flavor cherry F-232	Oral; solution	1.5	%
Flavor cherry FMC 8513	Oral; solution	0.05	%

Ingredient	Dosage Form	Qty	Unit
Flavor cherry FMC 8513	Oral; syrup	0.08	%
Flavor cherry FONA 825.662	Oral; suspension, liquid	0.205	%
Flavor cherry IFF 13530912	Oral; solution, elixir	0.005	%
Flavor cherry MINT 5073A	Oral; solution	0.5	%
Flavor cherry PFC-9768	Oral; concentrate	0.7	%
Flavor cherry PFC-9768	Oral; solution	2	%
Flavor cherry PFC-9768	Oral; syrup	2	%
Flavor cherry pistachio PFC-8450	Oral; concentrate	0.9	%
FLAVOR cherry vanilla compound A77487	Oral; syrup	0.1057	%
Flavor cherry wixon 3566	Oral; syrup	1	%
Flavor cherry WL-1093	Oral; syrup	0.08	%
Flavor cherry WL-4658	Oral; solution	0.65	%
Flavor cherry anise PFC-9758	Oral; syrup	0.5313	%
Flavor coconut toasted 1323PG	Oral; solution	0.06	%
Flavor cola FMC 15740	Oral; solution, elixir	1.5	%
Flavor cotton candy 30–92-0011	Oral; solution	1.02	%
Flavor cotton candy F-9967	Oral; solution	0.7	%
Flavor cough syrup 110257	Oral; solution	0.1	%
Flavor cough syrup 134681	Oral; syrup	0.6	%
Flavor cough syrup 819	Oral; syrup	0.15	%
Flavor creamy vanilla 16345	Oral; solution	0.2	%
Flavor creme de menthe 14677	Oral; suspension	0.0003	%
Flavor creme de menthe 14677	Oral; solution	0.3	%
Flavor creme de vanilla 28156	Oral; drops	0.16	%
Flavor E-472	Oral; concentrate	0.4	%
Flavor F-5397A	Oral; concentrate	8	%
Flavor F-9843	Oral; suspension	0.05	%
Flavor felton 6-R-9	Oral; syrup	0.15	%
Flavor fritzsche 73959	Oral; syrup	0.5	%
Flavor fritzsche 78087	Oral; syrup	0.1	%
Flavor fruit 01–10428	Oral; concentrate	0.025	%
Flavor fruit punch 28140	Oral; suspension	0.75	%
Flavor fruit TAK 20008	Oral; concentrate	0.1	%
Flavor grape 501040A	Oral; solution	0.03	%
Flavor grape 6175	Oral; suspension	0.2	%
Flavor grape firmenich 587.444	Oral; suspension, liquid	0.37	%
Flavor grape firmenich 597.303/C	Oral; suspension, liquid	0.133	%
Flavor grape givaudan 433160	Oral; suspension, liquid	0.37	%
Flavor grape manheimer 522463	Oral; suspension	0.5	%
Flavor grape nector PFC-8599	Oral; syrup	0.2	%
Flavor grape PFC 8439	Oral; syrup	1.003	%
Flavor grape PFC-9711	Oral; syrup	0.0015	%
Flavor grape PFC-9924	Oral; solution	0.4	%

Ingredient	Dosage Form	Qty	Unit
Flavor guarana FMC-15417	Oral; suspension	0.756	%
Flavor lemon 812	Oral; suspension	0.176	%
Flavor lemon FMC-10471	Oral; syrup	0.5	%
Flavor lemon givaudan 74940–74	Oral; suspension, liquid	9	%
Flavor lemon mint 862.547	Oral; solution	0.12	%
Flavor lemon mint fritzsche 54369	Oral; syrup	0.1	%
Flavor magnasweet 110	Oral; solution	2.95	%
Flavor mixed fruit PFC-9970	Oral; syrup	0.235	%
Flavor orange 7679	Oral; solution	0.4	%
Flavor orange 7679	Oral; syrup	1.25	%
Flavor orange 607217	Oral; syrup	0.5	%
Flavor orange givaudan 74388–74	Oral; suspension, liquid	0.02	%
Flavor orange PFW-730016U	Oral; suspension, sustained action	1.5	%
Flavor orange pineapple FV-43	Oral; solution, elixir	0.2454	%
Flavor orange WONF 608352	Oral; solution	0.01	%
Flavor peach 10457	Oral; solution	0.06	%
Flavor peach 13503584	Oral; syrup	0.308	%
Flavor peach 302789	Oral; solution	0.12	%
Flavor peach mint fritzsche 106109	Oral; syrup	0.1	%
Flavor peach pineapple FMC 14258	Oral; solution	0.0003	%
Flavor peach pineapple FMC 14258	Oral; suspension	0.0003	%
Flavor peppermint 104	Oral; solution	0.05	%
Flavor peppermint 104	Oral; suspension	0.2	%
Flavor peppermint 894.143	Oral; solution	0.03	%
Flavor peppermint PFC 9927	Oral; solution	0.07	%
Flavor pharmasweet 10772900	Oral; syrup	0.2	%
Flavor pineapple N-2766	Oral; syrup	1	%
Flavor punch WL-7126	Oral; suspension	0.3	%
Flavor raspberry 1840	Oral; solution, elixir	0.125	%
Flavor raspberry 21028d	Oral; solution	0.044	%
Flavor raspberry 21028d	Oral; syrup	0.5	%
Flavor raspberry 28106	Oral; drops	0.5	%
Flavor raspberry 50776	Oral; syrup	0.05	%
Flavor raspberry 65934	Oral; solution	0.075	%
Flavor raspberry 8456	Oral; syrup	0.336	%
Flavor raspberry 998	Oral; solution	0.75	%
Flavor raspberry 998	Oral; syrup	1	%
Flavor raspberry A11693	Oral; syrup	0.075	%
Flavor raspberry arome PFC-9908	Oral; syrup	0.5	%
Flavor raspberry D9599	Oral; suspension	0.2	%
Flavor raspberry F-1784	Oral; solution	1	%
Flavor raspberry F-1784	Oral; syrup	7	%
Flavor raspberry F-1840	Oral; solution	0.25	%

Ingredient	Dosage Form	Qty	Unit
Flavor raspberry F-1840	Oral; syrup	0.6	%
Flavor raspberry PFC-8407	Oral; solution, elixir	0.025	%
Flavor raspberry POLAK 5000064	Oral; solution	0.0001	%
Flavor strawberry 14953	Oral; solution	0.3	%
Flavor strawberry 17C56217	Oral; solution	0.3	%
Flavor strawberry 5210(FD&D)	Oral; syrup	0.078	%
Flavor strawberry 523121a	Oral; suspension	4.2	%
Flavor strawberry 55058	Oral; concentrate	0.1	%
Flavor strawberry 55058	Oral; syrup	0.1	%
Flavor strawberry 5951	Oral; drops	0.2	%
Flavor strawberry 9843	Oral; syrup	0.1	%
Flavor strawberry FN-13819	Oral; solution	0.87	%
Flavor strawberry PFC-9626	Oral; syrup	1.5795	%
Flavor strawberry trusil windsor 2373031	Oral; suspension, sustained action	2.21	%
Flavor sweet tone 28837	Oral; solution	0.05	%
Flavor sweet-AM 918.005	Oral; solution	0.04	%
Flavor sweetness enhancer 5401b	Oral; syrup	0.3	%
Flavor tangerine fritzsche 51465	Oral; syrup	0.05	%
Flavor tetrarome	Oral; suspension	0.01	%
Flavor TM 313298	Oral; suspension	0.075	%
Flavor TPF 135	Oral; suspension	0.007	%
Flavor TPF 143	Oral; suspension	0.13	%
Flavor tropical blend FV-50	Oral; solution, elixir	0.2999	%
Flavor tropical fruit punch 1591	Oral; solution	0.8	%
Flavor tropical fruit punch N&A 50432	Oral; syrup	0.52	%
Flavor tropical fruit punch N&A 50432	Oral; solution	18.2	%
Flavor tutti frutti 0002028	Oral; suspension	0.35	%
Flavor tutti frutti 51.880/AP05.51	Oral; suspension	0.05	%
Flavor vanilla 323453	Oral; solution	0.156	%
Flavor vanilla 33869	Oral; solution	1.27	%
Flavor vanilla beck C7984	Oral; syrup	0.6	%
Flavor vanilla F-6257	Oral; solution	0.6	%
Flavor vanilla PFC-8541	Oral; concentrate	0.01	%
Flavor vanilla PFC-9772	Oral; concentrate	1	%
Flavor wild cherry 29653	Oral; solution	0.04	%
Flavor wild cherry 695047u	Oral; concentrate	1	%
Flavor wild cherry PFC-14783	Oral; suspension	0.037	%
Flavor wild cherry PFC-14783	Oral; syrup	0.4	%
Flavor wild cherry WL-1093 florasynth	Oral; syrup	0.25	%
Flavor wintergreen PFC-8421	Oral; solution	0.0001	%
Flavor yellow plum lemon 39K 020	Oral; suspension	0.05	%
Florasynth	Oral; solution	0.5	%
Formaldehyde	Topical; solution	0.2	%

Ingredient	Dosage Form	Qty	Unit
Fragrance 3949–5	Topical; shampoo, suspension	0.4	%
Fragrance 91–122	Topical; shampoo, suspension	3	%
Fragrance felton 066M	Topical; solution	0.12	%
Fragrance firmenich 47373	Topical; solution	0.1	%
Fragrance givaudan ESS 9090/1C	Topical; solution	0.101	%
Fragrance herbal 10396	Topical; shampoo	0.3	%
Fragrance P O FL-147	Topical; aerosol, metered	0.1	%
Fragrance P O FL-147	Topical; solution	0.13	%
Fragrance P O FL-147	Topical; aerosol	0.274	%
Fragrance P O FL-147	Topical; emulsion	0.274	%
Fragrance PA 52805	Topical; solution	5	%
Fragrance PA 52805	Topical; swab	50	MG
Fragrance pera derm D	Topical; solution	0.0217	%
Fragrance RBD-9819	Topical; solution	0.025	%
Fragrance RBD-9819	Topical; emulsion, aerosol foam	0.1	%
Fragrance shaw mudge U-7776	Topical; solution	0.01	%
Fragrance TF 044078	Topical; solution	0.5	%
Fragrance ungerer honeysuckle K 2771	Topical; shampoo	1	%
Fructose	Rectal; solution	0.6667	%
Fructose	Oral; suspension	2	%
Fructose	Oral; solution	35	%
Fumaric acid	Oral; syrup	0.075	%
Fumaric acid	Oral; suspension	0.5	%
Galactose	Rectal; solution	14.6667	%
Galactose	Oral; solution	14.7	%
Gelatin	Oral; solution	3.48	%
Ginger fluidextract	Oral; solution, elixir	1	%
Ginger fluidextract	Oral; syrup	1	%
Gluconolactone	Topical; aerosol, metered	0.25	%
Gluconolactone	Topical; solution	0.25	%
Glucose, liquid	Oral; solution	49.78	%
Glucose, liquid	Oral; syrup	62	%
Glycerin	Topical; emulsion, aerosol foam	2.11	%
Glycerin	Topical; suspension	5	%
Glycerin	Oral; drops	10	%
Glycerin	Oral; suspension, drops	10	%
Glycerin	Oral; suspension, liquid	10	%
Glycerin	Oral; solution, concentrate	20	%
Glycerin	Oral; solution, syrup	20	%
Glycerin	Oral; liquid	22	%
Glycerin	Topical; solution	50	%
Glycerin	Oral; solution, elixir	62.3	%
Glycerin	Oral; concentrate	75	%

Ingredient	Dosage Form	Qty	Unit
Glycerin	Oral; syrup	77	%
Glycerin	Oral; suspension	79	%
Glycerin	Oral; solution	94	%
Glyceryl caprylate	Oral; solution	34.91	%
Glyceryl palmitostearate	Oral; suspension	3	%
Glyceryl ricinoleate	Topical; shampoo, suspension	2	%
Glyceryl stearate SE	Topical; suspension	1.25	%
Glycine	Oral; suspension	2	%
Glycine	Oral; solution	5	%
Glycine	Rectal; solution	5	%
Glycol distearate	Topical; shampoo	1.25	%
Glycol stearate	Topical; shampoo, suspension	1	%
Glycol stearate	Topical; shampoo	3	%
Glycyrrhizic acid	Oral; syrup	0.125	%
Glycyrrhizin, ammoniated	Oral; syrup	0.125	%
Glycyrrhizin, ammoniated	Oral; solution	0.13	%
Guar gum	Oral; suspension	0.493	%
Hexylene glycol	Topical; solution	12	%
High fructose corn syrup	Oral; solution	16.86	%
Histidine	Oral; suspension	0.5	%
Hydrocarbon	Rectal; aerosol, metered	5.21	%
Hydrochloric acid	Oral; syrup	0.203	%
Hydrochloric acid	Topical; solution	1.24	%
Hydrochloric acid	Oral; concentrate	3.1	%
Hydrochloric acid	Topical; shampoo	4	%
Hydrochloric acid	Oral; solution	9.51	%
Hydrochloric acid	Oral; suspension	10	%
Hydrochloric acid, diluted	Topical; shampoo	2.35	%
Hydrochloric acid, diluted	Oral; solution	2.75	%
Hydrochloric acid, diluted	Topical; solution	5.55	%
Hydroxyethyl cellulose	Oral; suspension	0.1	%
Hydroxyethyl cellulose	Topical; suspension	0.686	%
Hydroxyethyl cellulose	Oral; solution	0.75	%
Hydroxyethyl cellulose	Topical; solution	0.75	%
Hydroxyethyl cellulose	Oral; syrup	10	%
Hydroxymethyl cellulose	Topical; solution	0.909	%
Hydroxypropyl cellulose	Topical; solution	0.6	%
Hydroxypropyl methylcellulose 100	Oral; syrup	0.25	%
Hydroxypropyl methylcellulose 100	Oral; suspension	5	%
Hydroxypropyl methylcellulose 2910	Oral; syrup	0.45	%
Hydroxypropyl methylcellulose 2910	Oral; suspension	0.5	%
Hydroxypropyl methylcellulose 4000	Oral; suspension	2	%
Hydroxypropyl methylcellulose 603	Oral; suspension	2.3	%

Ingredient	Dosage Form	Qty	Unit
Hydroxypropyl-*b*-cyclodextrin	Oral; solution	40	%
Imidurea	Topical; shampoo	0.4	%
Invert sugar	Oral; syrup	77	%
Isobutane	Topical; aerosol	6	%
Isoceteth-20	Topical; solution	2.3	%
Isopropyl alcohol	Topical; aerosol, metered	4	%
Isopropyl alcohol	Topical; aerosol, spray	10	%
Isopropyl alcohol	Topical; solution	51.5	%
Isopropyl myristate	Topical; emulsion, aerosol foam	7.9	%
Isostearyl alcohol	Topical; suspension	2.5	%
Kaolin	Oral; syrup	1	%
Kola nut extract	Oral; solution	2	%
Kola nut extract	Rectal; solution	2	%
Kola nut extract	Oral; concentrate	24.72	%
Lactic acid	Topical; suspension	0.7	%
Lactic acid	Topical; emulsion, aerosol foam	1.05	%
Lactic acid	Oral; concentrate	5	%
Lactic acid	Topical; solution	18.06	%
D-Tagatose	Topical; solution	7.4	%
Lactose	Rectal; solution	8	%
Lactose	Oral; solution	11.2133	%
Lactose monohydrate	Oral; dispersible tablet	543.6	MG
Laneth	Topical; solution	0.5	%
Lauramine oxide	Topical; solution	4.8	%
Laurdimonium hydrolyzed animal collagen	Topical; shampoo	1	%
Laureth-23	Topical; aerosol	0.45	%
Laureth-23	Topical; emulsion	0.45	%
Laureth-23	Topical; emulsion, aerosol foam	1.075	%
Laureth-4	Topical; solution	5.22	%
Lauric diethanolamide	Topical; suspension	0.475	%
Lauric diethanolamide	Topical; solution	1.4167	%
Lauric diethanolamide	Topical; shampoo, suspension	4	%
Lauric diethanolamide	Topical; emulsion	15	%
Lauric diethanolamide	Topical; shampoo	20	%
Lauryl sulfate	Topical; shampoo, suspension	25	%
Lecithin	Topical; solution	1.4	%
Lecithin	Oral; suspension	11	%
Lecithin, soybean	Oral; suspension	0.2	%
Levomenthol	Sublingual; aerosol, metered	0.002	%
Light mineral oil	Topical; emulsion, aerosol foam	5.26	%
Lithium hydroxide monohydrate	Oral; syrup	33.7	%
Magnasweet 110	Oral; solution	0.8	%
Magnasweet 180	Oral; solution	0.13	%

Ingredient	Dosage Form	Qty	Unit
Magnesium aluminum silicate	Oral; drops	0.166	%
Magnesium aluminum silicate	Topical; shampoo, suspension	0.85	%
Magnesium aluminum silicate	Rectal; suspension	1	%
Magnesium aluminum silicate	Oral; suspension	6.4	%
Magnesium aluminum silicate hydrate	Topical; shampoo	0.5	%
Magnesium aluminum silicate hydrate	Rectal; suspension	1	%
Magnesium aluminum silicate hydrate	Oral; syrup	10	%
Magnesium aluminum silicate hydrate	Oral; suspension	10.6	%
Magnesium aluminum silicate hydrate	Oral; concentrate	41	%
Magnesium stearate	Oral; suspension, sustained action	2.7	%
Magnesium stearate	Oral; mucilage	4.5	MG
Magnesium stearate	Oral; suspension	5.756	%
Maleic acid	Oral; syrup	0.0345	%
Malic acid	Oral; solution	0.042	%
Malic acid, DL-	Oral; solution	0.33	%
Maltitol	Oral; solution	65	%
Maltol	Oral; concentrate	0.01	%
Maltol	Oral; solution	0.01	%
Mannitol	Topical; solution, drops	1.6	%
Medical antifoam emulsion C	Oral; suspension	0.0528	%
Menthol	Oral; concentrate	0.005	%
Menthol	Oral; suspension	0.041	%
Menthol	Oral; solution, liquid, concentrate, oral	0.05	%
Menthol	Oral; solution	0.075	%
Menthol	Topical; solution	0.08	%
Menthol	Oral; syrup	0.4	%
Methyl alcohol	Oral; concentrate	4.42	%
Methyl gluceth-120 dioleate	Topical; shampoo	1.8	%
Methylcellulose	Oral; suspension	0.025	%
Methylparaben	Rectal; aerosol, metered	0.09	%
Methylparaben	Oral; solution, concentrate	0.1	%
Methylparaben	Rectal; suspension	0.1	%
Methylparaben	Topical; solution	0.1	%
Methylparaben	Topical; emulsion, aerosol foam	0.108	%
Methylparaben	Topical; shampoo, suspension	0.15	%
Methylparaben	Oral; solution, syrup	0.18	%
Methylparaben	Topical; shampoo	0.18	%
Methylparaben	Oral; concentrate	0.2	%
Methylparaben	Oral; suspension, liquid	0.2	%
Methylparaben	Topical; emulsion	0.2	%
Methylparaben	Topical; suspension	0.3	%
Methylparaben	Oral; solution, elixir	0.5	%
Methylparaben	Oral; liquid	0.5	%

Ingredient	Dosage Form	Qty	Unit
Methylparaben	Oral; suspension, sustained action	0.75	%
Methylparaben	Oral; suspension	1	%
Methylparaben	Oral; syrup	5	%
Methylparaben	Rectal; enema	10.8	%
Methylparaben	Oral; solution	13	%
Methylparaben	Rectal; solution	13	%
Methylparaben sodium	Oral; suspension	0.13	%
Mineral oil	Topical; suspension	2.013	%
Myristyl alcohol	Topical; suspension	1.05	%
N,*N*-dimethyl lauramine oxide	Topical; solution	3.5	%
Nipasept	Oral; syrup	0.1	%
Nonoxynol iodine	Topical; solution	15.11	%
Nonoxynol-15	Topical; solution	5.05	%
Nonoxynol-9	Topical; solution	0.01	%
Norflurane	Oral; aerosol, metered	5.4234	%
Norflurane	Oral; suspension, for inhalation	7.5	%
Nutmeg oil, expressed	Oral; solution, elixir	0.45	%
Oatmeal	Topical; shampoo	8	%
Octoxynol-9	Topical; solution	22	%
Octyldodecanol	Topical; suspension	2.013	%
Oleic acid	Topical; solution	7.4	%
Olive oil	Topical; solution	0.6	%
Olive oil	Oral; solution	42.5	%
Opadry oy-ls-58900 white	Oral; solution	0.3	%
Opadry ys-1–7003 white	Oral; mucilage	27	MG
Orange juice	Oral; solution	0.01	%
Orange oil	Oral; suspension	0.054	%
Orange oil	Oral; solution, elixir	0.12	%
Orange oil, terpeneless	Oral; syrup	0.0005	%
Orange oil, terpeneless	Oral; suspension	0.264	%
Orange peel extract	Oral; syrup	0.9	%
Orvus K liquid	Topical; aerosol	39.75	%
Palmitamine oxide	Topical; solution	3.75	%
Parabens	Topical; aerosol, metered	10	%
Peg-8 caprylic/capric glycerides	Oral; solution	6.12	%
Peglicol-5-oleate	Oral; solution	31.9	%
Peppermint oil	Oral; concentrate	0.005	%
Peppermint oil	Sublingual; aerosol, metered	0.0222	%
Peppermint oil	Sublingual; spray, metered	0.0345	%
Peppermint oil	Oral; solution	0.35	%
Peppermint oil	Oral; suspension	10	%
Peppermint oil	Oral; syrup	60	%
Perfume bouquet	Topical; shampoo	0.2	%

Ingredient	Dosage Form	Qty	Unit
Perfume W-1952–1	Topical; solution	10	%
Petrolatum	Topical; emulsion	5.3	%
Petrolatum, white	Topical; emulsion, aerosol foam	7.9	%
Phenoxyethanol	Topical; emulsion, aerosol foam	1.05	%
Phosphoric acid	Topical; solution	0.027	%
Phosphoric acid	Oral; solution	0.1282	%
Pineapple	Oral; concentrate	0.1	%
Polacrilin potassium	Oral; suspension, liquid	0.4	%
Poloxamer 124	Oral; suspension	0.009	%
Poloxamer 188	Oral; concentrate	0.025	%
Poloxamer 188	Oral; suspension	0.6	%
Poloxamer 188	Oral; solution	10	%
Poloxamer 331	Oral; suspension	1.25	%
Poloxamer 407	Oral; solution	1	%
Polyethylene glycol 1000	Oral; concentrate	10	%
Polyethylene glycol 1000	Oral; solution	20	%
Polyethylene glycol 1450	Oral; solution	20	%
Polyethylene glycol 1540	Oral; solution	3.364	%
Polyethylene glycol 1540	Topical; solution	29.7	%
Polyethylene glycol 200	Oral; solution	20	%
Polyethylene glycol 300	Topical; solution	29.7	%
Polyethylene glycol 3350	Oral; suspension	4.5	%
Polyethylene glycol 400	Oral; syrup	0.05	%
Polyethylene glycol 400	Oral; suspension	5	%
Polyethylene glycol 400	Oral; concentrate	60	%
Polyethylene glycol 400	Oral; solution	60	%
Polyethylene glycol 400	Topical; solution	69.9	%
Polyethylene glycol 600	Topical; solution	0.3	%
Polyethylene glycol 600	Oral; solution	65	%
Polyethylene glycol 900	Topical; solution	0.95	%
Polyglyceryl-10 oleate	Oral; solution	19	%
Polyglyceryl-3 oleate	Oral; solution	31	%
Polyoxyl 150 distearate	Topical; solution	1.25	%
Polyoxyl 20 cetostearyl ether	Topical; emulsion, aerosol foam	4.74	%
Polyoxyl 35 castor oil	Oral; suspension	0.04	%
Polyoxyl 35 castor oil	Oral; solution	51.5	%
Polyoxyl 40 hydrogenated castor oil	Oral; solution	45	%
Polyoxyl 40 stearate	Topical; emulsion, aerosol foam	1.075	%
Polyoxyl 6 laurate	Topical; shampoo	2	%
Polyoxyl 75 lanolin	Topical; solution	1	%
Polyoxyl 75 lanolin	Topical; aerosol	1.5	%
Polyoxyl 75 lanolin	Topical; emulsion	1.5	%
Polyoxyl 8 laurate	Topical; suspension	0.633	%

Ingredient	Dosage Form	Qty	Unit
Polyoxyl 8 stearate	Oral; suspension	0.085	%
Polyoxyl 8 stearate	Oral; concentrate	2.5	%
Polyoxyl lanolin	Topical; solution	0.94	%
Polypropylene glycol	Oral; solution	20	%
Polyquaternium-1	Topical; solution, drops	0.0005	%
Polyquaternium-10	Topical; shampoo	2	%
Polyquaternium-7	Topical; shampoo	1	%
Polysorbate 20	Oral; suspension	0.5	%
Polysorbate 20	Topical; emulsion	2	%
Polysorbate 20	Topical; solution	15	%
Polysorbate 40	Oral; solution, elixir	0.005	%
Polysorbate 40	Oral; suspension	0.5	%
Polysorbate 60	Topical; aerosol	0.42	%
Polysorbate 60	Topical; emulsion, aerosol foam	0.42	%
Polysorbate 60	Oral; suspension	0.5	%
Polysorbate 60	Topical; suspension	2.85	%
Polysorbate 60	Topical; shampoo	15	%
Polysorbate 80	Oral; solution, elixir	0.0167	%
Polysorbate 80	Oral; suspension, for inhalation	0.02	%
Polysorbate 80	Oral; concentrate	0.1	%
Polysorbate 80	Oral; suspension, liquid	0.1	%
Polysorbate 80	Oral; drops	0.2	%
Polysorbate 80	Oral; suspension, sustained action	0.25	%
Polysorbate 80	Oral; suspension, drops	0.3	%
Polysorbate 80	Rectal; enema	0.6	%
Polysorbate 80	Oral; suspension	3	%
Polysorbate 80	Rectal; solution	10	%
Polysorbate 80	Oral; solution	12.6	%
Potash	Topical; solution	15	%
Potassium acetate	Rectal; enema	0.41	%
Potassium bicarbonate	Oral; solution	2.5	%
Potassium carbonate	Oral; solution	0.62	%
Potassium citrate	Topical; emulsion, aerosol foam	0.17	%
Potassium citrate	Topical; aerosol	0.26	%
Potassium hydroxide	Topical; solution	14.02	%
Potassium metabisulfite	Rectal; enema	0.468	%
Potassium phosphate, dibasic	Oral; solution	1.2	%
Potassium phosphate, dibasic	Oral; syrup	2.2	%
Potassium phosphate, monobasic	Oral; syrup	0.2732	%
Potassium phosphate, monobasic	Oral; solution	0.4	%
Potassium phosphate, monobasic	Oral; suspension	1	%
Potassium soap	Topical; solution	32.8	%
Potassium sorbate	Oral; concentrate	0.01	%

Ingredient	Dosage Form	Qty	Unit
Potassium sorbate	Rectal; solution	0.1067	%
Potassium sorbate	Oral; solution	0.15	%
Potassium sorbate	Topical; solution	0.47	%
Potassium sorbate	Oral; suspension	0.65	%
Potassium sorbate	Oral; syrup	0.65	%
Povidone acrylate copolymer	Topical; solution, liquid	6	%
Povidone K25	Oral; solution	50	%
Povidone K29–32	Oral; solution	3.05	%
Povidone K30	Oral; liquid	5	%
Povidone K30	Oral; dispersible tablet	51.2	MG
Povidone K90	Topical; solution	0.25	%
Primary taste modifier 29275	Oral; syrup	0.2	%
Product wat	Topical; aerosol	10.78	%
Promulgen G	Topical; shampoo	4	%
Propyl gallate	Oral; concentrate	0.02	%
Propylene glycol	Oral; drops	0.1252	%
Propylene glycol	Topical; shampoo, suspension	2	%
Propylene glycol	Topical; aerosol	2.11	%
Propylene glycol	Topical; shampoo	3.5	%
Propylene glycol	Oral; suspension, liquid	5	%
Propylene glycol	Rectal; suspension	5	%
Propylene glycol	Topical; solution, liquid	5	%
Propylene glycol	Topical; suspension	5.275	%
Propylene glycol	Topical; emulsion	8	%
Propylene glycol	Oral; solution, syrup	10	%
Propylene glycol	Oral; suspension, sustained action	15	%
Propylene glycol	Rectal; aerosol, metered	18	%
Propylene glycol	Topical; emulsion, aerosol foam	21.05	%
Propylene glycol	Topical; swab	25	ML
Propylene glycol	Rectal; gel	41.44	%
Propylene glycol	Oral; solution, elixir	45	%
Propylene glycol	Oral; solution	55	%
Propylene glycol	Oral; liquid	61	%
Propylene glycol	Topical; solution	61.5	%
Propylene glycol	Oral; concentrate	70	%
Propylene glycol	Oral; suspension	89.02	%
Propylene glycol	Oral; syrup	92	%
Propylene glycol—lecithin	Oral; solution	99.32	%
Propylene glycol ricinoleate	Topical; shampoo, suspension	2	%
Propylene glycol/diazolidinyl urea/methylparaben/propylparben	Topical; aerosol, metered	12.5	%
Propylparaben	Rectal; aerosol, metered	0.009	%
Propylparaben	Topical; emulsion, aerosol foam	0.011	%
Propylparaben	Oral; solution, concentrate	0.02	%

Ingredient	Dosage Form	Qty	Unit
Propylparaben	Oral; solution, syrup	0.02	%
Propylparaben	Oral; liquid	0.02	%
Propylparaben	Topical; shampoo	0.03	%
Propylparaben	Topical; solution	0.033	%
Propylparaben	Rectal; suspension	0.05	%
Propylparaben	Oral; suspension, liquid	0.06	%
Propylparaben	Topical; emulsion	0.06	%
Propylparaben	Oral; suspension, sustained action	0.15	%
Propylparaben	Oral; concentrate	0.25	%
Propylparaben	Oral; solution, elixir	0.3	%
Propylparaben	Rectal; solution	1.5	%
Propylparaben	Oral; solution	10	%
Propylparaben	Oral; suspension	20	%
Propylparaben	Oral; syrup	36	%
Propylparaben sodium	Oral; suspension	0.02	%
Propylparaben sodium	Oral; solution	0.0225	%
Prosweet	Oral; suspension	1	%
Prosweet	Oral; solution	5.275	%
Prosweet 604	Oral; syrup	0.5	%
Prosweet K	Oral; syrup	0.4	%
Rhodigel-23	Oral; suspension	0.0008	%
Rhodigel-23	Oral; suspension, drops	0.16	%
Saccharin	Oral; syrup	0.1	%
Saccharin	Oral; solution	1	%
Saccharin	Oral; suspension	1	%
Saccharin calcium	Oral; syrup	0.05	%
Saccharin calcium	Oral; solution	1.75	%
Saccharin sodium	Rectal; suspension	0.02	%
Saccharin sodium	Oral; suspension, liquid	0.05	%
Saccharin sodium	Oral; liquid	0.06	%
Saccharin sodium	Rectal; solution	0.085	%
Saccharin sodium	Oral; concentrate	0.15	%
Saccharin sodium	Oral; suspension	1.4	%
Saccharin sodium	Oral; solution, elixir	3	%
Saccharin sodium	Oral; solution	5	%
Saccharin sodium	Oral; syrup	5	%
Saccharin sodium, anhydrous	Oral; syrup	0.0793	%
Saccharin sodium, anhydrous	Oral; suspension	0.333	%
Saccharin sodium, anhydrous	Oral; solution	66.7	%
Saccharin sodium, anhydrous	Rectal; solution	66.7	%
SD alcohol 3A	Topical; solution, liquid	1.2	%
SD alcohol 40	Topical; emulsion, aerosol foam	46	%
SD alcohol 40–2	Topical; aerosol	57.65	%

Ingredient	Dosage Form	Qty	Unit
SD alcohol 40B	Topical; solution	26.14	%
SD alcohol 40B	Topical; emulsion, aerosol foam	56.09	%
Silicon dioxide, colloidal	Oral; suspension	1.113	%
Silicon dioxide, colloidal	Oral; suspension, sustained action	2.16	%
Silicon dioxide, colloidal	Oral; dispersible tablet	3.6	MG
Silicone emulsion	Oral; suspension	0.1	%
Simethicone	Topical; suspension	0.1055	%
Simethicone	Oral; suspension	0.2	%
Simethicone	Oral; suspension, liquid	0.2	%
Simethicone emulsion	Oral; suspension, liquid	0.01	%
Simethicone emulsion	Oral; suspension	0.5	%
Sipon I-20	Topical; emulsion	38	%
Sodium acetate	Topical; suspension	0.03	%
Sodium acetate	Oral; solution, syrup	0.11	%
Sodium acetate, anhydrous	Oral; solution	17.7	%
Sodium alginate	Oral; suspension	0.123	%
Sodium alginate	Oral; syrup	0.3	%
Sodium benzoate	Oral; solution, liquid	0.1	%
Sodium benzoate	Rectal; enema	0.1	%
Sodium benzoate	Oral; concentrate	0.2	%
Sodium benzoate	Oral; suspension, liquid	0.2	%
Sodium benzoate	Oral; suspension, drops	0.24	%
Sodium benzoate	Oral; drops	0.3	%
Sodium benzoate	Oral; solution, elixir	0.5	%
Sodium benzoate	Oral; liquid	0.5	%
Sodium benzoate	Oral; solution	1.08	%
Sodium benzoate	Oral; suspension	3.788	%
Sodium benzoate	Oral; syrup	5	%
Sodium bisulfate	Oral; concentrate	0.095	%
Sodium bisulfite	Oral; suspension	0.04	%
Sodium bisulfite	Oral; concentrate	0.0499	%
Sodium bisulfite	Topical; solution	0.055	%
Sodium bisulfite	Oral; solution	0.1	%
Sodium chloride	Oral; solution, elixir	0.1	%
Sodium chloride	Oral; syrup	0.3	%
Sodium chloride	Topical; suspension	0.53	%
Sodium chloride	Topical; solution	0.6	%
Sodium chloride	Oral; suspension, for inhalation	0.85	%
Sodium chloride	Oral; solution	1.9	%
Sodium chloride	Topical; shampoo	2.25	%
Sodium chloride	Oral; suspension	4.112	%
Sodium citrate	Oral; solution, concentrate	0.05	%
Sodium citrate	Oral; suspension, for inhalation	0.05	%

Ingredient	Dosage Form	Qty	Unit
Sodium citrate	Oral; suspension, liquid	0.1	%
Sodium citrate	Topical; solution	0.1	%
Sodium citrate	Topical; solution, drops	0.294	%
Sodium citrate	Oral; solution, elixir	0.45	%
Sodium citrate	Oral; concentrate	0.507	%
Sodium citrate	Oral; solution, liquid	0.7087	%
Sodium citrate	Oral; solution	1.1	%
Sodium citrate	Oral; drops	2	%
Sodium citrate	Oral; suspension, sustained action	2.35	%
Sodium citrate	Topical; shampoo	2.6	%
Sodium citrate	Oral; suspension	8	%
Sodium citrate	Oral; syrup	32.5	%
Sodium citrate hydrous	Oral; solution, elixir	0.03	%
Sodium citrate hydrous	Oral; suspension	0.3176	%
Sodium citrate hydrous	Oral; syrup	1.1048	%
Sodium citrate, anhydrous	Oral; suspension	0.15	%
Sodium citrate, anhydrous	Oral; syrup	0.159	%
Sodium cyclamate	Oral; suspension	0.5	%
Sodium hydroxide	Topical; solution	0.021	%
Sodium hydroxide	Topical; emulsion	0.2	%
Sodium hydroxide	Rectal; enema	0.44	%
Sodium hydroxide	Rectal; solution	0.629	%
Sodium hydroxide	Oral; concentrate	1	%
Sodium hydroxide	Oral; syrup	1.42	%
Sodium hydroxide	Oral; solution	8	%
Sodium hydroxide	Oral; suspension	40	%
Sodium hypochlorite	Oral; suspension	0.3	%
Sodium iodide	Topical; solution, liquid	0.74	%
Sodium lactate	Topical; solution	1.62	%
Sodium lactate	Oral; suspension	2	%
Sodium laureth sulfate	Topical; shampoo	27	%
Sodium laureth-2 sulfate	Topical; shampoo	36	%
Sodium laureth-5 sulfate	Topical; shampoo	38	%
Sodium lauroyl sarcosinate	Topical; suspension	0.75	%
Sodium lauryl sulfate	Oral; suspension	0.15	%
Sodium lauryl sulfate	Oral; dispersible tablet	8.4	MG
Sodium lauryl sulfate	Topical; shampoo, suspension	40	%
Sodium lauryl sulfoacetate	Topical; shampoo	3	%
Sodium metabisulfite	Oral; suspension	0.1	%
Sodium metabisulfite	Oral; syrup	0.1	%
Sodium metabisulfite	Oral; liquid	0.1	%
Sodium metabisulfite	Oral; concentrate	0.2	%
Sodium metabisulfite	Topical; suspension	0.3165	%

Ingredient	Dosage Form	Qty	Unit
Sodium phosphate	Topical; shampoo	0.667	%
Sodium phosphate	Oral; solution	1.25	%
Sodium phosphate, dibasic	Oral; syrup	1.37	%
Sodium phosphate, dibasic	Oral; concentrate	1.7	%
Sodium phosphate, dibasic	Oral; solution	2.06	%
Sodium phosphate, dibasic, anhydrous	Oral; suspension	0.1371	%
Sodium phosphate, dibasic, anhydrous	Oral; syrup	0.35	%
Sodium phosphate, dibasic, anhydrous	Oral; solution	3.82	%
Sodium phosphate, dibasic, heptahydrate	Oral; syrup	0.02	%
Sodium phosphate, dibasic, heptahydrate	Topical; solution	0.035	%
Sodium phosphate, dibasic, heptahydrate	Oral; suspension	0.45	%
Sodium phosphate, dibasic, heptahydrate	Oral; solution	2	%
Sodium phosphate, monobasic	Topical; shampoo, suspension	1	%
Sodium phosphate, monobasic	Oral; solution	1.37	%
Sodium phosphate, monobasic, anhydrous	Oral; syrup	0.07	%
Sodium phosphate, monobasic, anhydrous	Topical; solution	0.17	%
Sodium phosphate, monobasic, anhydrous	Topical; shampoo, suspension	1	%
Sodium phosphate, monobasic, anhydrous	Oral; solution	4	%
Sodium phosphate, monobasic, dihydrate	Oral; suspension	2	%
Sodium phosphate, monobasic, monohydrate	Oral; suspension	0.05	%
Sodium phosphate, monobasic, monohydrate	Topical; solution	0.09	%
Sodium phosphate, monobasic, monohydrate	Oral; solution	0.8	%
Sodium phosphate, monobasic, monohydrate	Oral; syrup	2.06	%
Sodium propionate	Oral; syrup	0.8	%
Sodium sulfite	Oral; concentrate	0.03	%
Sodium thiosulfate	Oral; solution	0.0093	%
Sodium thiosulfate, anhydrous	Oral; solution	0.2	%
Sodium xylenesulfonate	Topical; solution	4.6	%
Solulan	Topical; aerosol, metered	1.5	%
Solulan	Topical; solution	1.5	%
Somay 44	Topical; solution	0.1	%
Sorbic acid	Oral; concentrate	0.01	%
Sorbic acid	Oral; suspension	0.01	%
Sorbic acid	Oral; solution	0.1	%
Sorbic acid	Oral; syrup	0.5	%
Sorbitan monolaurate	Oral; suspension	0.25	%
Sorbitan monolaurate	Topical; emulsion, aerosol foam	4.74	%
Sorbitan monooleate	Oral; solution	15	%
Sorbitan monostearate	Oral; suspension	1.25	%
Sorbitan monostearate	Topical; suspension	2.15	%
Sorbitol	Oral; drops	3	%
Sorbitol	Topical; emulsion	7	%
Sorbitol	Oral; solution, elixir	20	%

Ingredient	Dosage Form	Qty	Unit
Sorbitol	Oral; solution	30	%
Sorbitol	Rectal; suspension	33.3333	%
Sorbitol	Oral; concentrate	40	%
Sorbitol	Oral; syrup	75	%
Sorbitol	Oral; suspension	91.283	%
Sorbitol anhydride	Oral; solution, elixir	60	%
Sorbitol solution	Oral; drops	5	%
Sorbitol solution	Oral; suspension, drops	10	%
Sorbitol solution	Oral; solution, concentrate	30	%
Sorbitol solution	Rectal; suspension	46.1817	%
Sorbitol solution	Oral; concentrate	60	%
Sorbitol solution	Oral; suspension	71.4	%
Sorbitol solution	Oral; syrup	75	%
Sorbitol solution	Oral; solution, elixir	83.33	%
Sorbitol solution	Oral; solution	90	%
Soybean flour	Topical; emulsion	3	%
Soybean oil	Topical; solution	5.82	%
Spearmint extract	Oral; solution	3.5	%
Spearmint oil	Oral; suspension	0.0029	%
Spearmint oil	Oral; solution	0.05	%
Spearmint oil	Oral; syrup	2	%
Squalane	Topical; solution	1	%
Starch	Oral; suspension	0.4	%
Starch, corn	Oral; suspension	7.25	%
Starch, pregelatinized	Oral; drops	1.2	%
Starch, pregelatinized	Oral; suspension, liquid	1.5	%
Starch, pregelatinized	Oral; suspension, sustained action	12.5	%
Steareth-10	Rectal; aerosol, metered	0.225	%
Steareth-10	Topical; aerosol, metered	6.25	%
Stearic acid	Topical; suspension	1.75	%
Stearic acid	Oral; suspension	86.184	%
Stearyl alcohol	Topical; aerosol	0.53	%
Stearyl alcohol	Topical; emulsion, aerosol foam	0.53	%
Stearyl alcohol	Topical; suspension	2.013	%
Strawberry	Oral; syrup	0.05	%
Succinic acid	Oral; concentrate	0.6	%
Sucralose	Oral; solution	0.8	%
Sucralose	Oral; suspension	1.1	%
Sucrose	Oral; drops	30.22	%
Sucrose	Oral; suspension, drops	50	%
Sucrose	Oral; suspension	55.5	%
Sucrose	Oral; solution	60	%
Sucrose	Oral; suspension, sustained action	60	%

Ingredient	Dosage Form	Qty	Unit
Sucrose	Oral; solution, elixir	61.3	%
Sucrose	Oral; concentrate	67	%
Sucrose	Oral; liquid	72	%
Sucrose	Oral; syrup	82.105	%
Sucrose syrup	Oral; suspension	33.4	%
Sucrose syrup	Oral; syrup	85.46	%
Sugar liquid type 0	Oral; syrup	0.375	%
Sugar/starch insert granules	Oral; suspension	45.048	%
Sulfacetamide sodium	Topical; emulsion, aerosol foam	3.013	%
Surfactol QS	Topical; solution	2	%
Tagatose, D-	Oral; solution	1.3333	%
Tagatose, D-	Rectal; solution	1.3333	%
Talc	Oral; solution, elixir	0.09	%
Talc	Oral; mucilage	1.53	MG
Talc	Topical; shampoo	24	%
Tallow glycerides	Topical; aerosol	2.55	%
Tallow glycerides	Topical; emulsion	2.55	%
Tartaric acid	Oral; solution	0.75	%
Tartaric acid, DL-	Oral; syrup	0.2	%
T-butyl hydroperoxide	Topical; solution	0.2	%
Titanium dioxide	Oral; suspension	2.215	%
Titanium dioxide	Topical; shampoo, suspension	3	%
Tocophersolan	Topical; solution, drops	0.5	%
Tocophersolan	Oral; solution	12	%
Tragacanth	Oral; suspension	1.33	%
Tragacanth	Oral; suspension, sustained action	2.25	%
Trichloromonofluoromethane	Oral; aerosol, metered	65	%
Trideceth-10	Topical; aerosol, metered	4	%
Trideceth-10	Topical; solution	4	%
Triglycerides, medium chain	Sublingual; spray, metered	3.6695	%
Triglycerides, medium chain	Oral; solution	94.46	%
Trisodium citrate dihydrate	Oral; suspension	0.1	%
Trisodium citrate dihydrate	Oral; solution	0.15	%
Trisodium hedta	Topical; solution	0.4	%
Triton X-200 sodium salt of alkylauryl polyether sulfonate	Topical; emulsion	40.3	%
Triton X-200 sodium salt of alkylauryl polyether sulfonate	Topical; shampoo	54	%
Trolamine	Topical; aerosol, metered	1	%
Trolamine lauryl sulfate	Topical; emulsion	10.78	%
Trolamine lauryl sulfate	Topical; shampoo	77.8	%
Tromethamine	Topical; solution	8.4	%
Tyloxapol	Topical; suspension	0.05	%
Vanillin	Oral; solution, elixir	0.0003	%

Ingredient	Dosage Form	Qty	Unit
Vanillin	Oral; solution	0.05	%
Vanillin	Oral; suspension	0.1	%
Vitamin E	Oral; solution	0.105	%
Wax, emulsifying	Rectal; aerosol, metered	1.5	%
Wax, emulsifying	Topical; aerosol, metered	20	%
Xanthan gum	Topical; suspension	0.1055	%
Xanthan gum	Oral; suspension, liquid	0.23	%
Xanthan gum	Rectal; enema	0.25	%
Xanthan gum	Oral; drops	0.29	%
Xanthan gum	Oral; suspension	1.2	%
Xanthan gum	Oral; suspension, sustained action	18.68	%
Xylitol	Oral; solution	30	%
Xylitol	Oral; suspension	67.09	%
Zarzarol	Oral; suspension	24.48	%
Zarzarol	Oral; solution	67.4	%
Zinc acetate	Topical; solution	0.0012	%
Zinc acetate	Topical; swab	12000	mg

Part II

Manufacturing Formulations

Manufacturing Formulations

Abacavir Sulfate Oral Solution

Ziagen oral solution is for oral administration. One milliliter of Ziagen oral solution contains abacavir sulfate equivalent to 20 mg of abacavir (20 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methyl paraben and propyl paraben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), and sorbitol solution.

Abacavir Sulfate Oral Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
20.00	1	Abacavir, use abacavir hemisulfate	23.40
344.40	2	Sorbitol 70%	344.40
0.30	3	Sodium saccharin	0.30
2.00	4	Strawberry flavor	2.00
2.00	5	Banana flavor	2.00
QS	6	Sodium citrate dihydrate for pH adjustment	10.00
QS	7	Citric acid anhydrous for pH adjustment	7.00
1.50	8	Methyl paraben	1.50
0.18	9	Propyl paraben	0.18
50.00	10	Propylene glycol	50.00
QS	11	Hydrochloric acid dilute for pH adjustment to 4.0	QS
QS	12	Sodium hydroxide for pH adjustment	QS

Manufacturing Directions

1. The pH range for this solution is from 3.8 to 4.5.
2. Charge 40% of the propylene glycol to an appropriately sized stainless steel and add methyl paraben and propyl paraben with mixing and mix until dissolved.
3. Charge purified water into a stainless steel manufacturing tank equipped with a suitable mixer to approximately 40% of final batch volume.
4. Add sorbitol solution to the manufacturing tank.
5. While mixing, add item 1 and mix until dissolved.
6. While continuing to mix the solution, the paraben/glycol solution, the remaining propylene glycol, artificial strawberry flavor, artificial banana flavor, saccharin sodium, citric acid anhydrous, and sodium citrate dihydrate are added and mixed until dissolved.
7. Turn off the mixer and bring the solution to a volume of 500 L and mix until a homogeneous solution is achieved.
8. Measure and adjust pH to 3.8 to 4.5 with sodium hydroxide or hydrochloric acid.
9. Filter the solution through a clarifying filter into an appropriately sized receiving vessel.

Acetaminophen, Chlorpheniramine, and Pseudoephedrine Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
24.00	1	Acetaminophen (fine powder)	24.00
3.00	2	Pseudoephedrine HCl	3.00
0.44	3	Chlorpheniramine maleate (10% excess)	0.44
14.00	4	Ascorbic acid	14.00
2.40	5	Sodium hydroxide	2.40
1.00	6	Edetate disodium (sodium EDTA)	1.00
0.50	7	Saccharin sodium	0.50
2.00	8	Sodium metabisulfite (sodium disulfite)	2.00
80.00	9	Alcohol (ethanol, 95%)	80.00
100.00	10	Propylene glycol	100.00
100.00	11	Sorbitol (70% solution)	100.00
250.00	12	Glycerin (glycerol)	250.00
300.00	13	Sucrose	300.00
0.04	14	Quinoline yellow	0.04
0.25	15	Pineapple flavor	0.25
QS	16	Purified water	QS to 1 L

Manufacturing Directions

1. Add 200 g of item 16 to the manufacturing vessel and heat to 90°C to 95°C.
2. Add item 13 while mixing at slow speed at a temperature of 90°C to 95°C.
3. Mix for 1 hour at high speed.
4. Add items 10, 11, and 12 to the manufacturing vessel while mixing at high speed. Mix for 10 minutes.
5. Cool the temperature to 50°C while mixing at slow speed.
6. Add 70 g of item 9 to the syrup solution while mixing at slow speed.
7. Load item 1 into the manufacturing vessel while mixing at high speed.
8. Mix for 30 minutes to obtain a clear solution. Check the clarity of the solution.
9. Flush the solution with nitrogen gas for 5 minutes at 1 bar.
10. Add items 2, 4, 6, and 8 to the manufacturing vessel while mixing at slow speed.
11. Dissolve item 3 in 2 g of item 16 (25°C) and check that the solution is complete.
12. Add the solution to the manufacturing vessel while mixing at slow speed.
13. Dissolve item 15 in 10 g of item 9 in a stainless steel container and add to the manufacturing vessel while mixing at slow speed.
14. Dissolve items 5 and 7 in 20 g of item 16 (25°C) and add to the manufacturing vessel while mixing at slow speed.
15. Dissolve item 14 in 2 g of item 16 (25°C).
16. Transfer the color solution to the manufacturing vessel while mixing at slow speed.
17. Rinse the container of color solution with 2 g of item 16 (25°C), then transfer the rinsing to the manufacturing vessel and mix for 5 minutes at high speed.
18. Bring the volume up to 1 L with item 16 and finally mix for 15 to 20 minutes at high speed.
19. Check and record the pH (limit: 5.1–5.2). If required, adjust pH with 10% citric acid or 10% sodium citrate solution.
20. Assemble the filter press with 13.1 T-1000 12 sheets (K 800 14 sheets). Use changeover plate. Wash the filters using purified water (25°C) by passing through filters at 0.2 bar; discard the washings. Filter the syrup at 1.5 bar. Recirculate about 20 to 30 mL syrup.
21. Connect the hose to the manufacturing vessel and transfer the filtered syrup to the storage vessel.

Acetaminophen Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
739.00	1	Propylene glycol	739.00
90.00	2	Acetaminophen	90.00
17.50	3	Saccharin sodium	17.50
8.75	4	Sodium chloride	8.75
0.05	5	FD&C red dye No. 40[a]	0.05
2.50	6	Purified water, USP	2.50
2.00	7	Wild cherry artificial flavor	2.00
65.00	8	Alcohol (ethanol; 190 proof; Nonbeverage), USP	65.00
QS	9	Deionized purified water, USP	QS to 1 L

[a]Check for local regulatory allowance to use red dyes.

Manufacturing Directions

Caution: Ensure that the solution in the tank never exceeds 65°C.

1. Add 739 g of propylene glycol to jacketed mixing tank and start heating with slow mixing.
2. Dissolve dye in 2.5 mL of purified water and add to tank while mixing.
3. Rinse container with small amount of purified water and add to tank.
4. While mixing, add acetaminophen, saccharin sodium, and sodium chloride.
5. Hold at 60°C to 65°C with continued moderate mixing until all are in solution.
6. Force cool to less than 30°C with slow mixing.
7. Blend flavor with alcohol and add to tank with slow mixing.
8. Add purified water with mixing QS to make 1 L.
9. Mix well with moderate agitation until uniform.
10. Filter through an 8-μm millipore membrane (or equivalent).

Acetaminophen Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
250.00	1	Acetaminophen (micronized) (2.0% excess)	51.00
2500.00	2	Sucrose	500.00
5.00	3	Methyl paraben	1.00
1.50	4	Propyl paraben	0.30
0.30	5	Sodium citrate	0.06
35.00	6	Glycerin (glycerol)	7.00
400.00	7	Glycerin (glycerol)	80.00
2000.00	8	Sorbitol (70%)	400.00
10.00	9	Xanthan gum (Keltrol® F)	2.00
0.50	10	Dye	0.10
22.50	11	Flavor	4.50
3.50	12	Strawberry flavor	0.70
–	13	Purified water	QS to 1 L

Manufacturing Directions

Note: Acetaminophen dispersion should be uniformly mixed. If acetaminophen dispersion is either added to hot syrup base or homogenized for a long time, flocculation may appear. While handling the syrup or mucilage or drug dispersion, the handling loss should not be more than 1%. If it exceeds 1%, a poor suspension may result.

1. Add 180 g of purified water to the mixer and heat to 90°C.
2. Dissolve items 3 and 4 while mixing.
3. Add and dissolve item 2 while mixing.
4. Cool down to approximately 50°C to 55°C.
5. Add and dissolve item 5 while mixing.
6. Filter the syrup through T-1500 filters washed with purified water.
7. Collect the syrup in a clean stainless steel tank.
8. Disperse item 9 in item 6 in a separate stainless steel container.
9. Add 40 g of hot purified water (90°C) at once while mixing.
10. Mix for 20 minutes to make a homogeneous smooth mucilage.
11. Mix item 7 in 10 g of purified water (25°C) in a separate stainless steel container.
12. Add item 1 while mixing with stirrer.
13. Mix for 25 minutes to make uniform suspension.
14. Add sugar syrup and mucilage to the mixer.
15. Rinse the container of mucilage with 15 g of purified water and add the rinsings to the mixer.
16. Cool to 25°C while mixing.
17. Add item 1 dispersion to the mixer.
18. Rinse the container of dispersion with 15 g of purified water and add rinsings to the mixer.
19. Check the suspension for uniformity of dispersion.
20. Mix for additional 5 minutes at 18 rpm and a vacuum of 0.5 bar, if required.
21. Add item 8 to the mixer and mix for 10 minutes.
22. Dissolve item 10 in 7 g of purified water and add to the mixer.
23. Disperse item 11 in 7 g of purified water and add to the mixer.
24. Add item 12 to the mixer.
25. Add cold purified water (25°C) to bring the volume up to 1 L.
26. Homogenize for 5 minutes at low speed under a vacuum of 0.5 bar, 18 rpm, and temperature of 25°C.
27. Check the dispersion for uniformity.
28. Check the pH (limit: 5.7 ± 0.5 at 25°C). If required, adjust the pH with a 20% solution of citric acid or sodium citrate.
29. Transfer the suspension through a 630-μm sieve to the stainless steel storage tank, after mixing for 5 minutes at 18 to 20 rpm at room temperature.

Acetaminophen Rectal Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
QS	1	Vehicle (pluronic P105 44.21%, propylene glycol 52.635, water 3.16%)	QS to 1 L
50.00	2	Acetaminophen micronized	50.00

Manufacturing Directions

1. Mill and screen the acetaminophen to further reduce the particle size.
2. Add the acetaminophen into a clean vessel.
3. Add propylene glycol to the vessel.
4. Subsequently add the poloxamer and water to the vessel. Mix until uniform.

Acetaminophen Suspension

Bill of Materials			
Scale (mg/10 mL)	Item	Material Name	Qty/L (g)
500.00	1	Acetaminophen (powder)	50.00
50.00	2	Citric acid (powder)	5.00
50.00	3	Sodium citrate	5.00
500.00	4	Kollidon® CL-M	50.00
10.00	5	Orange flavor	1.00
3000.00	6	Dextrose	300.00
QS	7	Water	589.00

Manufacturing Directions

1. Prepare the solution of dextrose in water and add the other solid ingredients with stirring in the following sequence: citric acid, sodium citrate, orange flavor, Kollidon CL-M, and acetaminophen.
2. A white homogeneous suspension is obtained that is a practically tasteless, stable suspension showing almost no sedimentation over 24 hours and good redispersibility (easily homogenized by shaking 2–3 times).

Acetaminophen Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
569.00	1	Sucrose (granulated sugar), NF	560.000
2.00	2	Sodium citrate (dihydrate powder), USP	2.000
1.00	3	Citric acid (anhydrous powder), USP	1.000
1.00	4	Saccharin sodium (powder), USP	1.000
1.00	5	Sodium chloride (powder), USP	1.000
204.00	6	Propylene glycol, USP	204.000
35.00	7	Acetaminophen, USP	35.000
77.11	8	Alcohol (ethanol; 190 proof), USP	77.112
0.12	9	Cherry flavor (artificial), N59456/A	0.120
0.12	10	FD&C red dye No. 40	0.100
QS	11	Deionized purified water, USP	400.000
—	12	HyFlo filter aid	QS

Manufacturing Directions

1. Add 300 mL of purified water to a jacketed stainless steel mixing tank. Start heating.
2. Add sugar with mixing.
3. Heat to 60°C to 65°C and hold. Mix for complete solution.
4. Add, while mixing, sodium citrate, citric acid, saccharine sodium, and sodium chloride. Mix for complete solution.
5. Add propylene glycol with mixing.
6. Add acetaminophen powder with moderate mixing.
7. Continue mixing at 60°C to 65°C for complete solution.
8. Force cool to 25°C to 30°C with slow mixing.
9. Blend cherry flavor with approximately twice its volume of alcohol and add with mixing.
10. Rinse the container with several portions of alcohol and add. Mix until uniform.
11. Dissolve red dye in approximately 4 g of slightly warmed (50–60°C) purified water and add with mixing.
12. Rinse the container twice with approximately 1.5 g purified water and add. Mix until uniform.
13. Adjust volume to 1 L with purified water. Mix well.
14. Add a small amount of HyFlo filter aid to the mixing tank and continue to mix slowly while filtering.
15. Filter through press until sparkling clear.
16. Use clarifying pad backed by lint-free filter paper.

Acetaminophen Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Acetaminophen (Merck)	50.00
50.00	2	Sorbitol (crystalline)	50.00
40.00	3	Cyclamate sodium	40.00
1.00	4	Strawberry flavor	1.00
200.00	5	Kollidon® 25	200.00
150.00	6	Glycerol	150.00
200.00	7	1,2-Propylene glycol	200.00
310.00	8	Water	310.00

Manufacturing Directions

1. First dissolve Kollidon 25 and then the other solid components in the solvent mixture of glycerol, propylene glycol, and water.
2. The clear solution has a slightly bitter taste.
3. The solution remains clear for more than 1 week at 6°C and for more than 3 months at 25°C and 40°C.
4. The color of the solution changes only a little during 3 months at 25°C and 40°C.
5. To prevent discoloration during storage, 0.2% to 0.5% of cysteine could be added as antioxidant.

Acetaminophen Syrup for Children

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
25.00	1	Acetaminophen (crystalline)	25.00
300.00	2	Kollidon® 25 or Kollidon® 30	300.00
60.00	3	Glycerol	600.00
40.00	4	Sodium cyclamate	40.00
QS	5	Orange flavor	<01.0
QS	6	Raspberry flavor	2.00
QS	7	Water	575.00

Manufacturing Directions

1. Dissolve Kollidon in water, add acetaminophen and cyclamate, heat to 50°C, and stir to obtain a clear solution.
2. Dissolve the flavors and mix with glycerol.
3. The obtained syrup is a viscous, clear, sweet, and only slightly bitter liquid.

Acetaminophen Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.0	1	Acetaminophen (Merck)	50.0
50.0	2	Sorbitol, crystalline	50.0
40.0	3	Cyclamate sodium	40.0
1.0	4	Strawberry flavor	1.0
200.0	5	Kollidon 25	200.0
150.0	6	Glycerol	150.0
200.0	7	1,2-Propylene glycol	200.0
310.0	8	Water	310.0

Manufacturing Directions

1. Dissolve first Kollidon 25 and then the other solid components in the solvent mixture of glycerol, propylene glycol, and water.
2. The result is a clear solution of certain viscosity having only a slightly bitter taste. To prevent discoloration during storage, 0.2% to 0.5% cysteine could be added as an antioxidant.

Acetaminophen Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
569.00	1	Sucrose (sugar granulated)	560.000
2.00	2	Sodium citrate dihydrate powder	2.000
1.00	3	Acid citric anhydrous powder	1.000
1.00	4	Saccharin sodium powder	1.000
1.00	5	Sodium chloride powder	1.000
204.00	6	Propylene glycol	204.000
35.00	7	Acetaminophen	35.000
77.11	8	Alcohol (ethanol) 190 proof	77.112
0.12	9	Flavor cherry artifical N59456/A	0.1200
0.12	10	Dye red FD&C N40	0.1000
QS	11	Water purified	400.000
QS	12	Filter aid HyFlo	QS

Manufacturing Directions

1. Add 300 mL purified water to a jacketed stainless steel mixing tank. Start heating.
2. Add sugar with mixing.
3. Heat to 60°C to 65°C and hold. Mix for complete solution.
4. Add, while mixing, sodium citrate, citric acid, sodium saccharine, and sodium chloride. Mix for complete solution. Add propylene glycol by mixing.
5. Add acetaminophen powder with moderate mixing. Continue mixing at 60°C to 65°C for complete solution. Force cool to 25°C to 30°C with slow mixing.
6. Blend cherry flavor with approximately twice its volume of alcohol and add with mixing. Rinse the container with several portions of alcohol and add. Mix until uniform.
7. Dissolve red dye in approximately 4 g of slightly warmed (50–60°C) purified water and add by mixing. Rinse the container twice with approximately 1.5 g purified water and add to step 6.
8. Mix until uniform. Adjust volume to 1 L with purified water. Mix well.
9. Add a small amount of HyFlo filter aid to the mixing tank and continue to mix slowly while filtering.
10. Filter through press until sparkling clear. Use clarifying pad backed by lint-free filter paper.

Acne Scrub

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Magnesium aluminum silicate magnabrite HV	20.00
582.00	2	Water	582.00
100.00	3	Propylene glycol	100.00
150.00	4	Mineral oil and acetylated lanolin alcohol	150.00
30.00	5	Glyceryl stearate and PEG-100 stearate	30.00
14.00	6	Myristyl propionate	14.00
100.00	7	PEG-600	100.00
4.00	8	Eucalyptus oil	4.00
QS	9	Preservatives	QS

Manufacturing Directions

1. Slowly sift item 1 into water, mixing until smooth.
2. Heat to 75°C.
3. Heat items 3 to 6 separately; mix and heat to 70°C.
4. Add this portion to item 1 dispersion and mix well until smooth.
5. Add item 7 to mixture and mix.
6. Finally, add items 8 and 9 and mix until cool.
7. If using parabens, prepare a solution in a portion of water and add before adding item 8 and after allowing parabens to cool to 50°C.

Acyclovir Oral Suspension (2% = 200 mg/10 mL)

Formulation

Acyclovir, 2 g; Kollidon CL-M [1], 6 g; Kollidon 30 [1], 3 g; sorbitol [10], 28 g; citric acid, 0.5 g; preservative, QS; water, 60.5 g.

Manufacturing Directions

Suspend acyclovir and Kollidon CL-M in the solution of the other components under vigorous stirring.

Acyclovir Oral Suspension

Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
215.00	1	Acyclovir	43.00
5.00	2	Methyl paraben	1.00
1.00	3	Propyl paraben	0.20
75.00	4	Microcrystalline cellulose (Avicel RC-591)	15.00
750.00	5	Glycerin (glycerol)	150.00
2250.00	6	Sorbitol (70% solution)	450.00
20.00	7	Orange, banana dry flavor	4.00
–	8	Water purified	QS to 1 L

Manufacturing Directions

1. Disperse item 1 in item 6. Keep stirring for 1 hour.
2. Heat 333.33 g of item 8 in mixer to 90°C to 95°C. Dissolve items 2 and 3 while mixing. Cool to 30°C.
3. Disperse items 4 and 5 in a stainless steel container and keep stirring for 1 hour.
4. Add step 3 into step 2 at 30°C. Mix and homogenize for 5 minutes at high speed under vacuum 0.5 bar.
5. Add step 1 in to step 2 and mix for 5 minutes.
6. Disperse item 7 in 13.33 g of item 8. Add into step 2.
7. Make up the volume with item 8. Finally homogenize for 5 minutes at high speed under vacuum 0.5 bar.

Acyclovir Oral Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
20.00	1	Acyclovir	20.00
60.00	2	Kollidon CL-M	60.00
30.00	3	Kollidon 30	30.00
28.00	4	Sorbitol	28.00
0.50	5	Citric acid	0.50
QS	6	Preservative	QS
QS	7	Water purified	QS to 1 L

Manufacturing Directions

1. Suspend item 1 and item 2 in the solution of items 3 through 7.
2. Mix vigorously to suspend.
3. Fill.

Adapalene Solution

Differin® solution, containing adapalene, is used for the topical treatment of acne vulgaris. Each milliliter of Differin solution contains adapalene 0.1% (1 mg) in a vehicle consisting of polyethylene glycol 400 and SD alcohol 40-B, 30% (w/v).

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1.00	1	Adapalene	1.00
700.00	2	Polyethylene glycol 400	700.00
QS	3	Alcohol	QS to 1 L

Manufacturing Directions

1. Add and dissolve item 1 and mix.
2. Charge items 1 and 2 in a suitable mixing vessel. Stir.

Albendazole Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
100.000	1	Albendazole	20.00
7.500	2	Saccharin sodium	1.50
7.500	3	Potassium sorbate	1.50
550.000	4	Propylene glycol	110.00
15.000	5	Xanthan gum	3.00
2.500	6	Passion fruit flavor 502010A	0.50
7.500	7	Polysorbate 80 (Tween 80)	1.50
2.000	8	Citric acid	0.40
2.500	9	Vanilla dry flavor	0.50
2.500	10	Blood orange dry flavor	0.50
QS to 5 mL	11	Water purified	QS to 1 L

Manufacturing Directions

This product dispersion should be uniformly mixed and levigated. Xanthan gum dispersion should be uniform and smooth.

1. Disperse items 1 and 6 in 100 g of item 4 in a stainless steel container, using stirrer.
2. Dissolve item 7 in 100 g of item 11 (50–60°C) in a stainless steel container while stirring with the stirrer. Cool to 25°C to 30°C. Add in to step 1 while mixing.
3. Levigate to make smooth slurry and keep aside for 2 hours.
4. Make slurry of item 5 in 10 g of item 4 in a stainless steel container while stirring with the stirrer. Add 200 g of item 11 (25–30°C) while stirring and continue stirring for 30 minutes.
5. Dissolve item 8 in 10 g of item 11 (25–30°C) in a stainless steel container using a spatula.
6. Add 500 g of item 11 (25–30°C) into mixer. Dissolve items 2 and 3 while mixing.
7. Add the content from steps 1, 2, and 3 into step 4. Mix and homogenize at 25°C to 30°C, mixer speed 18 rpm, homogenizer high speed, and vacuum 0.4 to 0.6 bar for 10 minutes.
8. Add items 9 and 10 in step 4.
9. Mix and homogenize at 25°C to 30°C, mixer speed 18 rpm, homogenizer at high speed, and vacuum 0.4 to 0.6 bar for 15 minutes.
10. Make up the volume with item 11. Mix for 20 minutes.
11. Check the suspension for homogeneity. Transfer the suspension through a 630-micron sieve to stainless steel storage tank. It is important that you do not store the bulk suspension more than 48 hours in the storage tank without stirring. Before sending for filling in packaging, stir no fewer than 30 minutes for uniform dispersion to avoid the problem of content uniformity.

Albendazole Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
200.00	1	Albendazole	40.00
1.25	2	Simethicone	0.24
5.00	3	Tween 80	1.00
15.00	4	Xanthan gum	3.00
1950.00	5	Sucrose	390.00
650.00	6	Sorbitol	130.00
20.00	7	Sodium benzoate	4.00
20.00	8	Potassium sorbate	4.00
3.00	9	Citric acid	0.60
QS	10	Flavor	QS
QS	11	Water purified	QS to 1 L

Manufacturing Directions

1. Charge in a tank 20% of item 11 and heat to 90°C.
2. Add and dissolve item 7; reduce temperature to 40°C and add item 3.
3. In a separate vessel, add and dissolve item 9 in a portion of item 11.
4. Add step 3 to step 2.
5. In a separate vessel, disperse item 4 in 40% of item 11 at 65°C and allow to hydrate to make it into a paste. Cool to room temperature.
6. Add to step 3 through a stainless steel filter.
7. In a separate vessel, add and make a paste of items 1 (passed through No. 100 mesh), 3, and 6. Add to step above.
8. Add item 2. Stir well.
9. Add flavor and item 11 to make up the volume.

Albuterol Inhalation Solution

Each milliliter of Proventil inhalation solution 0.083% contains 0.83 mg albuterol (as 1 mg albuterol sulfate) in an isotonic aqueous solution containing sodium chloride and benzalkonium chloride; sulfuric acid is used to adjust the pH between 3 and 5. The 0.083% solution requires no dilution before administration by nebulization. Proventil inhalation solution 0.083% contains no sulfiting agents. It is supplied in 3-mL high-density polyethylene (HDPE) bottles for unit-dose dispensing. AccuNeb (albuterol sulfate) inhalation solution is supplied in two strengths in unit-dose vials. Each unit-dose vial contains either 0.75 mg of albuterol sulfate (equivalent to 0.63 mg of albuterol) or 1.50 mg of albuterol sulfate (equivalent to 1.25 mg of albuterol) with sodium chloride and sulfuric acid in a 3-mL isotonic, sterile aqueous solution. Sodium chloride is added to adjust isotonicity of the solution and sulfuric acid is added to adjust the pH of the solution to 3.5.

Albuterol Inhalation Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1.25	1	(R)-Albuterol, use albuterol sulfate	1.50
27.00	2	Sodium chloride	27.00
QS	3	Sulfuric acid	QS
QS	4	Water purified	QS to 1 L

Manufacturing Directions

1. Charge all items in a suitable stainless steel vessel and mix. Keep nitrogen flushing throughout and also into item 4 before adding other ingredients.
2. Check and adjust pH, using sulfuric acid, to 3.5.
3. Fill.

Alginic Acid + Aluminium Hydroxide + Magnesium Silicate Tablets (500 mg + 100 mg + 25 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Alginic acid	500.00
100.00	2	Aluminum hydroxide dried gel (Giulini)	100.00
25.00	3	Magnesium trisilicate	25.00
170.00	4	Sodium bicarbonate	170.00
160.00	5	Sorbitol crystalline	160.00
627.00	6	Sucrose crystalline	627.00
900.00	7	Ludipress	900.00
70.00	8	Kollidon VA 64	70.00
50.00	9	Magnesium stearate	50.00
5.00	10	Vanillin	5.00

1. Manufacturing Directions

Pass all components through a 0.8-mm sieve. Mix and press with high compression force.

Alpha-Bisabolol Aqueous Mouthwash Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
2.00.00	1	Alpha-bisabolol, natural (BASF)	2.00
QS	2	Flavor	QS
25.00	3	Cremophor RH 40	25.00
50.00	4	Glycerol	50.00
1.00	5	Saccharin sodium	1.00
QS	6	Preservative	QS
922.00	7	Water	922.00

2. Manufacturing Directions

1. Heat mixture of items 1 to 3 to approximately 60°C and slowly add the warm solution of items 4 to 7 (60°C).
2. The clear, colorless liquid has a low viscosity.

Alpha-Bisabolol Buccal or Topical Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1.20	1	Alpha-bisabolol (racemic) (BASF)	1.20
10.00	2	Cremophor RH 40	10.00
0.10	3	Butylhydroxytoluene (BHT)	0.10
QS	4	Preservative	QS
990.00	5	Water	990.00

3. Manufacturing Directions

Heat mixture of items 1 to 3 to approximately 60°C, stir well, and slowly add the warm solution of items 4 in 5 to obtain a clear solution.

Alpha-Bisabolol Ethanolic Mouthwash Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Alpha-bisabolol, racemic (BASF)	10.00
100.00	2	Flavor	100.00
60.00	3	Cremophor RH 40	60.00
10.00	4	Glycerol	10.00
2.00	5	Saccharin sodium	2.00
818.00	6	Ethanol, 96%	818.00

4. Manufacturing Directions

1. Heat mixture of items 1 to 3 to approximately 60°C and slowly add the warm solution of items 4 to 6.
2. The clear, colorless liquid can be diluted with water.

Alpha-Bisabolol Mouthwash Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
5.00	1	(–)Alpha-Bisabolol, natural (BASF)	5.00
50.00	2	Lutrol F 127 [1]	50.00
QS	3	Flavor	QS
100.00	4	Propylene glycol (pharma)	100.00
300.00	5	Ethanol 96%	300.00
545.00	6	Water	545.00

5. Manufacturing Directions

1. Prepare solution of items 1 through 5 and slowly add the water.
2. The clear, colorless solution should have a pH of 8. Do not adjust.

Aluminium Hydroxide + Magnesium Silicate Chewable Tablets (120 mg + 250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
120.00	1	Aluminum hydroxide dried gel (Giulini)	120.00
250.00	2	Magnesium trisilicate	250.00
232.00	3	Ludipress	232.00
6.00	4	Aerosil 200	6.00
6.00	5	Magnesium stearate	6.00
12.00	6	Cyclamate sodium	12.00
1.50	7	Menthol	1.50

6. Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press with a compression force of 20 kN at 640 mg.

Aluminum Chloride Solution

Aluminum chloride (hexahydrate) 6.25% (w/v) in anhydrous ethyl alcohol (SD alcohol 40) 96% (v/v).

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
62.50	1	Aluminum chloride hexahydrate	62.50
QS	2	Alcohol anhydrous	QS to 1 L

Manufacturing Directions

1. Charge items 1 and 2 in a suitable stainless steel container and mix.
2. Fill.

Aluminum Hydroxide and Magnesium Carbonate Dry Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
200.00	1	Aluminum hydroxide dry gel (Giulini)	200.00
200.00	2	Basic magnesium carbonate	200.00
240.00	3	Kollidon® CL-M	240.00
211.50	4	Sorbitol (crystalline)	211.50
41.30	5	Orange flavor	41.30
82.60	6	Kollidon® 30	82.60
3.30	7	Coconut flavor	3.30
4.13	8	Banana flavor	4.13
4.13	9	Saccharin sodium	4.13
8.26	10	Water	8.26

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with solution of items 6 to 10, pass through a sieve, and dry.
2. Shake 58 g of the granules with 100 mL of water.
3. Product remains homogeneous and without sedimentation for more than 24 hours.

Aluminum Hydroxide and Magnesium Carbonate Dry Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
200.00	1	Aluminum hydroxide dry gel (Giulini)	200.00
200.00	2	Basic magnesium carbonate	200.00
240.00	3	Kollidon CL-M	240.00
211.50	4	Sorbitol, crystalline	211.50
41.30	5	Orange flavor	41.3
82.60	6	Kollidon 30	82.6
3.30	7	Coconut flavor	3.30
4.13	8	Banana flavor	4.13
4.13	9	Saccharin sodium	4.13
8.26	10	Water	8.26

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with solution of items 6 to 10.
2. Pass through a sieve and dry.
3. Shake 58 g of the granules with 100 mL of water. Homogenize.

Aluminum Hydroxide and Magnesium Hydroxide Antacid Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
5.00	1	Purified bentonite (Veegum® HS)	5.00
2.00	2	Xanthan gum (Rhodigel)	2.00
401.00	3	Water	401.00
200.00	4	Sorbitol (70%)	200.00
360.00	5	Aluminum hydroxide gel	360.00
320.00	6	Magnesium hydroxide, USP	320.00
QS	7	Preservative, flavor	QS

Manufacturing Directions

1. Slowly add a dry blend of item 1 and 2 to item 3, agitating with maximum available shear until a smooth and uniform mix is obtained.
2. Mix items 4 to 6 together in another vessel until uniform and then add to previous mix.
3. Agitate until uniform.
4. Add item 7 and mix until uniform.

Aluminum Hydroxide and Magnesium Hydroxide Antacid Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
200.00	1	Magnesium aluminum silicate (Magnabrite S) (5% suspension)	200.00
2.00	2	Methyl paraben	2.00
1.00	3	Propyl paraben	1.00
0.50	4	Saccharin sodium	0.50
500.00	5	Aluminum hydroxide/Magnesium hydroxide fluid gel	500.00
3.00	6	Polysorbate 80	3.00
2.00	7	Flavor	2.00
291.50	8	Deionized water	291.50

Manufacturing Directions

1. Add the parabens and saccharin to item 1 with stirring until dissolved (may heat to 80°C to dissolve).
2. Add item 5 with mixing.
3. Finally, add item 6 and 7. Mix well.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
405.000	1	Aluminum hydroxide gel	290.0000
100.000	2	Magnesium hydroxide paste 30%	67.0000
0.210	3	Ammonia solution 25%	0.0420
0.053	4	Ammonia solution 25%	0.0106
10.000	5	Methyl paraben	2.0000
0.250	6	Menthol	0.0500
3.000	7	Propyl paraben	0.6000
1.000	8	Peppermint oil	0.2000
50.000	9	Propylene glycol	10.0000
1.250	10	Saccharin sodium	0.2500
150.00	11	Sorbitol (70% solution)	30.0000
4.500	12	Sodium hypochlorite 5%	0.9000
1.250	13	Sodium hypochlorite 5%	0.2500
15.000	14	Magnesium aluminum silicate (Veegum HV)	3.0000
–	15	Water purified	QS to 1 L

Note. Quantity of the sodium hypochlorite solution to be adjusted according to the assay.

Manufacturing Directions

1. Disperse item 14 in 60 g of hot item 15 (70–80°C) in stainless steel vessel, using stirrer.
2. Continue stirring for 30 minutes.
3. Transfer the dispersion into mixer (e.g., Krieger) vessel by vacuum and mix for 30 minutes at mixer speed 16/32.
4. Cool down to 30°C. Add 200 g of hot item 15 (70–80°C) into the mixer.
5. Mix and homogenize at rpm 1420 mixer speed 16/32, vacuum 0.5 bar for 30 minutes.
6. Cool down to 30°C.
7. Add 1 kg of item 15 (70°C) to a suitable vessel and heat to 85°C to 90°C for 1 hour.
8. Cool to 20°C to 25°C.
9. Mix items 4 and 13 and immediately add to item 15 (20–25°C) in the storage vessel.
10. Mix for 2 minutes. Store in a previously cleaned storage vessel.
11. Load item 2 and 100 g of item 15 (25–30°C) in a stainless steel mixing vessel with lid and stirrer.
12. Mix for 5 minutes at medium speed.
13. Transfer by vacuum into mixer. Load 80 g of item 1 and 80 g of item 15 (25–30°C) from step above in a stainless steel mixing vessel with lid and stirrer.
14. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer.
15. Load 80 g of item 1 and 80 g of item 15 (25–30°C) from step above in a stainless steel mixing vessel with lid and stirrer. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer.
16. Load 80 g of item 1 and 80 g of item 15 (25–30°C) from step above in a stainless steel mixing vessel with lid and stirrer.
17. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer. Load 50 g of item 1 and 50 g of item 15 (25–30°C) from step above in a stainless steel mixing vessel with lid and stirrer.
18. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer. Transfer item 11 into mixer by vacuum.
19. Dissolve item 10 in 2 g of item 15 (25–30°C) and transfer into mixer. Mix and homogenize for 30 minutes at 1420 rpm under vacuum 0.5 bar.
20. Dissolve items 5 and 7 in item 9 (50–60°C) by stirring in stainless steel container in a water bath.
21. Dissolve items 8 and 6 and add it to parabens–glycol solution.
22. Mix well; add to mixer. Mix and homogenize for 10 minutes under vacuum 0.5 bars.
23. Mix items 3, 12, and 2 g of item 15 and immediately add to the mixer. Mix for 10 minutes without vacuum.
24. Add cold item 15 to make up the volume up to 1 L. Mix for 15 minutes.
25. Transfer the suspension through 630-micron sieve to the stainless steel storage tank. Final pH 7.5 to 8.0, density 1.04 to 1.06.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
200.00	1	Aluminum hydroxide gel	214.00
80.00	2	Magnesium hydroxide paste 30%	54.20
150.00	3	Sorbitol (70% solution)	30.00
10.00	4	Methyl paraben	2.00
1.00	5	Propyl paraben	0.20
2.00	6	Saccharin sodium	0.40
15.00	7	Magnesium aluminum silicate (Veegum HV)	3.00
0.20	8	Ammonia solution 25%	0.04
4.50	9	Sodium hypochlorite 5%	0.90
100.00	10	Propylene glycol	20.00
0.75	11	Lemon-mint flavor	0.15
—	12	Water purified	QS to 1 L

Manufacturing Directions

See previous entry for manufacturing directions for Aluminum Hydroxide and Magnesium Hydroxide Suspension.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
5.00	1	Purified bentonite (Veegum HS)	5.00
2.00	2	Xanthan gum (Rhodigel)	2.00
401.00	3	Water	401.00
200.00	4	Sorbitol 70%	200.00
360.00	5	Aluminum hydroxide gel	360.00
320.00	6	Magnesium hydroxide	320.00
QS	7	Preservative, flavor	QS

Manufacturing Directions

1. Add a dry blend of items 1 and 2 to item 3 slowly, agitating with maximum available shear until a smooth and uniform mix is obtained.
2. Mix together items 4 to 6 in another vessel until uniform and then add to the above mix and agitate until uniform.
3. Add item 7 and mix until uniform.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
40.0	1	Aluminum hydroxide	40.0
40.0	2	Magnesium hydroxide	40.0
50.0 g	3	Cremophor RH 40	50.0
1.0	4	Silicon oil DC 200 (Serva)	1.0
100.0	5	Kollidon CL-M	100.0
QS	6	Water	76.9

Manufacturing Directions

1. Mix Cremophor RH 40 well with the silicon oil.
2. Add the water and suspend the solid substances.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
200.0	1	Magnesium aluminum silicate (Magnabrite S) 5% suspension	200.0
2.0	2	Methyl paraben	2.0
1.0	3	Propyl paraben	1.0
0.5	4	Saccharin sodium	0.5
500.0	5	Aluminum hydroxide–magnesium hydroxide fluid gel	500.0
3.0	6	Polysorbate 80	3.0
2.0	7	Flavor	2.0
291.5	8	Water purified	291.5

Manufacturing Directions

1. Add the parabens and saccharin to item 1 with stirring until dissolved (may heat to 80°C to dissolve).
2. Add item 5 with mixing. Finally, add items 6 and 7.
3. Mix well.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
405.00	1	Aluminum hydroxide gel	290.00
100.00	2	Magnesium hydroxide paste (30%)	67.00
0.21	3	Ammonia solution (25%)	0.04
0.05	4	Ammonia solution (25%)	0.01
10.00	5	Methyl paraben	2.00
0.25	6	Menthol	0.05
3.00	7	Propyl paraben	0.60
1.00	8	Peppermint oil	0.20
50.00	9	Propylene glycol	10.00
1.25	10	Saccharin sodium	0.25
150.00	11	Sorbitol (70% solution)	30.00
4.50	12	Sodium hypochlorite (5%)	0.90
1.25	13	Sodium hypochlorite (5%)	0.25
15.00	14	Magnesium aluminum silicate (Veegum® HV)	3.00
QS	15	Purified water	QS to 1 L

Note: The quantity of the sodium hypochlorite solution should be adjusted according to the assay.

Manufacturing Directions

1. Disperse item 14 in 60 g of hot purified water (70–80°C) in stainless steel vessel using a stirrer. Continue stirring for 30 minutes.
2. Transfer the dispersion into mixer (e.g., Krieger) vessel by vacuum and mix for 30 minutes at 16/32 mixer speed.
3. Cool down to 30°C.
4. Add 200 g of hot purified water (70–80°C) to the mixer.
5. Mix and homogenize at 1420 rpm, mixer speed of 16/32, and vacuum of 0.5 bar for 30 minutes.
6. Cool down to 30°C.
7. Add 1 kg of purified water (70°C) to a suitable vessel and heat to 85°C to 90°C for 1 hour.
8. Cool to 20°C to 25°C.
9. Mix items 13 and 4 and immediately add to purified water (20–25°C) in the storage vessel.
10. Mix for 2 minutes. Store in a previously cleaned storage vessel.
11. Load item 2 and 100 g of purified water (25–30°C) in a stainless steel mixing vessel with lid and stirrer.
12. Mix for 5 minutes at medium speed.
13. Transfer by vacuum into mixer.
14. Load 80 g of item 1 and 80 g of purified water (25–30°C) from step above in a stainless steel mixing vessel with lid and stirrer. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer.
15. Load 50 g of item 1 and 50 g of purified water (25–30°C) from step above in a stainless steel mixing vessel with lid and stirrer.
16. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer.
17. Transfer item 11 into mixer by vacuum.
18. Dissolve item 10 in 2 g of purified water (25–30°C) and transfer to mixer.
19. Mix and homogenize for 30 minutes at 1420 rpm under vacuum of 0.5 bar.
20. Dissolve items 5 and 7 in item 9 (50–60°C) by stirring in stainless steel container in a water bath.
21. Dissolve items 8 and 6 and add to parabens/glycol solution. Mix well and add to mixer.
22. Mix and homogenize for 10 minutes under vacuum of 0.5 bars.
23. Mix items 12 and 3 and 2 g of purified water and immediately add to the mixer.
24. Mix for 10 minutes without vacuum.
25. Add cold purified water to bring the volume up to 1 L. Mix for 15 minutes.
26. Transfer the suspension through 630-μm sieve to the stainless steel storage tank. Final pH is 7.5 to 8.0 and density is 1.04 to 1.06.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/5mL)	Item	Material Name	Qty/L (g)
200.00	1	Aluminum hydroxide gel	214.00
80.00	2	Magnesium hydroxide paste (30%)	54.20
150.00	3	Sorbitol (70% solution)	30.00
10.00	4	Methyl paraben	2.00
1.00	5	Propyl paraben	0.20
2.00	6	Saccharin sodium	0.40
15.00	7	Magnesium aluminum silicate (Veegum® HV)	3.00
0.20	8	Ammonia solution (25%)	0.04
4.50	9	Sodium hypochlorite (5%)	0.90
100.00	10	Propylene glycol	20.00
0.75	11	Lemon-mint flavor	0.15
QS	12	Purified water	QS to 1 L

Manufacturing Directions

See previous entry for manufacturing directions for Aluminum Hydroxide and Magnesium Hydroxide Suspension.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
40.00	1	Aluminum hydroxide	40.00
40.00	2	Magnesium hydroxide	40.00
50.00 g	3	Cremophor RH 40	50.00
1.00	4	Silicon oil DC 200 (Serva)	1.00
100.00	5	Kollidon® CL-M	100.00
QS	6	Water	76.90

Manufacturing Directions

Mix Cremophor RH 40 well with the silicon oil, add the water, and suspend the solid substances.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension

Bill of Materials			
Scale (g/5 mL)	Item	Material Name	Qty/L (g)
215.00	1	Aluminum hydroxide gel	217.00
80.00	2	Magnesium hydroxide paste (30%)	56.00
25.00	3	Simethicone emulsion (simethicone antifoam M30)	18.50
150.00	4	Sorbitol (70% solution)	30.00
0.20	5	Ammonia solution 25%	0.04
10.00	6	Methyl paraben	2.00
1.00	7	Propyl paraben	0.20
28.00	8	Methylcellulose 4000 (Methocel A4M)	5.60
2.00	9	Saccharin sodium	0.40
4.50	10	Sodium hypochlorite (5%)	0.90
1.00	11	Lemon-mint flavor	0.20
QS	12	Purified water	QS to 1 L

Manufacturing Directions

See manufacturing directions for Aluminum Hydroxide and Magnesium Hydroxide Suspension.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
27.00	1	Simethicone 30%	27.00
30.00	2	Cremophor RH 40	30.00
70.00	3	Water	70.00
80.00	4	Aluminum hydroxide dry gel (Giulini)	80.00
80.00	5	Magnesium hydroxide	80.00
90.00	6	Kollidon® CL-M	90.00
100.00	7	Sorbitol (crystalline)	100.00
4.00	8	Banana flavor	4.00
5.00	9	Coconut flavor	5.00
1.00	10	Saccharin sodium	1.00
QS	11	Water	QS to 1 L
QS	12	Citric acid (to adjust pH)	QS

Manufacturing Directions

1. Mix Cremophor RH 40 with simethicone and heat to about 50°C, stirring well.
2. Add warm water.
3. Dissolve the flavors and saccharin in water and suspend aluminum hydroxide, magnesium hydroxide, and Kollidon CL-M.
4. Add emulsion of items 1 to 3 to the stirred suspension of items 4 to 11 and adjust the pH to about 9 with item 12, if needed.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
215.00	1	Aluminum hydroxide gel	217.00
80.00	2	Magnesium hydroxide paste 30%	56.00
25.00	3	Simethicone emulsion (simethicone antifoam M30)	18.50
150.00	4	Sorbitol (70% solution)	30.00
0.20	5	Ammonia solution 25%	0.04
10.00	6	Methyl paraben	2.00
1.00	7	Propyl paraben	0.20
28.00	8	Methylcellulose 4000 (Methocel A4M)	5.60
2.00	9	Saccharin sodium	0.40
4.50	10	Sodium hypochlorite 5%	0.90
1.00	11	Lemon-mint flavor	0.20
—	12	Water purified	QS to 1 L

Manufacturing Directions

See previous entry for manufacturing directions for Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
27.00	1	Simethicone 30%	27.00
30.00	2	Cremophor RH 40	30.00
70.00	3	Water	70.00
80.00	4	Aluminum hydroxide dry gel (Giulini)	80.00
80.00	5	Magnesium hydroxide	80.00
90.00	6	Kollidon CL-M	90.00
100.00	7	Sorbitol, crystalline	100.00
4.00	8	Banana flavor	4.00
5.00	9	Coconut flavor	5.00
1.00	10	Saccharin sodium	1.00
QS	11	Water	QS to 1 L
QS	12	Citric acid to adjust pH to 9	QS

Manufacturing Directions

1. Mix Cremophor RH 40 with simethicone, heat to about 50°C, stirring well.
2. Add the warm water.
3. Dissolve the flavors and saccharin in water and suspend aluminum hydroxide, magnesium hydroxide and Kollidon CL-M.
4. Add emulsion of items 1 to 3 to the stirred suspension of items 4 to 11 and adjust pH to about 9 with item 12 if needed.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Aluminum hydroxide gel (dried)	260.00
200.00	2	Magnesium hydroxide powder	200.00
200.00	3	Mannitol	200.00
45.00	4	Sorbitol powder	45.00
65.00	5	Dextrose (glucose) monohydrate	65.00
16.50	6	Povidone (PVP K-30)	16.50
2.50	7	Saccharin sodium	2.50
1.00	8	FD&C yellow dye No.10 lake	1.00
2.50	9	Mint flavor (dry)	2.50
1.50	10	Lemon flavor (dry)	1.50
25.00	11	Simethicone GS granules	84.00
315.00	12	Dextrates (Emdex®)	315.00
1.00	13	Colloidal silicon dioxide (Aerosil® 200)	1.00
6.00	14	Magnesium stearate	6.00
–	15	Purified water	160.00

Manufacturing Directions

1. Processing should be done at relative humidity of 50% ± 5% and temperature of 26°C ± 1°C.
2. Dissolve items 4, 5, and 7 in cold purified water (25–30°C) by using stirrer, then add item 6 while mixing.
3. Add item 8 and disperse the color completely.
4. Check final weight; if required, adjust with purified water.
5. Load items 1, 2, and 3 into mixer and mix for 5 minutes using mixer and chopper at high speed.
6. Add binding solution at a rate of 16 to 20 g/min to the dry powders in mixer while mixing at low speed. Mix for 2 to 3 minutes. Scrape the sides, blade, and lid of the mixer.
7. Mix and chop at low speed for an additional 2 to 3 minutes or until the granules stop flying around the chopper. Add extra purified water if required and continue mixing until a satisfactory mass is obtained. Record extra quantity of purified water added.
8. Unload the wet mass into clean Aeromatic bowl for drying.
9. Avoid big lump formation as this leads to nonuniform drying.
10. Dry the wet mass in an Aeromatic fluid bed dryer at 60°C for 90 minutes.
11. After 30 minutes of drying, scrape the semidried granules to break up the lumps to promote uniform drying.
12. Pass the dried granules through a 1.5-mm sieve using a granulator at medium speed. Collect in stainless steel drums.
13. Load the granules into blender.
14. Add items 11 and 12 to stainless steel drum and mix for 2 minutes using drum mixer, then load into the blender and mix along with the granules for 2 minutes.
15. Pass items 9, 10, 13, and 14 through sifter using 250-μm sieve.
16. Load the sieved material into blender and mix for 2 minutes. Unload into stainless steel drums.
17. Check temperature and humidity of the room before beginning compression.
18. Compress 1.2 g per tablet using 15.8-mm flat punch at relative humidity of 50% ± 5% at a temperature of 26°C ± 1°C.

Aminacrine Hydrochloride Topical Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1.00	1	Aminacrine hydrochloride	1.00
60.00	2	Thymol	60.00
100.00	3	Glyceryl monostearate	100.00
30.00	4	Cetostearyl alcohol	30.00
20.00	5	Polyoxyl 40 stearate	20.00
100.00	6	Liquid paraffin	100.00
5.00	7	Cetrimide	5.00
1.50	8	Isopropyl alcohol	1.50
QS	9	Water purified	QS to 1 L

Manufacturing Directions

1. Charge item 6 in a suitable stainless steel vessel and add and dissolve item 1 by heating to 65°C.
2. Charge items 3 to 5, 7, and 9 in a separate vessel and mix.
3. Add above items to step 1.
4. On cooling, add items 8 and 2 and mix.
5. Fill.

Aminolevulinic Acid HCl for Topical Solution (20%)

Aminolevulinic acid HCl for topical solution, 20%, contains the hydrochloride salt of aminolevulinic acid, an endogenous 5-carbon aminoketone. The stick for topical application is a two-component system consisting of a plastic tube containing two sealed glass ampules and an applicator tip. One ampule contains 1.5 mL of solution vehicle comprising alcohol (ethanol content = 48% v/v), water, laureth-4, isopropyl alcohol, and polyethylene glycol. The other ampule contains 354 mg of aminolevulinic acid hydrochloride as a dry solid. The applicator tube is enclosed in a protective cardboard sleeve and cap. The 20% topical solution is prepared just before the time of use by breaking the ampules and mixing the contents by shaking the stick applicator.

Amoxicillin Powder for Suspension

Bill of Materials			
Scale (mg/5 mL)[a]	Item	Material Name	Qty/5 L (g)
125.00	1	Amoxicillin, USE amoxicillin trihydrate, 8% excess	143.50
1.04	2	Simethicone A	1.04
111.11	3	Castor sugar	111.11
444.44	4	Castor sugar	444.44
2479.86	5	Castor sugar	2479.86
23.33	6	Sodium citrate	23.33
1.67	7	Xanthan gum	1.67
13.33	8	Blood orange dry flavor	13.33
0.74	9	Vanilla dry flavor	0.74
4.44	10	Orange, banana dry flavor	4.44
14.44	11	Aerosil 200	14.44

[a]After reconstitution

Manufacturing Directions

1. Charge items 3 and 2 in a mixer and mix for 2 minutes.
2. Add item 4 and items 6 to 11 and mix for 5 minutes.
3. Pass through Fitz mill, impact forward at high speed using sieve 24228.
4. In a separate mixer, charge items 5 and 1 and mix well, passing through a sifter.
5. Add to step 3 and mix for 20 minutes.
6. Fill 65 g for 100 mL and 39 g for 60-mL pack size.

Amoxicillin–Clavulanate Syrup

Bill of Materials			
Scale (g/60 mL volume)	Item	Material Name	Qty/kg (g)
1.500	1	Amoxicillin (1.25 g/60 mL),[a] USE amoxicillin trihydrate	215.67
0.393	2	Potassium clavulanate (equivalent to clavulanic acid 0.312 g)	56.59
0.150	3	Xanthan gum	21.56
1.800	4	Hydroxy propyl methyl cellulose	258.80
0.150	5	Saccharin sodium	21.56
0.300	6	Colloidal silica	43.13
0.010	7	Succinic acid	1.44
1.500	8	Silica gel	215.67
0.180	9	Peach dry flavor	26.39
0.230	10	Strawberry dry flavor	33.99
0.730	11	Lemon dry flavor	105.16

[a]6.955 g/60 mL: 156 mg/5 mL syrup 60 mL (125 mg amoxicillin and 31.25 mg clavulanic acid).

Manufacturing Directions

Throughout the process of manufacturing and filling, maintain relative humidity of NMT 40%.

1. Mill 50% of amoxicillin trihydrate, saccharin sodium (dried to NMT 2% moisture by Karl Fischer method), and succinic acid through a No. 100 mesh sieve using Fitz mill or equivalent with blades forward.
2. Transfer to a blending mixer and mix for 15 minutes.
3. Mill remaining amoxicillin trihydrate through a No. 100 mesh using Fitz mill or equivalent and mix with above screened powders; mix for 15 minutes.
4. Mill xanthan gum, hydroxypropylmethylcellulose (dried to NMT 2% moisture dried at 105°C for 2 hours), colloidal silica, and silica gel through a No. 100 screen using Fitz mill or equivalent with knives forward. Add to above mixture in step 2 and mix for 15 minutes at medium speed.
5. Screen all dry flavors through a No. 100 mesh screen and add to above mixture.
6. Fill dry powder approximately 7 g in dry 60-mL glass bottles at a fill weight based on the assay of the active constituent.

Amoxicillin–Clavulanate Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	
400.00	1	Amoxicillin as trihydrate	
57.00	2	Clavulanic acid as potassium salt	
2.69	3	Citric acid	
8.33	4	Sodium citrate	
28.10	5	Microcrystalline cellulose and sodium carboxymethylcellulose	
10.00	6	Xanthan gum	
16.67	7	Colloidal silicon dioxide	
216.60	8	Silicon dioxide	
13.30	9	Strawberry flavor	
15.00	10	Caramel flavor	
6.70	11	Saccharin sodium	
QS	12	Cellulose microcrystalline[a]	

[a]Total amount filled per bottle to deliver 12 doses is 15 g for 400 and 600 mg label of amoxicillin; For 200- and 300-mg amoxicillin label, the total fill weight is 12 g; adjust using item 12. Use method above to manufacture the final product.

Ampicillin Powder for Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/5 L (g)
125.00	1	Ampicillin, USE ampicillin trihydrate, 8% excess	144.25
1.00	2	Simethicone A	1.00
138.90	3	Castor sugar	138.90
27.44	4	Sodium citrate	27.44
7.00	5	Xanthan gum	7.00
15.00	6	Blood orange dry flavor	15.00
0.78	7	Vanilla dry flavor	0.78
7.55	8	Strawberry dry flavor	7.55
10.00	9	Aerosil 200	10.00
138.90	10	Castor sugar	138.90
2747.90	11	Castor sugar	2747.90

Manufacturing Directions

1. All operations to be completed in relative humidity 45% to 55% and temperature 23°C to 25°C.
2. Charge items 2 and 3 in a suitable blender and mix for 5 minutes.
3. Charge in a separate mixer items 1, 4 to 10 and mix for 5 minutes.
4. Add step 2 into step 3 and mix for 10 minutes.
5. Add item 11 and mix for 10 minutes.
6. Fill 65 g for 100-mL pack and 39 g for 60-mL pack. For 250-mg strength, adjust active ingredient and adjust with item 11.

Ampicillin Powder for Suspension

Bill of Materials			
Scale (mg/g)	item	Material Name	Qty/kg (g)
50.00	1	Ampicillin trihydrate	50.00
50.00	2	Sodium citrate	50.00
21.00	3	Citric acid crystalline	21.00
50.00	4	Sodium gluconate	50.00
400.00	5	Sorbitol crystalline	400.00
60.00	6	Kollidon CL-M	60.00
15.00	7	Orange flavor	15.00
5.00	8	Lemon flavor	5.00
4.00	9	Saccharin sodium	4.00

Manufacturing Directions

Mix all components and fill appropriate amount.

Ampicillin and Cloxacillin Oily Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
15.00	1	Ampicillin sodium	15.00
40.00	2	Cloxacillin sodium	40.00
30.00	3	Lutrol F 68	30.00
QS	4	Antioxidant	QS
915.00	5	Castor oil	915.00

Manufacturing Directions

1. Charge items 4 and 5 in a suitable stainless steel jacketed vessel; heat to 50°C. Do not overheat as castor oil may decompose.
2. Add and dissolve item 3.
3. Add and dissolve items 1 and 2.
4. Homogenize and fill.

Amprenavir Capsules

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
150.00	1	Amprenavir	150.00
400.00	2	D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS)	400.00
200.50	3	Polyethylene glycol 400	200.50
39.40	4	Polyethylene glycol 400	39.50

Manufacturing Directions

1. Charge item 2 in a suitable stainless steel-jacketed vessel and heat to 50°C until liquefied.
2. Add item 3 (90%) at 50°C and mix until homogenous solution obtained.
3. Increase temperature to 65°C, add item 1, and stir to dissolve.
4. Add item 4 and balance of item 2, cool to room temperature, apply vacuum to remove air entrapped.
5. Fill in size 12 oblong, white opaque soft gelatin capsules using a capsule-filling machine.
6. Dry the capsule shells to moisture of 3% to 6% water and a shell hardness of 7 to 10 N and pack in a suitable container.

Amprenavir Capsules

The capsules are available for oral administration in strengths of 50 and 150 mg. Each 50-mg capsule contains the inactive ingredients: D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS), polyethylene glycol 400 (PEG 400) 246.7 mg, and propylene glycol 19 mg. Each 150-mg capsule contains the inactive ingredients: TPGS, PEG 400 740 mg, and propylene glycol 57 mg. The capsule shell contains the inactive ingredients: D-sorbitol and sorbitans solution, gelatin, glycerin, and titanium dioxide. The soft gelatin capsules are printed with edible red ink. Each 150-mg capsule contains 109 U vitamin E in the form of TPGS. The total amount of vitamin E in the recommended daily adult dose is 1744 U.

Amprenavir Oral Solution

One milliliter of Agenerase oral solution contains 15 mg of amprenavir in solution and the inactive ingredients acesulfame potassium, artificial grape bubble-gum flavor, citric acid (anhydrous), D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS), menthol, natural peppermint flavor, polyethylene glycol 400 (PEG 400) (170 mg), propylene glycol (550 mg), saccharin sodium, sodium chloride, and sodium citrate (dihydrate). Solutions of sodium hydroxide and/or diluted hydrochloric acid may have been added to adjust pH. Each milliliter of Agenerase oral solution contains 46 U vitamin E in the form of TPGS. Propylene glycol is in the formulation to achieve adequate solubility of amprenavir.

Anise Oil Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Anise oil	10.00
17.00	2	Cremophor RH 40	17.00
340.00	3	Ethanol	340.00
QS	4	Preservatives	QS
633.00	5	Water	633.00

Manufacturing Directions

1. Mix the anise oil with Cremophor RH 40, heat to approximately 65°C.
2. Stir vigorously and slowly add the hot solution of items 3 to 5 to produce a clear or slightly opalescent, colorless liquid.

Antipyrine and Benzocaine Elixir

Each milliliter contains antipyrine 54 mg, benzocaine 14 mg, and glycerin anhydrous QS to volume (also contains oxyquinoline sulfate).

Antiseptic Wet Wipes

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
3.75	1	Cetrimonium bromide	3.75
0.15	2	Chlorhexidine gluconate	0.15
10.0–20.0	3	Polysorbate 20	10.0–20.0
10.0–20.0	4	Glycerin	10.0–20.0
QS	5	Deionized water	QS to 1 L

Manufacturing Directions

1. Preblend Polysorbate 20 and perfume.
2. Combine remaining components with stirring, add perfume/Polysorbate 20, blend.
3. Stir until clear.
4. Package in wipes.

Apraclonidine Hydrochloride Ophthalmic Solution

Each milliliter of Iopidine® 0.5% ophthalmic solution contains apraclonidine hydrochloride 5.75 mg equivalent to apraclonidine base 5 mg, benzalkonium chloride 0.01%, sodium chloride, sodium acetate, sodium hydroxide or hydrochloric acid (pH 4.4–7.8), and purified water.

Ascorbic Acid Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Ascorbic acid	100.00
QS	2	Propylene glycol	QS to 1 L

Manufacturing Directions

Keep under CO_2 protection at all times. Avoid contact with iron. Use stainless steel or glass-lined equipment only. Propylene glycol must be water white.

1. Load 86.8 g propylene glycol into a glass-lined or suitable stainless steel-jacketed tank. While mixing, heat to 70°C to 80°C. Bubble CO_2 gas into the propylene glycol from the bottom of the tank.
2. Add and dissolve the ascorbic acid into the propylene glycol with a minimum of stirring under CO_2 protection.
3. When the ascorbic acid is in solution, immediately cool to approximately 25°C while continuing to mix. Also, while cooling, change CO_2 addition from tank bottom to tank top.
4. QS to 1 L using propylene glycol and mix for at least 10 minutes.
5. Use a prefilter pad and a lint-free filter paper, E&D No. 950 or its equivalent; alternatively, a Sparkler filter (or equivalent) may be used.
6. Recirculate the product through the filter press until sparkling clear.
7. Flush a suitable storage tank with CO_2 gas and continue CO_2 gas protection while product is being collected.
8. Filter the product into the storage tank and hold under CO_2 protection.
9. Flush headspace of storage tank with CO_2 gas protection.

Atovaquone Suspension

Mepron suspension is a formulation of microfine particles of atovaquone. The atovaquone particles, reduced in size to facilitate absorption, are significantly smaller than those in the previously marketed tablet formulation. Mepron suspension is for oral administration and is bright yellow with a citrus flavor. Each teaspoonful (5 mL) contains 750 mg of atovaquone and the inactive ingredients benzyl alcohol, flavor, poloxamer 188, purified water, saccharin sodium, and xanthan gum.

Atovaquone Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
150.00	1	Atovaquone microflulidized[a]	150.00
5.00	2	Poloxamer 188	5.00
10.00	3	Benzyl alcohol	10.00
QS	4	Water purified	QS to 1 L

[a]Preparation of microfluidized particles of atovaquone: 600 mL of a mixture consisting of 2.5% w/v atovaquone in 0.25% w/v aqueous Celacol M2500 and passed through fluidizer such as model 120B Microfluidizer connected to a 90-psi pneumatic supply and adjusted to produce a fluid pressure of 15000 psi. Recirculate continuously through the interaction chamber for at least 45 minutes (65–77 passes) to achieve particle size less than 3 microns.

Manufacturing Directions

1. Charge items 4 and 3 in a suitable stainless steel vessel and mix well.
2. Add and mix item 2 with gentle mixing.
3. Add gradually item 1 and mix; pass through homogenizer.

Azelastine Hydrochloride Nasal Spray

Astelin nasal spray contains 0.1% azelastine hydrochloride in an aqueous solution at pH 6.8 ± 0.3. It also contains benzalkonium chloride (125 μg/mL), edetate disodium (EDTA), hydroxypropylmethylcellulose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water.

Azelastine Hydrochloride Nasal Spray

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1.00	1	Azelastine hydrochloride	1.00
0.50	2	Edetic acid disodium dehydrate	0.50
6.80	3	Sodium chloride	6.80
0.125	4	Benzalkonium chloride	0.125
0.44	5	Citric acid	0.44
6.48	6	Sodium monohydrogen phosphase 12 H_2O	6.48
1.00	7	Hydroxypropyl methyl cellulose–Methocel E4M	1.00
QS	8	Water purified	QS to 1 L

Manufacturing Directions

1. Charge 90% of item 8 in a suitable stainless steel vessel.
2. Dissolve in the following order: azelastine hydrochloride, edetic acid, sodium chloride, benzalkonium chloride, citric acid, and sodium monohydrogenphosphate, and mix well.
3. Bring to volume with item 8.
4. Pass the solution through a membrane filter of pore size 0.22 microns.
5. The filtrate has a pH value of 6.8 ± 0.3.
6. Fill in plastic bottles that are closed with a conventional spray insert or into plastic or glass bottles that are closed with a conventional pump sprayer. In the latter case, pumps with nasal spray inserts are, for example, used that spray approximately 0.14 mL of solution per actuation. In this manner, 0.14 mg of azelastine hydrochloride is sprayed into the nose per actuation in the form of the solution.

Azithromycin Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
200.0000	1	Azithromycin, USE azithromycin dehydrate	69.30
4.4100	2	Sucrose	883.00
0.0650	3	Sodium phosphate 12 hydrate	13.00
0.0075	4	Xanthan gum	1.50
0.0200	5	Sodium cyclamate	4.00
0.0200	6	Sodium saccharin	2.00
0.0250	7	Glycamil	5.00
0.5000	8	Starch pregelatinized	100.00
0.0200	9	Flavor	4.00
0.0550	10	Flavor	11.00
0.0400	11	Flavor	8.00
0.7500	12	Sorbitol 70%	150.00
0.7500	13	Propylene glycol	140.00
0.0075	14	Methyl paraben	1.50
0.0015	15	Propyl paraben	0.30
QS	16	Water purified	QS to 1 L

Manufacturing Directions

1. Charge in a suitable stainless steel double-cone blender sucrose, sodium phosphate, xanthan gum, sodium cyclamate, sodium saccharin, glycamil, and starch pregelatinized.
2. Mix for 15 minutes.
3. Mill the mixture in step 2 using a hammer mill (hammer forward) equipped with a 2-mm screen at high speed.
4. Charge into a double-cone mixer the mixture from step 3 and add azithromycin and flavors.
5. Mix for 15 minutes.
6. Fill 11.01 g per bottle. The bottle must be reconstituted with 10 mL of the diluent (see step below) to obtain 16.5 mL of suspension with concentration of 200 mg/5 mL.
7. Prepare the diluent by first dissolving items 14 and 15 in item 13 at 69°C to 70°C, then mix with items 12 and 16.

Azithromycin Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Azithromycin dihydrate	50.00
50.00	2	Sodium citrate	50.00
20.00	3	Citric acid	20.00
600.00	4	Sucrose	600.00
90.00	5	Kollidon CL-M	90.00
5.00	6	Cremophor RH 40	5.00
2.00	7	Chocolate flavor	2.00
100.00	8	Water purified	100.00
QS	9	Water purified	QS to 1 L

Manufacturing Directions

1. Charge items 1 to 5 in a suitable mixing vessel and mix.
2. In a separate vessel, add and mix items 6 to 8 and add to step 1. Mix.
3. Bring to volume. Homogenize and fill.

Azulene Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Azulene	10.00
30.00	2	Cremophor RF 40	30.00
QS	3	Water purified	QS to 1 L

Manufacturing Directions

1. Charge items 1 and 2 in a suitable mixing vessel and heat to 60°C.
2. In a separate vessel, heat item 3 to 60°C and then add to step 1. Mix well for a clear solution.

Azulene Solution (1%)

Manufacturing Directions

1. Mix 1 g azulene, 3 g Cremophor RH 40, and heat to approximately 60°C.
2. Add slowly the water (60°C) to 100 mL and cool to room temperature.

Barium Sulfate Oral Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
230.00	1	Barium sulfate	230.00
11.50	2	Kollidon 90F	11.50
0.92	3	Carboxymethylcellulose sodium	0.92
0.70	4	Sodium bisulfite	0.70
QS	5	Preservatives	QS
QS	6	Water purified	QS to 1 L

Manufacturing Directions

1. Charge 90% of item 6 in a suitable jacketed vessel.
2. Add and mix preservatives and item 3. Mix well. Allow to hydrate.
3. Add item 2 and mix well until clear solution is obtained.
4. Add item 1 and mix to a smooth suspension. Homogenize if necessary.

Beclomethasone Dipropionate Inhalation Aerosol

It is a pressurized, metered-dose aerosol intended for oral inhalation only. Each unit contains a solution of beclomethasone dipropionate in propellant HFA-134a (1,1,1,2 tetrafluoroethane) and ethanol. The 40-μg strength delivers 40 μg of beclomethasone dipropionate from the actuator and 50 μg from the valve. The 80-μg strength delivers 80 μg of beclomethasone dipropionate from the actuator and 100 μg from the valve. It is a metered-dose manual-pump spray unit containing a suspension of beclomethasone dipropionate, monohydrate equivalent to 0.084% w/w, beclomethasone dipropionate in an aqueous medium containing microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, and phenylethyl alcohol. The suspension is formulated at a target pH of 6.4 with a range of 5.5 to 6.8 over its shelf life.

Beclomethasone Dipropionate Inhalation Aerosol

Bill of Materials			
Scale (μg/mg)	Item	Material Name	Qty/kg (g)
1.60	1	Beclomethasone dipropionate	1.60
35.20	2	Ethanol	35.20
0.16	3	Oleic acid	0.16
960.00	4	HFA 227	960.00

Manufacturing Directions

1. Charge beclomethasone dipropionate into a pressure addition vessel and dissolve with stirring in ethanol in which oleic acid has been previously dissolved.
2. After sealing and evacuation of step 1, add item 4, which has previously been aerated with carbon dioxide and adjusted to a pressure of 6.5 bar (20°C), in another pressure vessel with stirring. The solution obtained is dispensed into aluminum containers sealed with metered valves by means of the pressure-filling technique (e.g., units from Pamasol W. Maeder, Pfaffikon, Switzerland).

Beclomethasone Dipropionate and Salbutamol Sulfate Nasal Spray

Dissolve 15.6 g of beclomethasone dipropionate in 811 g of ethanol, which contains 3 g of oleic acid. The clear solution is mixed with 7.3 kg of HFA 227. The mixture obtained is added to 9.4 g of initially introduced salbutamol sulfate and adequately homogenized. After conclusion of the homogenization, the mixture is diluted with 2 kg of HFA 227 that has been aerated with carbon dioxide and adjusted to a pressure of 5 bar (20°C), diluted, and finally homogenized. The finished preparation is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Benzethonium Chloride Solution

Benzethonium chloride 1%, water, amphoteric 2, aloe vera gel, DMDM hydantoin, citric acid.

Benzethonium Chloride and Benzocaine Topical Anesthetic

Benzethonium chloride 0.2%, benzocaine 20%; inactive ingredients: acetulan, aloe vera oil, menthol, methyl paraben, *N*-butane/P152a (65:35), PEG 400, monolaurate, polysorbate 85.

Benzocaine and Tetracaine Topical Solution

Bill of Materials			
Scale (g/100 mL)	Item	Material Name	Qty/L (g)
14.00	1	Benzocaine	140.00
2.00	2	Butyl aminobenzoate	20.00
2.00	3	Tetracaine hydrochloride	20.00
0.50	4	Benzalkonium chloride	5.00
0.005	5	Cetyl dimethyl ethyl ammonium bromide	0.05
QS	6	Water purified	QS to 1 L

Benzyl Benzoate Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Benzyl benzoate	100.00
220.00	2	Cremophor RH 40	220.00
410.00	3	Ethanol (96%)	410.00
270.00	4	Water	270.00

Manufacturing Directions

1. Heat the mixture of benzyl benzoate and Cremophor RH 40 to approximately 60°C.
2. Stir strongly and slowly add the water.
3. Finally, add the ethanol to produce a clear, colorless liquid.

Beta-Estradiol Vaginal Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
QS	1	Vehicle (pluronic P105 45%, propylene glycol 48%, water 7%)	QS to 1 L
0.10	2	Beta-estradiol	0.10
QS	3	Perfumes	QS

Manufacturing Directions

1. Add the beta-estradiol and propylene glycol into a clean vessel.
2. Subsequently add the poloxamer and water to the vessel.
3. Mix until uniform.

Betamethasone Syrup

Celestone syrup contains 0.6 mg betamethasone in each 5 mL. The inactive ingredients for celestone syrup include alcohol; cellulose, powdered; citric acid, anhydrous; FD&C red No. 40; FD&C yellow No. 6; flavor cherry artificial 13506457 IFF; flavor orange natural terpeneless 73502530 IFF; propylene glycol; sodium benzoate; sodium chloride; sorbitol solution; sugar, granulated; and water, purified.

Bismuth Carbonate Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
266.66 mg	1	Light kaolin	266.66
8.30 mg	2	Pectin	8.30
6.70 mg	3	Bismuth carbonate	6.70
9.40 mg	4	Cellulose (microcrystalline; Avicel™ RC-591)	9.40
1.40 mg	5	Methyl paraben	1.40
0.20 mg	6	Saccharin sodium	0.20
0.40 mg	7	Aspartame	0.40
40.00 mL	8	Sorbitol	40.00 mL
5.00 mL	9	Ethanol	5.00 mL
QS	10	Deionized water	QS to 1 L

Manufacturing Directions

1. Dissolve item 2 in hot water.
2. Disperse item 1 in 75 mL of item 10 at room temperature.
3. With constant agitation, add item 3 and continue stirring.
4. Mix and cool to room temperature.
5. Disperse item 4 in item 10 and add it to the batch.
6. Dissolve item 2 in item 1 dispersion and add to the batch.
7. Dissolve items 6 and 7 in water and add to the batch.
8. Add flavor, color, and water to volume.
9. Pass through homogenizer or colloid mill if necessary.

Bismuth Subsalicylate Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
15.00	1	Magnesium aluminum silicate (Magnabrite K)	15.00
1.50	2	Methylcellulose	1.50
910.00	3	Deionized water	910.00
0.50	4	Saccharin sodium	0.50
30.00	5	Bismuth subsalicylate	30.00
4.00	6	Salicylic acid	4.00
10.00	7	Sodium salicylate	10.00
29.00	8	Ethanol	29.00
QS	9	Preservatives	QS
QS	10	Colorings	QS

Manufacturing Directions

1. Dry blend items 1 and 2 and slowly add them to item 3, agitating until smooth.
2. Add items 4 to 7 to this dispersion, gradually mixing well each time.
3. Finally, add items 8 to 10 to smooth mix.

Bromazepam Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
2.50	1	Bromazepam	2.50
5.00	2	Saccharin sodium	5.00
0.10	3	Sequestrene disodium	0.10
5.00	4	Flavor	5.00
25.00	5	Flavor	25.00
QS	6	Sodium hydroxide for pH adjustment	QS
50.00	7	Water purified	50.00
QS	8	Propylene glycol	QS to 1 L

Manufacturing Directions

1. Charge item 8 in a suitable stainless steel mixing vessel and, while stirring, add item 3 and dissolve.
2. Add item 7 and stir continuously. Add item 2 and then item 1 and stir to dissolve.
3. Add flavors and mix.
4. Check and adjust pH to 5, if necessary, using item 5.
5. Make up volume with item 8.

Bromhexine Hydrochloride Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
4.00	1	Bromhexine HCl	0.80
1000.00	2	Glycerin (glycerol)	200.00
10.00	3	Benzoic acid	2.00
1.70	4	All fruits flavor	0.34
5.00	5	Tartaric acid	1.00
151.58	6	Alcohol (ethanol, 95%)	30.31
2857.00	7	Sorbitol (70% solution)	571.40
10.00	8	Sodium carboxymethyl cellulose (sodium CMC)	2.00
0.72	9	Sodium hydroxide pellets	0.14
QS	10	Purified water	QS to 1 L

Manufacturing Directions

1. Add 250 g of item 10 to the manufacturing vessel and heat to 65°C to 70°C.
2. Add 20 g of item 2 in a separate stainless steel container and mix item 8 using an Ekato stirrer, carefully avoiding lump formation.
3. Transfer the slurry to the manufacturing vessel and continue mixing to make a clear mucilage. Avoid air entrapment.
4. Cool to 30°C while mixing at slow speed. Transfer the mucilage to container.
5. Load 100 g of item 2 to the manufacturing vessel.
6. Add item 6 in a separate stainless steel container and dissolve item 3 using stirrer.
7. Add 60 g of item 2 to the container while mixing at slow speed.
8. Add and dissolve item 1 to the container while mixing at slow speed. Avoid splashing of the solution. Ensure bromhexine is dissolved completely.
9. Add item 4 to the container and mix well.
10. Transfer the solution to the manufacturing vessel while mixing at high speed.
11. Rinse the container with 20 g of item 2 and transfer the rinsing to the manufacturing vessel while mixing.
12. Rinse the container with 20 g of item 10 and transfer the rinsing to the manufacturing vessel while mixing.
13. Add 15 g of item 10 in a separate stainless steel container.
14. Dissolve item 5 using a stirrer and transfer it to the manufacturing vessel while mixing. Check for clarity of the solution in the manufacturing vessel. The solution must be clear without any undissolved particles of the drug.
15. Add item 7 to the manufacturing vessel while mixing at high speed.
16. Transfer the cooled mucilage of item 8 to the manufacturing vessel used above while mixing at slow speed.
17. Check and record the pH of the solution (limit: 3.3–3.6).
18. Dissolve item 9 in 5 g of cooled item 10 (30°C) in a separate stainless steel container.
19. Adjust the pH of the syrup in the manufacturing vessel using the sodium hydroxide solution.
20. Add sodium hydroxide solution, small portions at a time. Mix well and check the pH after every addition. Adjust the pH to 3.5 (limit: 3.3–3.6).
21. Bring the volume up to 1 L with item 10 and finally mix for 15 to 20 minutes at high speed.
22. Check and record the pH (limit: 3.3–3.6).
23. Filter the syrup at 1.5 bar.
24. Recirculate.

Bromhexine Hydrochloride Syrup—Alcohol Free

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
4.00	1	Bromhexine HCl	0.80
1000.00	2	Glycerin (glycerol)	200.00
12.00	3	Sodium benzoate	2.40
1.70	4	All fruit flavor	0.34
17.00	5	Tartaric acid	3.40
2250.00	6	Sorbitol (70% solution)	450.00
10.00	7	Sodium carboxymethyl cellulose (sodium CMC)	2.00
QS	8	Purified water	QS to 1 L

Manufacturing Directions

1. Add 240 g of item 8 (25°C) to the manufacturing vessel.
2. Add item 5 and mix for 20 minutes at high speed.
3. Load 180 g of item 2 into the manufacturing vessel and mix for 3 minutes.
4. Add item 1 to the manufacturing vessel and mix for 30 minutes at high speed.
5. Add 20 g of item 2 in a suitable vessel and levigate item 7 using stirrer, carefully avoiding lump formation.
6. Add 40 g of item 8 (70°C) to the stainless steel container while mixing to make a clear mucilage; mix for 15 minutes. Avoid air entrapment.
7. Cool down to 25°C to 30°C while mixing at slow speed.
8. Transfer the mucilage to the manufacturing vessel.
9. Rinse the vessel with 10 g of item 8 and transfer to the manufacturing vessel.
10. Mix at slow speed for 20 minutes.
11. Transfer item 6 to the manufacturing vessel while mixing. Mix at low speed for 5 minutes.
12. Add 20 g of item 8 (25°C) in a separate stainless steel container and dissolve item 3 using an Ekato stirrer until a clear solution is obtained.
13. Transfer this solution to the manufacturing vessel and mix at low speed for 3 minutes.
14. Add item 4 to the manufacturing vessel and mix at low speed for 3 minutes.
15. Record the pH of the solution (limit: 3.3–3.7). Adjust the pH of the solution with 10% solution of sodium hydroxide, if required.
16. Make the volume up to 1 L with item 8 (25°C) and finally mix for 15 to 20 minutes at high speed.
17. Filter the syrup at 1.5 bar.
18. Recirculate.

Bromhexine Hydrochloride Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
4.00	1	Bromhexine HCl	0.80
1000000	2	Glycerin (glycerol)	200.00
10.00	3	Benzoic acid	2.00
1.00	4	All fruits flavor	0.34
5000	5	Tartaric acid	1.00
151.50	6	Alcohol (ethanol 95%)	30.31
2857000	7	Sorbitol (70% solution)	571.40
10.00	8	Carboxymethylcellulose sodium (sodium CMC)	2.00
0.70	9	Sodium hydroxide pellets	0.14
QS	10	Water purified	QS to 1 L

Manufacturing Directions

1. Add 250 g of item 10 to a suitable stainless steel manufacturing vessel and heat to 65°C to 70°C.
2. Add 20 g of item 2 in a separate stainless steel container and mix item 8 using Ekato stirrer, carefully avoiding lump formation.
3. Transfer the slurry to the manufacturing vessel while continuing to mix to make a clear mucilage. Avoid air entrapment.
4. Cool down to 30°C while mixing at slow speed.
5. Transfer the mucilage to container. Load 100 g of item 2 to the manufacturing vessel.
6. Add item 6 in a separate stainless steel container and dissolve item 3 using stirrer.
7. Add 60 g of item 2 to the container while mixing at slow speed.
8. Add and dissolve item 1 to the container while mixing at slow speed. Avoid splashing of the solution. Check that bromhexine is dissolved completely.
9. Add item 4 to the container and mix well. Transfer the solution to the manufacturing vessel while mixing at high speed.
10. Rinse the container with 20 g of item 2 and transfer the rinsing to the manufacturing vessel while mixing.
11. Rinse the container with 20 g of item 10 and transfer the rinsing to the manufacturing vessel while mixing. Add 15 g of item 10 in a separate stainless steel container and dissolve item 5 using stirrer and transfer to the manufacturing vessel while mixing.
12. Check clarity of the solution in manufacturing vessel. The solution must be clear without any undissolved particles of the drug.
13. Add item 7 to the manufacturing vessel while mixing at high speed.
14. Transfer the cooled mucilage of item 8 to the manufacturing vessel used above while mixing at slow speed.
15. Check and record the pH of the solution (limit: 3.3–3.6).
16. Dissolve item 9 in 5 g of cooled item 10 (30°C) in a separate stainless steel container.
17. Adjust the pH of the syrup in manufacturing vessel using the sodium hydroxide solution. Add sodium hydroxide solution in small portions at a time. Mix well and check the pH after every addition. Adjust the pH to 3.5 (limit: 3.3–3.6).
18. Make up the volume up to 1 L with item 10 and, finally, mix for 15 to 20 minutes at high speed. Check and record the pH (limit: 3.3–3.6). Filter the syrup at 1.5 bar. Recirculate.

Budesonide Inhaler

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Budesonide	20.00
1190.00	2	Oleic acid	1190.00
1372.00	3	Trichloromonofluoromethane (propellant 11)	1372.00
2745.00	4	Dichlorodifluoremethane (propellant 12)	2745.00
1373.00	5	Dichlorotetrafluoroethane (propellant 114)	1373.00

Manufacturing Directions

1. Mix oleic acid in trichloromonofluoromethane in a suitable mixer.
2. Suspend budesonide in step 1 while mixing. Homogenize for 10 minutes.
3. On quality control release, fill the suspension 2.582 g in aluminum containers.
4. Crimp the valve and pressurize with the mixture of dichlorodifluoromethane and dichlorotetrafluoromethane, 4.118 g per container.

Butamirate Citrate Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/5 L (g)
4.00	1	Butamirate citrate	4.00
12.50	2	Citric acid monohydrate	12.50
1750.00	3	Sorbitol	1750.00
1250.00	4	Glycerin	1250.00
6.25	5	Saccharin sodium	6.25
5.00	6	Sodium benzoate	5.00
10.00	7	Lemon flavor	10.00
QS	8	Sodium hydroxide	2.50
QS	9	Water purified	QS to 5 L

Manufacturing Directions

1. Dissolve items 2 to 4 in item 9 (90%).
2. Add and dissolve item 1.
3. Add items 5 to 7.
4. Add item 8.
5. Bring to volume.

Caffeine Citrate Oral Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Caffeine, USE caffeine citrate	20.00
5.00	2	Citric acid monohydrate	5.00
8.30	3	Sodium citrate monohydrate	8.30
QS	4	Water purified	QS to 1 L

Manufacturing Directions

1. Dissolve item 1 in a solution of items 2 and 3 in item 4.
2. Adjust pH to 4.7

Calcipotriene Solution

Dovonex® (calcipotriene solution) scalp solution 0.005% is a colorless topical solution containing 0.005% calcipotriene in a vehicle of isopropanol (51% v/v) propylene glycol, hydroxypropyl cellulose, sodium citrate menthol, and water.

Calcitonin Nasal Spray

Calcitonin-salmon, 2200 U/mL (corresponding to 200 U/0.09 mL actuation), sodium chloride, benzalkonium chloride, nitrogen, hydrochloric acid (added as necessary to adjust pH), and purified water.

Calcitonin Nasal Spray

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.1375	1	Salmon calcitonin, 10% excess	0.152
7.500	2	Sodium chloride	7.500
0.100	3	Benzalkonium chloride	0.100
QS	4	Hydrochloric acid (1 N) to adjust pH	QS
QS	5	Water purified	QS to 1 L

Manufacturing Directions

1. Charge items 1 (90%), 2, and 3 in a suitable stainless steel mixing vessel under protection of nitrogen gas and mix well.
2. Measure and adjust pH to 3.7 using item 4.
3. Filter through 0.20-micron filter.
4. Add balance of item 1 in item 5 to step 3. Mix.
5. Fill into a spray nasal dispenser with a solution volume of 2 mL. The composition comprises approximately 550 MRC units active ingredient per milliliter and the applicator delivers a quantity comprising 55 units per actuation.

Calcium Carbonate and Guar Gum Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
400.000	1	Calcium carbonate	80.000
3935.000	2	Water purified	787.000
1000.000	3	Sorbitol solution (70%)	200.000
13.000	4	Xanthan gum	2.600
5.000	5	Hydroxyethyl cellulose	1.000
120.000	6	Magnesium hydroxide	24.000
25.000	7	Flavor strawberry[a]	5.000
1.425	8	Saccharin sodium	0.285
100.000	9	Guar gum	20.000

[a]Powder flavor is used; can change according to requirement.

Manufacturing Directions

This is a preservative-free formula; shelf life stability is achieved by maintaining pH of the suspension above 9 through the addition of magnesium hydroxide. Absence of preservatives makes it a more palatable formula but requires extra care in the manufacturing process. Rigidly control the microbial specification of all ingredients. Thoroughly clean all equipment and rinse with 1% sodium hypochlorite solution before use. Finally, rinse with purified water.

1. In a clean vessel, heat item 2°C to 90°C and maintain for 20 minutes. Cool to room temperature.
2. In approximately 90% of the quantity of item 2, add item 3 to step 1 and mix well. Set aside the balance of quantity of item 2 for bringing to volume the suspension in the step 8.
3. Add by sprinkling items 3, 4, and 9, gradually mixing aggressively to ensure fine dispersion; the powders may be passed through an appropriate sieve to break any lumps.
4. Mix for 30 minutes.
5. Add and mix item 1 for 15 minutes after passing through a fine mesh to break any lumps.
6. Add item 6 after passing through 100-mesh screen and mix for 15 minutes.
7. Add flavor and sweetener and stir for another 15 minutes. Bring to volume (if necessary) and mix for 10 minutes.
8. Check the pH of suspension to 9 and above. Add small quantity of magnesium hydroxide if needed to bring pH to above 9.
9. Heat the suspension in a covered container for 30 minutes at 68°C (maintain 68°C for 30 minutes); this is a pasteurizing step to reduce microbial load.
10. Fill in clean bottles tested for microbial contamination.

Calcium Iodide and Ascorbic Acid Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
311.60	1	Glucose liquid (corn syrup)	311.60
53.90	2	Glycerin (96%)	53.90
30.00	3	Anhydrous calcium iodide; use calcium iodide solution 27% w/w	111.11
1.00	4	Ascorbic acid (white powder)	1.00
485.30	5	Sucrose (granulated sugar)	485.30
0.80	6	Saccharin sodium (powder)[a]	0.80
8.00	7	Sodium cyclamate (XIII powder)	8.00
1.31	8	Honey artificial flavor, AU-73	1.31
0.33	9	Floral mint artificial flavor	0.33
51.53	10	Alcohol (ethanol; 190 proof)	51.53
0.60	11	Isoproterenol sulfate (powder)	0.60
0.05	12	FD&C yellow dye No. 5	
0.25	13	Caramel (acid proof)	0.25
QS	14	Water purified	~344.0 mL

[a]Use 1.2 g of saccahrin to replace cyclamate; adjust balance with sucrose.

Manufacturing Directions

Isoproterenol is toxic; wear a dust mask and avoid contact. The product is sensitive to oxidation. Manufacture under N_2 protection and protect product from light and heat; all water must be boiled, cooled, and gassed with nitrogen.

1. Load glucose and glycerin into a suitable mixing tank.
2. Add 187 mL purified water to tank with mixing.
3. Begin bubbling N_2 protection for the balance of the process.
4. Add and dissolve saccharin sodium and sodium cyclamate, if used, with mixing.
5. Add calcium iodide to the tank with good mixing.
6. Add and dissolve ascorbic acid and sugar.
7. Dissolve the flavors in alcohol and add with mixing to the main batch.
8. Dissolve isoproterenol in 10 to 13 mL of water and add, with mixing, to the main batch.
9. Dissolve dye in 3.5 mL purified water and add solution to tank with mixing. (*Note*: Dye may be deleted.) Add caramel with mixing to main batch.
10. Move N_2 source from the bottom to the top of the tank.
11. Turn off mixer.
12. Allow to stand overnight under N_2 protection to let entrapped gases escape.
13. QS to 1 L. Mix for 1 hour.
14. Filter and circulate product through a suitable filter press until sparkling clear.

Carbamazepine Oral Suspension 2%

Formulation

Carbamazepine (Flavine), 2 g; 1,2-propylene glycol, 20 g; Kollidon 90F, 3 g; saccharine sodium, 0.1 g; sodium citrate, 1 g; sorbitol, crystalline, 25 g; Kollidon CL-M, 7 g; water, 41.9 g;

Manufacturing Directions

1. Stir the mixture of carbamazepine and propylene glycol at least during 2 hours.
2. Add Kollidon 90F, saccharine, sodium citrate, and the water and stir again until these components are dissolved.
3. Dissolve sorbitol in this mixture and add Kollidon CL-M to the well-stirred suspension to obtain a homogeneous suspension.

Carbetapentane Tannate and Chlorpheniramine Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/5 L (g)
30.00	1	Carbetapentane tannate	30.00
4.00	2	Chlorpheniramine tannate	4.00
50.00	3	Pectin medium viscosity	50.00
1000.00	4	Kaolin colloidal powder	1000.00
35.00	5	Magnesium aluminum silicate	35.00
10.00	6	Benzoic acid	10.00
2.50	7	Methyl paraben	2.50
1000.00	8	Sucrose	1000.00
0.75	9	Saccharin sodium	0.75
225.00	10	Glycerin	225.00
0.91	11	Flavor black currant imitation	0.91
2.28	12	Flavor strawberry with other flavors	2.28
0.45	13	Purpose shade “R” dye	0.45
0.80	14	FD&C red No.3 dye	0.80
0.30	15	FD&C yellow No.5	0.30
3.17	16	Sodium hydroxide solution 50%	3.17
	17	Purified water, deionized	QS to 5 mL

Carnitine and Coenzyme Q Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1.00	1	Coenzyme Q10	1.00
1.00	2	Lutrol E 400	1.00
4.00	3	Cremophor RH 40	4.00
QS	4	Preservative	QS
QS	5	Water	QS to 1 L
40.00	6	Carnitine	40.00

Manufacturing Directions

1. Heat the mixture of items 1 to 5 to 60°C and stir well.
2. Add and dissolve item 6 after cooling to room temperature.

Cefaclor Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
250.00	1	Cefaclor	50.00
5.00	2	Emulsion silicone 30%	1.00
7.50	3	Xanthan gum	1.50
10.00	4	Starch modified	2.00
4.00	5	Erythrosine aluminum lake	0.80
20.00	6	Flavor	4.00
0.75	7	Sodium lauryl sulfate	0.15
3.00	8	Methylcellulose	0.60
2960.00	9	Sucrose	592.00

Note: For 125-mg dose, adjust with sucrose the final quantity.

Cefadroxil Monohydrate Oral Suspension

Duricef for oral suspension contains the following inactive ingredients: FD&C yellow No. 6, flavors (natural and artificial), polysorbate 80, sodium benzoate, sucrose, and xanthan gum.

Cefpodoxime Proxetil Oral Suspension

Each 5 mL of Vantin oral suspension contains cefpodoxime proxetil equivalent to 50 or 100 mg of cefpodoxime activity after constitution and the following inactive ingredients: artificial flavorings, butylated hydroxy anisole, carboxymethylcellulose sodium, microcrystalline cellulose, carrageenan, citric acid, colloidal silicon dioxide, croscarmellose sodium, hydroxypropylcellulose, lactose, maltodextrin, natural flavorings, propylene glycol alginate, sodium citrate, sodium benzoate, starch, sucrose, and vegetable oil.

Cefpodoxime Proxetil Oral Suspension

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Cefpodoxime proxetil	123.50
563.75	2	Sucrose	563.50
290.00	3	D-Mannitol	290.00
1.25	4	Saccharin sodium	1.25
20.00	5	Hydroxypropyl cellulose	20.00
0.50	6	Dye yellow No. 5	0.50
1.00	7	Ethylenediamine tetraacetate disodium	1.00
QS	8	Orange essence	QS
QS	9	Water purified	QS

Manufacturing Directions

1. Charge item 1, sucrose, D-mannitol, saccharin sodium, and disodium ethylenediamine tetraacetate in an agitating granulator.
2. Granulate the mixture by agitation while spraying it with a binder of hydroxypropylcellulose and yellow No. 5 in water.
3. Pass wet mass through a 42-mesh screen in an extrusion granulator.
4. Dry the granules in a fluidized bed granulator.
5. Spray the granules with orange essence.
6. Dry granules further in the fluid bed dryer.
7. Pass granules through 30-mesh sieve and fill.

When purified water is added to the resulting dry syrup at a concentration of item 1 of 49.4 mg/mL, the dry syrup rapidly dissolves in it to give a clear orange solution.

Cefpodoxime Proxetil for Oral Suspension

Each 5 mL of Vantin oral suspension contains cefpodoxime proxetil equivalent to 50 or 100 mg of cefpodoxime activity after constitution and the following inactive ingredients: artificial flavorings, butylated hydroxyanisole, carboxymethylcellulose sodium, microcrystalline cellulose, carrageenan, citric acid, colloidal silicon dioxide, croscarmellose sodium, hydroxypropylcellulose, lactose, maltodextrin, natural flavorings, propylene glycol alginate, sodium citrate, sodium benzoate, starch, sucrose, and vegetable oil.

Ceftin for oral suspension, when reconstituted with water, provides the equivalent of 125 or 250 mg of cefuroxime (as cefuroxime axetil) per 5 mL of suspension. Ceftin for oral suspension contains the inactive ingredients polyvinyl pyrrolidone K30, stearic acid, sucrose, and tutti-frutti flavoring.

Cefuroxime Axetil Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
25.00	1	R-Cefuroxime axetil	25.00
0.40 mL	2	Sorbitol solution 70%	0.40 L
20.00	3	Saccharin	20.00
QS	4	Water purified	QS to 1 L

Manufacturing Directions

1. Charge the sorbitol solution and 20% of item 5 in a mixing vessel.
2. Add item 1 and mix vigorously to form a suspension.
3. Add items 3 and any flavors, if needed, and mix.
4. Bring to volume.
5. Fill.

Cetirizine Hydrochloride Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
5.00	1	Cetirizine hydrochloride	1.03
1750.00	2	Lycosin 80/55	350.00
600.00	3	Sorbitol 70%	120.00
5.00	4	Sodium citrate	1.00
300.00	5	Propylene glycol	60.00
4.50	6	Methyl paraben	0.90
0.50	7	Propyl paraben	0.10
3.75	8	Saccharin sodium	0.75
10.00	9	Flavor raspberry	2.00
QS	10	Water purified	QS to 1 L

Manufacturing Directions

1. Charge 30% of item 10 in a stainless steel jacketed kettle and heat to 90°C to 95°C.
2. Add and dissolve items 6 and 7; cool to 40°C.
3. Add to step above item 4 and item 8 and mix to dissolve.
4. Add items 2, 3, and 5 and mix to dissolve.
5. In a separate vessel, charge 30% of item 10 and add to it item 1, mix to dissolve, and then add to step 4.
6. Add flavor(s) and bring to volume with item 10.

Chlophedianol, Ipecac, Ephedrine, Ammonium Chloride, Carbinoxamine, and Balsam Tolu Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
0.001 mL	1	Ipecac fluid extract	1.00 mL
5.00	2	Chlophedianol hydrochloride	5.00
1.32	3	Ephedrine hydrochloride (powder)	1.32
8.80	4	Ammonium chloride (reagent-grade granules)	8.80
0.80	5	Carbinoxamine maleate	0.80
0.90	6	Methyl paraben	0.90
0.10	7	Propyl paraben	0.10
6.25	8	Balsam of Tolu (eq. aqueous extract)	6.25
2.66	9	Saccharin sodium (dihydrate powder)	2.66
319.22	10	Sucrose (granulated sugar)	319.22
238.33	11	Glucose liquid (corn syrup)	238.33
83.93	12	Sorbitol solution (calculate as 70% sorbitol crystals)	83.93
40.00	13	Alcohol	40.00
166.67	14	FD&C red dye (Amaranth E123)	166.67 mg
0.80	15	Raspberry flavor	0.80
100.00	16	Propylene glycol	100.00
QS	17	HyFlo filter aid	0.50
QS	18	Water purified	~450.00 mL

Manufacturing Directions

1. Charge balsam of Tolu and 25 mL of water in a steam bath.
2. Raise the temperature, stirring continuously to mix water with the balsam.
3. Boil for half an hour and allow to decant while cooling.
4. Discard extracted balsam of Tolu.
5. Filter the supernatant liquid through filter paper and store apart.
6. Charge 150 mL water in a jacketed mixing tank and heat to boiling.
7. Add and dissolve parabens with mixing.
8. Add and dissolve sugar with constant mixing.
9. Heat to 70°C to 75°C.
10. Once sugar is dissolved, add glucose, sorbitol, and saccharin sodium. Mix well until dissolved.
11. Dissolve ammonium chloride in 28 mL water.
12. Add to mixing tank.
13. Add extract balsam of Tolu from first step with mixing. Mix well and cool to 25°C to 30°C.
14. Add and dissolve ephedrine and carbinoxamine in 20 mL water and add to mixing tank. Mix well.
15. Add and dissolve chlophedianol in 50 g of propylene glycol and add to mixing tank.
16. Add balance of propylene glycol to mixing tank.
17. Add and dissolve Ipecac fluid extract and raspberry flavor in alcohol.
18. Add to mixing tank.
19. Dissolve dye in 5 mL water and add to tank with continuous mixing.
20. Rinse container with 5 mL of water and add rinsing.
21. Adjust to volume with purified water.
22. Add HyFlo filter aid to syrup and mix well.
23. Recirculate through filter press or equivalent until sparkling clear.

Chlophedianol, Ipecac, Ephedrine, Ammonium Chloride, Carbinoxamine, and Balsam Tolu Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
0.001 mL	1	Ipecac fluid extract	1.000 mL
5.000	2	Chlophedianol hydrochloride	5.000
1.320	3	Ephedrine hydrochloride	1.320
8.800	4	Ammonium chloride	8.800
0.800	5	Carbinoxamine maleate	0.800
0.900	6	Methyl paraben	0.900
0.100	7	Propyl paraben	0.100
6.250	8	Balsam, tolu (aqueous extract)	6.250
2.660	9	Saccharin sodium powder dihydrate	2.660
319.220	10	Sucrose (sugar, granulated)	0.320
238.330	11	Glucose liquid (corn syrup)	0.240
83.933	12	Sorbitol solution 70%	0.084
40.000	13	Alcohol (ethanol)	40.000
166.670	14	Dye red	0.160
0.800	15	Flavor	0.800
100.000	16	Propylene glycol	100.000
QS	17	Filter aid HyFlo	0.500
QS	18	Water purified	~450.000 mL

Manufacturing Directions

1. Charge balsam tolu and 25 mL of water in a steam bath.
2. Raise the temperature, stirring continuously, to mix water with balsam. Boil for half an hour and allow decanting while cooling. Discard extracted balsam tolu. Filter the supernatant liquid through filter paper and store apart.
3. Charge 150 mL water in a jacketed mixing tank; heat to boiling.
4. Add and dissolve parabens with mixing. Add and dissolve sugar with constant mixing. Heat to 70°C to 75°C.
5. Once sugar is dissolved, add glucose, sorbitol, and saccharin sodium.
6. Mix well until dissolved.
7. Dissolve ammonium chloride in 28 mL water. Add to mixing tank.
8. Add extract balsam tolu with mixing.
9. Mix well and cool to 25°C to 30°C. Add and dissolve ephedrine, carbinoxamine in 20 mL water and add to mixing tank. Mix well.
10. Add and dissolve chlophedianol in 50 g of propylene glycol and add to mixing tank. Add balance of propylene glycol to mixing tank.
11. Add and dissolve Ipecac fluid extract and flavor raspberry in alcohol. Add to mixing tank. Dissolve dye in 5 mL water; add to tank with continuous mixing.
12. Rinse container with 5 mL of water and add rinsing.
13. Adjust to volume with purified water.
14. Add filter aid HyFlo to syrup and mix well.
15. Recirculate through filter press or equivalent until sparkling clear.

Chloramphenicol Palmitate Oral or Topical Emulsion (2.5% = 250 mg/10 mL)

Formulation

I. Chloramphenicol palmitate, 2.5 g; Lutrol E 400 [1], 4 g; Cremophor RH 40 [1], 4 g
II. Sucrose, crystalline, 40 g; water, 40 g
III. Water, add 100 mL

Manufacturing Directions

1. Mix components I at 70°C to obtain a clear solution.
2. Cool to 40°C and add this solution slowly to the well-stirred solution II.
3. Fill up with III to 100 mL.

Chloramphenicol Palmitate Oral or Topical Emulsion (5% = 500 mg/10 mL)

Formulation

I. Chloramphenicol palmitate, 5 g; Lutrol E400 [1], 6 g; Cremophor RH 40 [1], 4 g
II. Sucrose, crystalline, 40 g; preservative, QS; water, 45 g

Manufacturing Directions

1. Mix components I at 70°C to obtain a clear solution and cool to approximately 40°C.
2. Add the warm solution II slowly to the well-stirred solution I.

Chloramphenicol Opthalmic Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
30.00	1	Chloramphenicol	30.00
150.00	2	Kollidon 25	150.00
QS	3	Preservatives	QS
QS	4	Water purified	QS to 1 L

Manufacturing Directions

1. Charge 90% of item 4 in a stainless steel jacketed vessel and heat to 90°C to 95°C.
2. Add and dissolve preservatives.
3. Add and dissolve item 2.
4. Add and stir item 1 until a clear solution is obtained.
5. Optionally add 0.2% to 0.5% cysteine as antioxidant to prevent discoloration of item 2.

Chloramphenicol Palmitate Oral or Topical Emulsion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
25.00	1	Chloramphenicol palmitate	25.00
40.00	2	Lutrol E 400	40.00
40.00	3	Cremophor RH 40	40.00
400.00	4	Sucrose	400.00
400.00	5	Water purified	400.00
QS	6	Water purified	QS to 1 L

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Chloramphenicol palmitate	50.00
60.00	2	Lutrol E 400	50.00
40.00	3	Cremophor RH 40	40.00
400.00	4	Sucrose	400.00
450.00	5	Water purified	450.00
QS	6	Water purified	QS to 1 L

Manufacturing Directions

1. Charge items 1 to 3 in a suitable stainless steel jacketed vessel. Heat to 70°C to obtain a clear solution.
2. Cool to 40°C.
3. In a separate vessel, add and dissolve items 4 and 5 and then add this solution to step 2.
4. Bring to volume with item 6. Mix.

Chlorhexidine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Chlorhexidine diacetate	20.00
300.00	2	1,2-Propylene glycol (pharma)	300.00
220.00	3	Lutrol F 127	220.00
460.00	4	Water	460.00

Manufacturing Directions

1. Dissolve chlorhexidine diacetate in propylene glycol at >70°C.
2. Stir well and slowly add Lutrol F 127 and water.
3. Maintain the temperature until the air bubbles escape.
4. A clear, colorless gel is obtained.

Chlorpheniramine Maleate Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
2.00	1	Chlorpheniramine maleate	0.40
3000.00	2	Sucrose	600.00
4.50	3	Methyl paraben	0.90
1.50	4	Propyl paraben	0.30
1.00	5	Citric acid (monohydrate)	0.20
2.40	6	Sodium citrate	0.48
2.00	7	Green banana flavor	0.40
–	8	Purified water	QS to 1 L

Manufacturing Directions

1. Add 500 g of purified water to the manufacturing vessel and heat to 95°C to 98°C.
2. Add items 3 and 4 while mixing to dissolve at high speed.
3. Mix for 5 minutes.
4. Add item 2 while mixing at slow speed.
5. Maintain a temperature of 95°C to 98°C.
6. Mix for 1 hour at high speed.
7. Cool down to 30°C while mixing at slow speed.
8. Dissolve items 5 and 6 in 20 g of cooled purified water (25°C).
9. Transfer the solution to the manufacturing vessel while mixing at high speed.
10. Mix for 2 minutes.
11. Add 8 g of cold purified water (25–30°C) in a separate container and dissolve item 1 by using stirrer.
12. Mix for 10 minutes and transfer to the manufacturing vessel.
13. Rinse the container with 2 g of cooled purified water (25°C) and transfer the rinsings to the manufacturing vessel while mixing at high speed.
14. Add item 7 to the manufacturing vessel while mixing.
15. Mix for 10 minutes at high speed.
16. Bring the volume up to 1 L with purified water and finally mix for 15 to 20 minutes at high speed.
17. Check and record the pH (limit: 5.0–5.2 at 25°C).
18. If required, adjust pH with 10% citric acid or 10% sodium citrate solution.
19. Filter the syrup at 1.5 bar.
20. Bubble the syrup with nitrogen gas.

Chloroxylenol Surgical Scrub

Chloroxylenol 3% and cocamidopropyl PG-dimonium chloride phosphate 3%. Inactive ingredients: water, sodium lauryl sulfate, cocamide DEA, propylene glycol, cocamidopropyl betaine, citric acid, tetrasodium EDTA, aloe vera gel, hydrolyzed animal protein, D&C yellow No. 10. In addition, chloroxylenol 5%, terpineol 10%, absolute alcohol 20%, soft potassium soap 8.5%, and caramel 25% and lemon oil QS in a water base.

Ciclopirox Topical Solution

Each gram of Penlac nail lacquer (ciclopirox) topical solution, 8%, contains 80 mg ciclopirox in a solution base consisting of ethyl acetate, isopropyl alcohol, and butyl monoester of poly(methylvinyl ether/maleic acid) in isopropyl alcohol. Ethyl acetate and isopropyl alcohol are solvents that vaporize after application.

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
80.00	1	Ciclopirox	80.00
330.00	2	Ethyl acetate	330.00
300.00	3	Butyl monoester of poly(methylvinyl ether/maleic acid) in isopropyl alcohol (50%)	300.00
QS	4	Isopropyl alcohol	QS to 1 L

Manufacturing Directions

1. Charge item 4 in a suitable stainless steel vessel in an explosion-proof room.
2. Add item 2 and item 3 in a separate vessel, mix, and add to step 1.
3. Add item 1 and mix; seal immediately.

Cimetidine Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L(g)
200.00	1	Cimetidine USE cimetidine hydrochloride	45.80
0.161 mL	2	Alcohol	32.50 mL
5.000	3	Methyl paraben	1.00
1.000	4	Propyl paraben	0.20
20.000	5	Pluronic F68	4.00
0.500 mL	6	Propylene glycol	100.00 mL
20.000	7	Saccharin sodium	4.00
15.000	8	Sodium chloride	3.00
27.000	9	Disodium hydrogen phosphate	5.40
0.500 mL	10	Sorbitol solution 70%	100.00 mL
2.070 g	11	Sucrose	414.00
0.050	11	Yellow dye	0.01
0.0014	12	Flavor	0.28 mL
0.0014	13	Flavor	0.28 mL
2.000	14	Sweetener additional	0.40
QS	15	Water purified	QS to 1 L

Manufacturing Directions

1. Charge items 3 and 4 in a stainless steel vessel and add 70% item 15; heat to 80°C to 90°C to dissolve.
2. In a separate vessel, add and mix items 5 through 11.
3. Add step 2 to step 1.
4. Add and dissolve remaining items and mix.
5. Fill.

Ciprofloxacin Hydrochloride and Hydrocortisone Otic Suspension

Ciprofloxacin hydrochloride and hydrocortisone otic suspension contains the synthetic broad-spectrum antibacterial agent, ciprofloxacin hydrochloride, combined with the anti-inflammatory corticosteroid, hydrocortisone, in a preserved, nonsterile suspension for otic use. Each milliliter contains ciprofloxacin hydrochloride (equivalent to 2 mg ciprofloxacin), 10 mg hydrocortisone, and 9 mg benzyl alcohol as a preservative. The inactive ingredients are polyvinyl alcohol, sodium chloride, sodium acetate, glacial acetic acid, phospholipon 90HB (modified lecithin), polysorbate, and purified water. Sodium hydroxide or hydrochloric acid may be added for adjustment of pH.

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
2.00	1	Ciprofloxacin (use ciprofloxacin hydrochloride)	2.33
10.00	2	Hydrocortisone	10.00
1.00	3	Polysorbate 80	1.00
20.00	4	Polyvinyl alcohol	20.00
1.50	5	Phospholipon 90H (lecithin)	1.50
9.00	6	Benzyl alcohol	9.00
7.00	7	Acetic acid glacial	7.00
4.10	8	Sodium acetate trihydrate	4.10
9.00	9	Sodium chloride	9.00
QS	10	Hydrochloric acid 1 N for pH adjustment	QS
QS	11	Sodium hydroxide 1 N for pH adjustment	QS
QS	12	Water purified	QS to 1 L

Manufacturing Directions

1. Use well-passivated stainless steel vessels; use only sodium vapor lamps or yellow light in the manufacturing area. Avoid forming foam during transfer of liquids.
2. Charge approximately 1 L of item 12 in a suitable vessel and heat to 90°C to 95°C and then cool to 20°C to 25°C under a nitrogen environment and hold for later use for premixing, rinsing, and final volume makeup.
3. To 50% of volume of item 11, add item 4 at 90°C to 95°C.
4. Add and mix item 5 while maintaining nitrogen blanket cover. Cool to 40°C to 50°C.
5. Add and mix item 6 and cool to 20°C to 25°C.
6. In a separate vessel, mix acetic acid, sodium chloride, and sodium acetate trihydrate in approximately 10% of item 12 as prepared in step 1.
7. In a separate vessel, charge item 2 and item 3 and 30% of item 12, mix, and then pass through a micronizing chamber.
8. Add to step 6 and mix well.
9. Add item 1 to in a separate vessel and 20% of item 12 and portions of item 7 and then add to the main batch.
10. Bring to volume.
11. Adjust pH to 4.75 using item 10 or 11 as needed. Fill.

Cisapride Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
5.00	1	Cisapride USE: cisapride monohydrate	1.04
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
1000.00	4	Sucrose	200.00
50.00	5	Microcrystalline cellulose (Avicel RC 591)	10.00
12.50	6	Methylcellulose 4000	2.50
5.00	7	Sodium chloride	1.00
2.50	8	Polysorbate 80 (Tween 80)	0.50
2.50	9	All fruit flavor	0.50
–	10	Water purified	QS to 1 L

Manufacturing Directions

Cisapride dispersion should be uniformity mixed or levigated. Avicel RC-591 and methylcellulose dispersion should be uniform and smooth.

1. Mix item 8 in 100 g of item 10 (35–40°C) in a stainless steel vessel, using stirrer. Add item 1 and mix to make smooth dispersion and keep aside. Check the smoothness of dispersion.
2. Add 185 g of item 10 to a suitable mixer and heat to 90°C to 95°C. Dissolve items 2 and 3 while mixing. Add and dissolve item 4 while mixing.
3. Cool down to approximately 50°C to 55°C.
4. Filter the syrup through T-1500 filter pads (8–10) washed with purified water. Collect the syrup in clean stainless steel tank. Avoid any loss of syrup quantity.
5. Disperse item 6 in 150 g of hot item 10 (70–80°C) in mixer while mixing.
6. Mix and homogenize at temperature 70°C to 80°C, mixer speed 18 rpm, homogenizer high speed, and vacuum 0.4 to 0.6 bar for 5 minutes.
7. Cool down to 25°C to 30°C with continuous mixing. Check the smoothness of dispersion.
8. Disperse item 5 in 250 g of item 10 (25–30°C) in stainless steel vessel, using stirrer. Keep on stirring for 30 minutes to make smooth dispersion. Check the smoothness of dispersion.
9. Transfer syrup mixer. Transfer Avicel mucilage to mixer.
10. Mix at high homogenizer speed and under vacuum for 5 minutes.
11. Dissolve item 7 in 10 g of item 10 and add to mixer while mixing. Add drug dispersion to mixer.
12. Rinse the drug container with 40 g of item 10 and add the rinsing to mixer.
13. Add item 9 to mixer while mixing.
14. Add item 10 up to final volume 1 L.
15. Finally, mix and homogenize for 5 minutes at mixer speed 18 rpm, homogenizer at high speed, vacuum 0.4 to 0.6 bar.
16. Check the suspension for homogeneity. Transfer the suspension through 630-micron sieve to the stainless steel storage tank, previously sanitized.

Citalopram Hydrobromide Oral Solution

Celexa oral solution contains citalopram HBr equivalent to 2 mg/mL citalopram base. It also contains the following inactive ingredients: sorbitol, purified water, propylene glycol, methyl paraben, natural peppermint flavor, and propyl paraben.

Clarithromycin Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/kg (g)
125.00	1	Clarithromycin	35.47
	2	Carbopol 974P	21.28
	3	Polyvinyl pyrrolidone K90	4.96
	4	Water purified	145 mL
	5	Hydroxypropyl methylcellulose phthalate HP-55	43.17
	6	Castor oil	4.56
QS	7	Acetone, approximate	172 mL
QS	8	Ethanol, approximate	164 mL
	9	Potassium sorbate	5.96
	10	Sucrose	600.80
	11	Maltodextrin	67.58
	12	Water purified	10 mL
	13	Xanthan gum	1.08
	14	Flavor dry	10.14
	15	Silicon dioxide	1.42
	16	Citric acid	1.20
	17	Titanium dioxide	10.14
	18	Maltodextrin	13.50
QS	19	Sucrose	QS to 1 kg

Manufacturing Directions

1. This product requires coated clarithromycin granules. Add polyvinyl pyrrolidone to water and mix.
2. Use water to granulate a blend of clarithromycin and Carbopol 974P.
3. Dry granules at 70°C until loss on drying is NMT 5%.
4. Collect fraction between 177 and 420 microns.
5. Regranulate smaller particles to meet the above range.
6. Blend the regranulate in step 5 to step 6.
7. Prepare coating solution by adding ethanol and acetone and hydroxypropyl methylcellulose phthate and castor oil in a mixing vessel; mix until solution is clear.
8. Coat granules in step 6 in a particle coater and dry to loss on drying of NMT 5%.
9. Sift coated granules and retain the fraction between 149 and 590 microns.
10. In a separate vessel, dissolve potassium sorbate in purified water.
11. Blend sucrose and the maltodextrin until a homogenous mix is achieved.
12. Granulate the step 11 mixture with step 10.
13. Dry the granulation until loss on drying is NMT 1%.
14. Mill dried granules and blend.
15. Mix to clarithromycin-coated granules in appropriate quantity, add silicon dioxide, and blend. Fill appropriate quantity.
16. Reconstitute 3.13 g to yield 125 mg/5 mL solution.

Clindamycin Phosphate Topical Solution

Cleocin T topical solution and Cleocin T topical lotion contain clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per milliliter. Cleocin T topical gel contains clindamycin phosphate at a concentration equivalent to 10 mg clindamycin per gram. Each Cleocin T topical solution pledget applicator contains approximately 1 mL of topical solution. Clindamycin phosphate is a water-soluble ester of the semisynthetic antibiotic produced by a 7(S)-chloro-substitution of the 7(R)-hydroxyl group of the parent antibiotic lincomycin. The solution contains isopropyl alcohol 50% v/v, propylene glycol, and water.

Clotrimazole Topical Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
30.00	1	Clotrimazole	30.00
300.00	2	Cremophor RH 40	300.00
QS	3	Preservatives	QS
340.00	4	Alcohol	340.00
330.00	5	Water purified	QS to 1 L

Manufacturing Directions

1. Charge item 1 and 2 in a stainless steel jacketed mixing vessel. Heat to 60°C and mix well.
2. In a separate vessel, charge items 3 to 5 at 90°C and add to step 1.
3. Mix well and fill.

Clotrimazole Topical Solution (3%)

Formulation

I. Clotrimazole, 3 g; Cremophor RH 40, 30 g
II. Preservative, QS; Ethanol 96%, 34 g; Water, 33 g

Manufacturing

Dissolve clotrimazole in Cremophor RH 40 at approximately 60°C, stir strongly, and add slowly the hot solution II.

Codeine Phosphate and Acetaminophen Elixir

Each 5 mL of elixir contains codeine phosphate 12 mg, acetaminophen 120 mg, alcohol 7%, citric acid, propylene glycol, sodium benzoate, saccharin sodium, sucrose, natural and artificial flavors, and FD&C yellow No. 6.

Colistin Sulfate, Neomycin, Thonzonium Bromide, and Hydrocortisone Otic Suspension

Cortisporin-TC otic suspension with neomycin and hydrocortisone (colistin sulfate–neomycin sulfate–thonzonium bromide–hydrocortisone acetate otic suspension) is a sterile aqueous suspension containing in each milliliter: colistin base activity, 3 mg (as the sulfate); neomycin base activity, 3.3 mg (as the sulfate); hydrocortisone acetate, 10 mg (1%); thonzonium bromide, 0.5 mg (0.05%); polysorbate 80, acetic acid, and sodium acetate in a buffered aqueous vehicle. Thimerosal (mercury derivative), 0.002%, is added as a preservative. The suspension is a nonviscous liquid, buffered at pH 5, for instillation into the canal of the external ear or direct application to the affected aural skin.

Cotrimoxazole Oral Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
40.00	1	Trimethoprim micronized (98% particles less than 50 microns)	8.00
200.00	2	Sulfamethoxazole powder (100% particles less than 50 microns)	40.00
20.00	3	Magnesium aluminum silicate (Veegum HV)	4.00
22.50	4	Carboxymethylcellulose sodium	4.50
350.00	5	Glycerin	70.00
400.00	6	Propylene glycol	80.00
5.00	7	Polyvinyl pyrrolidone (polyvinyl pyrrolidone K-30)	1.00
20.00	8	Polysorbate 80	4.00
12.50	9	Colloidal silicon dioxide (Aerosil 200)	2.50
375.00	10	Sorbitol (70% solution)	75.00
5.00	11	Saccharin sodium	1.00
3.00	12	Citric acid	0.60
2200.00	13	Sucrose	440.00
5.00	14	Methyl paraben	1.00
1.50	15	Propyl paraben	0.30
0.035	16	Raspberry red color	0.007
0.025	17	FD&C red No. 40	0.005
5.00	18	Banana flavor	1.00
5.00	19	Apricot flavor	1.00
–	20	Water purified	QS to 1 L

Manufacturing Directions

1. Disperse item 4 in item 5 in a stainless steel vessel, using stirrer. Check that the dispersion is even.
2. Disperse item 3 in the dispersion of items 4 and 5 (sodium CMC-glycerol) at step 1, using stirrer. Check that the final dispersion is even.
3. Add 100 g of hot item 20 (75–85°C) to the dispersion at step 2 while stirring to make the mucilage. Mix for 30 minutes using stirrer.
4. Keep aside the mucilage, for hydration, overnight in a well-closed container.
5. Add item 6 in a stainless steel container and mix items 2 and 1 while mixing using stirrer to make homogenous slurry.
6. Add 100 g of cold item 20 (25–30°C) in a stainless steel container and dissolve item 7 to make a clear solution. Add item 8 while mixing to make a clear solution, then add item 9 while mixing at slow speed.
7. Transfer the mix from step 6 to the slurry of sulpha-trimethoprim step 3 while mixing.
8. Mix for 30 minutes.
9. Add item 10 to the slurry. Mix for 10 minutes.
10. Add 250 g of item 20 in mixer and heat to 90°C to 95°C.
11. Add items 14 and 15 while mixing to dissolve, homogenize at high speed for 2 minutes.
12. Add item 13 to the parabens solution at step 6. Mix well to dissolve completely.
13. Cool down to 30°C.
14. Filter the syrup through T-1500 filters using filter press. (Wash the filters with cooled item 20 approximately 100 mL before use.) Collect the filtered syrup in stainless steel containers.
15. Wash the mixer with item 20.
16. Load items 4 and 3 (CMC-Veegum) mucilage from step 2 to the mixer. Homogenize while mixing for 2 minutes at high speed under vacuum 0.4 to 0.6 bar, mixer speed 20 rpm, temperature 25°C. Check the suspension for uniformity.
17. Load the sulpha-trimethoprim slurry from step 5 to the mixer. Homogenize while mixing for 10 minutes at high speed under vacuum 0.4 to 0.6 bar, mixer speed 20 rpm, temperature 25°C, Check the suspension for uniformity.
18. Transfer the sugar syrup from step 7 to the mixer. Homogenize while mixing for 2 minutes at high speed under vacuum 0.4 to 0.6 bar, mixer speed 20 rpm, temperature 25°C. Check the suspension for uniformity.
19. Dissolve item 12 in 4 g of cooled item 20 and transfer to the mixer while mixing.
20. Dissolve item 11 in 10 g of cooled item 20 and transfer to the mixer while mixing.
21. Dissolve items 16 and 17 and FD&C red No. 40 in 1 g of cooled item 20 and transfer to the mixer while mixing.
22. Mix items 18 and 19 and transfer to the mixer while mixing.
23. Add cold item 20 to make up the volume to 1 L.

24. Set the mixer on high speed, rpm 20, manual mode, vacuum 0.4 to 0.6 bar, temperature 25°C. Mix for 15 minutes.
25. Check and record the pH (limit: 5.5–5.8) at 25°C. If required, adjust pH with 10% citric acid or 10% sodium citrate solution.
26. Transfer the suspension through 630-micron sieve to the stainless steel storage tank, previously sanitized by 70% ethanol.

Cromolyn Sodium Nasal Spray

Each milliliter of NasalCrom nasal spray contains 40 mg of cromolyn sodium in purified water with 0.01% benzalkonium chloride to preserve and 0.01% EDTA to stabilize the solution. Each metered spray releases the same amount of medicine, 5.2 mg cromolyn sodium.

Cromolyn Sodium Oral Concentrate

Each 5-mL ampule of oral concentrate contains 100 mg cromolyn sodium in purified water. It is an unpreserved, colorless solution supplied in a low-density polyethylene plastic unit-dose ampule with 8 ampules per foil pouch.

Crospovidone Oral Suspension (2000 mg/10 mL)

Formulation

Kollidon CL-M [1], 20 g; sorbitol, crystalline [10], 10 g; Kollidon 90F [1], 2 g; Preservatives, QS; Flavor, QS; water, add 100 mL.

Manufacturing Directions

Dissolve sorbitol, Kollidon 90F, the preservatives, and the flavors in the water; add Kollidon CL-M; and homogenize by shaking.

Cyclosporin Oral Solution

Cyclosporine oral solution: Each milliliter contains cyclosporin 100 mg and alcohol 12.5% by volume dissolved in an olive oil, Labrafil M 1944CS (polyoxyethylated oleic glycerides), vehicle that must be further diluted with milk, chocolate milk, or orange juice before oral administration.

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Cyclosporin	100.00
125.00	2	Alcohol	125.00
532.00	3	Olive oil	532.00
242.50	4	Labrafil M 1944CS	242.50

Manufacturing Directions

1. Charge items 2 to 4 in a mixing vessel and stir well.
2. Homogenize step 1.
3. Add item 1 and homogenize again.
4. Fill.

Cyclosporine Soft Gelatin Capsules

Cyclosporine capsules are available in 25- and 100-mg strengths. Each 25- or 100-mg capsule contains cyclosporine 25 mg and alcohol 12.7% by volume. Inactive ingredients: corn oil, gelatin, glycerol, Labrafil M 2125CS (polyoxyethylated glycolysed glycerides), red iron oxide (25- and 100-mg capsule only), sorbitol, titanium dioxide, and other ingredients.

Desmopressin Acetate Nasal Spray

Desmopressin acetate is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin, an antidiuretic hormone affecting renal water conservation. It contains 1.5 mg/mL desmopressin acetate in a pH-adjusted aqueous solution with hydrochloric acid to 4; chlorobutanol (5 mg) and sodium chloride (9 mg) are the inactive ingredients. The compression pump delivers 0.1 mL (150 (μg) of solution per spray; 2.5 mL bottle.

Dexamethasone Elixir

Dexamethasone elixir contains 0.5 mg of dexamethasone in each 5 mL. Benzoic acid, 0.1%, is added as a preservative. It also contains alcohol 5%. Inactive ingredients are FD&C red No. 40, flavors, glycerin, purified water, and sodium saccharin.

Dextromethorphan and Chlorpheniramine Maleate Solution

Bill of Materials			
Scale (mg/mg)	Item	Material Name	Qty/kg (g)
14.70	1	Dextromethorphan base	14.70
2.60	2	Chlorpheniramine maleate	
QS	2	Vehicle (pluronic F 127 55.67%, ethanol 26.55%, and water 17.79%)	QS to 1 kg
3.00	3	Sodium saccharin	3.00
QS	4	Flavors and colors (menthol, eucalyptus oil, tienzoocane)	QS
0.50	5	Monoammonium glycyrrhizinate	0.50

Manufacturing Directions

1. Mill and screen the menthol and tienzoocaine to reduce the product particle size.
2. Add the menthol, benzocaine, sodium saccharin, and monoammonium glycyrrhizinate into a clean vessel.
3. Add eucalyptus oil and ethanol to the vessel.
4. Subsequently, add the poloxamer and water to the vessel. Mix until uniform.

Dextromethorphan, Pseudoephedrine, and Chlorpheniramine Maleate Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
2.00	1	Dextromethorphan hydrobromide	2.00
4.00	2	D-Pseudoephedrine hydrochloride	4.00
0.40	3	Chlorpheniramine maleate	0.40
25.00	4	Sorbitol syrup	25.00
0.20	5	Saccharin sodium	0.20
3.00	6	Hydroxyethyl cellulose (Natrosol®)	3.00
2.50	7	Sodium benzoate	2.50
1.05	8	Banana flavor	1.05
1.10	9	Custard flavor	1.10
1.20	10	Trisodium citrate dihydrate (powder)	1.20
QS	11	Deionized water	QS 1 L

Manufacturing Directions

1. In a suitable stainless steel vessel, combine sorbitol syrup, hydroxyethylcellulose, and deionized water; mix well.
2. Add sodium benzoate and stir again for 5 minutes.
3. After obtaining a clear solution, stir the hydroxyethyl cellulose suspension, rinse the container with deionized water, and transfer the rinsings to the vessel.
4. Heat the vessel to 40°C to 50°C and stir the mix for 1 hour.
5. After 1 hour, a clear gel without lumps is obtained.
6. Dilute the gel with sorbitol syrup and cool to 30°C.
7. In a separate vessel, add deionized water and heat while stirring to 50°C.
8. After reaching this temperature, dissolve, in this order, dextromethorphan hydrobromide, chlorpheniramine maleate, and pseudoephedrine hydrochloride and saccharin sodium.
9. Cool the solution to 25°C.
10. In a suitable stainless steel container, add deionized water and while stirring dissolve trisodium citrate under 0.6 bar vacuum and high speed.
11. Transfer the active substance solution to the syrup vehicle.
12. Rinse the vessel twice with deionized water.
13. Add while stirring (low) the custard and banana flavors.
14. Mix for 10 minutes.
15. Then, while stirring, add the solution from step above; keep stirring for 15 minutes at moderate speed.
16. Stop stirring and check pH (5.9–6.2); adjust with 10% trisodium citrate solution; after each addition, where necessary, stir for 5 minutes before recording pH again.
17. Finally, make up the volume with deionized water and stir once more for 15 minutes under vacuum (0.6 bar) at moderate speed.
18. Stop stirring and remove vacuum; check final volume once more.
19. Filter the clear syrup under compressed air pressure, first through a filter of 330-μm and then through a 20-μm filter of propylene type.

Dextromethorphan Liquid

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
22.00	1	Dextromethorphan base	22.00
QS	2	Vehicle (pluronic 33.56%, ethanol 10.51%, water 13.42%, propylene glycol 42.51%)[a]	QS to 1 L
1.00	3	Sodium metabisulfite	1.00
1.00	4	Disodium EDTA	1.00
4.00	5	Sodium saccharin	4.00
1.50	6	Monoammonium glycyrrhizinate	1.50
5.00	7	Acesulfame	5.00
14.00	8	Flavor	14.00

[a]Alternate vehicle composition: pluronic F 27 29.08%, ethanol 10.51%, water 24.61%, propylene glycol 35.80%. Second alternate vehicle: pluronic F127 40.27%, ethanol 10.51%, water 13.42%, propylene glycol 35.80%.

Manufacturing Directions

1. Add propylene glycol and poloxamer to a clean vessel (main mix).
2. While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer.
3. Once a uniform solution is obtained, remove from heat source and continue mixing.
4. In a separate vessel (alcohol premix), add alcohol, dextromethorphan base, and monoammonium glycyrrhizinate and mix until uniform.
5. In another vessel (water premix), add water, EDTA, sodium saccharin, acesulfame, and sodium metabisulfite. Mix until all materials are dissolved.
6. Add the alcohol containing premix to the main mixing vessel containing the poloxamer.
7. Mix until uniform.
8. While stirring, add the water containing premix to the main vessel and continue to mix until uniform.
9. Add desired flavor component and mix until uniform.
10. The preparation has a viscosity of approximately 0.67 Pa seconds and a triggered viscosity ratio at a 50% dilution with water of 10.5. If using alternate vehicle composition (above), the preparation has a viscosity of approximately 0.97 Pa seconds and a triggered viscosity ratio at a 50% dilution with water of 4.95. If using the second alternate vehicle, the preparation has a viscosity of approximately 2.14 Pa seconds and a triggered viscosity ratio at a 50% dilution.

Dextromethorphan Liquid

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
QS	1	Vehicle (pluraflo 1220 40.90%, ethanol 10.22%, propylene glycol 46.83%, anhydrous glycerin 2.05%)	QS to 1 L
22.00	2	Dextromethorphan base	22.00
QS	3	Flavors	QS

Manufacturing Directions

1. Weigh the dextomethophan into a clean vessel, add the ethanol, and begin mixing.
2. Add propylene glycol and mix until uniform and clear.
3. Add pluraflo and mix. Add glycerin and mix until uniform.
4. Add desired flavor component and mix until uniform.

Dextromethorphan, Pseudoephedrine, and Chlorpheniramine Maleate Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
20.00	1	Dextromethorphan hydrobromide	20.00
40.00	2	D-Pseudoephedrine hydrochloride	40.00
4.00	3	Chlorpheniramine maleate	4.00
250.00	4	Sorbitol syrup	250.00
2.00	5	Saccharin sodium	2.00
30.00	6	Hydroxyethyl cellulose (Natrosol HHY)	30.00
25.00	7	Sodium benzoate	25.00
10.50	8	Banana flavor	10.50
11.00	9	Custard flavor	11.00
12.00	10	Trisodium citrate dihydrate powder	12.00
QS	11	Water purified	QS

Manufacturing Directions

1. In a suitable vessel, add sorbitol syrup and hydroxyethylcellulose and purified water; mix well.
2. Add sodium benzoate and stir again for 5 minutes.
3. After obtaining clear solution, put under stirring hydroxyethyl cellulose suspension, rinse the container with purified water, and transfer the rinsing to the vessel.
4. Heat the vessel to 40°C to 50°C and keep the mix stirring for 1 hour.
5. After 1 hour, a clear gel without lumps is obtained.
6. The gel is then diluted with sorbitol syrup and cooled to 30°C.
7. In a separate vessel, add purified water and heat under stirring to 50°C.
8. After reaching this temperature, dissolve sequentially dextromethorphan hydrobromide, chlorpheniramine maleate and pseudoephedrine hydrochloride, and saccharin sodium.
9. Cool the solution to 25°C.
10. In a suitable stainless steel container, add purified water and under stirring dissolve trisodium citrate under 00.6 bar and high speed.
11. The active substance solution from step 10 is transferred to the syrup vehicle.
12. The vessel is rinsed twice with purified water.
13. In the larger vessel, add under stirring (low) the custard flavor and banana flavor and mix for 10 minutes.
14. Then, under stirring, add the solution from step 13; keep stirring for 15 minutes at moderate speed.
15. Stop stirring and check pH (5.9–6.2); adjust with 10% trisodium citrate solution; after each addition, where necessary, stir for 5 minutes before recording pH again.
16. Finally, make up the volume with purified water and stir once more for 15 minutes under vacuum (−0.6 bar) moderate speed. Stop stirring and vacuum; check final volume once more.
17. Clear syrup is filtered under compressed air pressure first through a filter of 330 microns and then through a 20-micron filter of propylene type.

Dextromethorphan Solution

Bill of Materials			
Scale mg/mg	Item	Material Name	Qty/kg (g)
14.70	1	Dextromethorphan base	14.70
QS	2	Vehicle (pluronic F 127 55.51%, ethanol 26.48%, and water 18.01%)	QS to 1 kg
3.00	3	Sodium saccharin	3.00
QS	4	Flavors and colors	QS
0.50	5	Monoammonium glycyrrhizinate	0.50

Manufacturing Directions

1. Add the dextromethorphan base, sodium saccharin, and monoammonium glycyrrhizinate into a clean vessel.
2. Add ethanol and then the poloxamer and water. Mix until clear and uniform.
3. Good pourable formula.

Dextrose, Levulose, and Phosphoric Acid Solution

Emetrol is an oral solution containing balanced amounts of dextrose (glucose) and levulose (fructose) and phosphoric acid with controlled hydrogen ion concentration. Available in original lemon-mint or cherry flavor. Each 5-mL teaspoonful contains dextrose (glucose), 1.87 g; levulose (fructose), 1.87 g; phosphoric acid, 21.5 mg; glycerin; methyl paraben; purified water; and D&C yellow No. 10 and natural lemon-mint flavor in lemon-mint Emetrol and FD&C red No. 40 and artificial cherry flavor in cherry Emetrol.

Diazepam Rectal Solution

Bill of Materials			
Scale (mg/2.5 mL)	Item	Material Name	Qty/L (g)
10.00	1	Diazepam	4.00
2.50	2	Benzoic acid	1.00
250.00	3	Alcohol	100.00
1000.00	4	Propylene glycol	400.00
122.50	5	Sodium benzoate	49.00
37.50	6	Benzyl alcohol	19.00
QS	7	Water purified	QS to 1 L

Manufacturing Directions

1. Dissolve benzoic acid in absolute alcohol previously warmed to 35°C.
2. Add diazepam to step 1, stir to dissolve.
3. Separately mix together polypropylene glycol and benzyl alcohol.
4. Separately dissolve sodium benzoate in one-fourth quantity of purified water and filter through a 0.6-μm millipore filter.
5. Under heavy stirring, mix together steps 2 and 3.
6. Bring to volume with water under stirring and filter through a 0.22-μ millipore filter.
7. Fill solution into rectal tubes; fill volume 2.9 mL.

Diclofenac Oral Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
15.00	1	Diclofenac sodium	15.00
25.00	2	Kollidon 30	24.00
5.00	3	Cremophor RH 40	5.00
400.00	4	Sucrose crystalline	400.00
QS	5	Water purified	QS to 1 L

Manufacturing Directions

1. Dissolve items 2 to 5 in a suitable stainless steel vessel.
2. Add item 1 and dissolve.
3. Fill.

Didanosine for Oral Solution

Videx buffered powder for oral solution is supplied for oral administration in single-dose packets containing 100, 167, or 250 mg of didanosine. Packets of each product strength also contain a citrate–phosphate buffer (composed of dibasic sodium phosphate, sodium citrate, and citric acid) and sucrose.

Digoxin Capsules

Digoxin is one of the cardiac (or digitalis) glycosides, a closely related group of drugs having in common specific effects on the myocardium. These drugs are found in a number of plants. Digoxin is extracted from the leaves of *Digitalis lanata*. The term "digitalis" is used to designate the whole group of glycosides. The glycosides are composed of two portions: a sugar and a cardenolide (hence "glycosides"). The capsule is a stable solution of digoxin enclosed within a soft gelatin capsule for oral use. Each capsule contains the labeled amount of digoxin dissolved in a solvent comprising polyethylene glycol 400, 8% ethyl alcohol, propylene glycol, and purified water. Inactive ingredients in the capsule shell include FD&C red No. 40 (0.05-mg capsule), D&C yellow No. 10 (0.1- and 0.2-mg capsules), FD&C blue No. 1 (0.2-mg capsule), gelatin, glycerin, methyl paraben and propyl paraben (added as preservatives), purified water, and sorbitol. Capsules are printed with edible ink.

Digoxin Elixir Pediatric

This is a stable solution of digoxin specially formulated for oral use in infants and children. Each milliliter contains 50 μg (0.05 mg) digoxin. The lime-flavored elixir contains the inactive ingredients alcohol 10%, methyl paraben 0.1% (added as a preservative), citric acid, D&C green No. 5, D&C yellow No. 10, flavor, propylene glycol, sodium phosphate, and sucrose. Each package is supplied with a specially calibrated dropper to facilitate the administration of accurate dosage even in premature infants. Starting at 0.2 mL, this 1-mL dropper is marked in divisions of 0.1 mL, each corresponding to 5 μg (0.005 mg) digoxin.

Dihydroergotamine Mesylate Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
2.00	1	Dihydroergotamine mesylate, 10% excess	2.20
153.00	2	Glycerin	153.00
48.25	3	Alcohol	48.25
QS	4	Methanesulfonic acid	QS
QS	5	Sodium hydroxide	QS
QS	6	Water purified	QS to 1 L
QS	7	Nitrogen gas	QS

Manufacturing Directions

The product is highly susceptible to oxidation and should be manufactured until continuous bubbling and cover of nitrogen; the oxygen level should be below 10 ppm at all times; nitrogen gas used should filtered through a 0.45-micron membrane filter; also, protect product from light; all tubing used for transferring product should be of stainless steel, Teflon, or silicon.

1. Heat sufficient quantity of item 6 to 95°C and hold for 1 hour. Begin bubbling nitrogen for 1 hour, cool slowly to 22°C while continuing to bubble nitrogen.
2. In another suitable glass-lined or stainless steel container, charge glycerin.
3. In another stainless steel container, charge alcohol and bubble it with nitrogen for more than 2 hours.
4. Check oxygen levels in step 1 to less than 1 ppm.
5. Flush a suitable tank with nitrogen and transfer approximately 700 mL of purified water from step above and begin bubbling nitrogen.
6. Add approximately 40 mL of purified water from step 4 to step 2 and bubble nitrogen again for 1 hour; do not discontinue bubbling throughout manufacturing process.
7. Weigh the alcohol container above, add 49 g of alcohol to water in step above, stir.
8. Dilute approximately 0.03 mL of methanesulfonic acid with purified water to make a 20% solution; measure and adjust pH to 3.25.
9. Add item 1 to batch and stir until completely dissolved.
10. Add glycerin/water mixture to the batch and adjust volume to 995 mL.
11. Dissolve 4 g of sodium hydroxide in 100 mL purified water and use this solution to adjust pH of step 10 to 3.75; stir for 1 minute and recirculate for at least 5 minutes.
12. Adjust the volume to 1 L with item 6.
13. Filter through 0.22-micron filter previously sterilized and fill in presterilized amber-colored bottle with nitrogen flushing.

Diphenhydramine and Ammonium Chloride Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
131.50	1	Ammonium chloride	26.30
15.00	2	Caramel	5.00
11.00	3	Citric acid	2.20
13.50	4	Diphenhydramine hydrochloride	2.70
200.00	5	Alcohol	40.00
318.00	6	Glycerin	63.60
1.10	7	Menthol	0.22
5.00	8	Flavor	1.00
9.80	9	Saccharin sodium	1.96
12.00	10	Sodium benzoate	2.40
2750.00	11	Sugar	550.00
QS	12	Water purified	QS to 1 L

Manufacturing Directions

1. Charge one-half of item 12 in a suitable stainless steel mixing vessel, heat to 90°C to 95°C, and add and mix item 11. Mix for 1 hour at 90°C to 95°C.
2. Cool to room temperature.
3. In separate vessels, charge 100 mL of item 12 in each and mix items 3, 4, or 10 separately. Then mix them all together and stir well.
4. Add item 6 to step 2 and mix well.
5. In 100 mL of water, dissolve item 4 and add to step 4.
6. Dissolve item 2 in 100 mL of water and add to step 5.
7. In a separate vessel, charge item 5 and add and mix items 7 and 8.
8. Add step 7 into step 6 and make up volume.

Diphenhydramine Hydrochloride Liquid

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
12.50	1	Diphenhydramine hydrochloride	2.50
1000.00	2	Lycasin 80/55	200.00
12.00	3	Sodium benzoate	2.40
4.40	4	Citric acid monohydrate	0.88
7.60	5	Sodium citrate	1.52
5.00	6	Saccharin sodium	1.00
250.00	7	Propylene glycol	50.00
1.25	8	Menthol	2.50
5.00	9	Flavor	1.00
QS	10	Water purified	QS to 1 L

Manufacturing Directions

1. Charge 600 mL of item 10 in a stainless steel vessel and bring to boil, cool to 40°C to 50°C.
2. Add and mix items 2 to 4 and stir to dissolve; mix for another 10 minutes.
3. In a separate vessel, charge 100 mL of item 10 and add and mix item 6.
4. In a separate vessel, charge 100 mL of item 10 and add and mix item 1. Add to step 1.
5. Add steps 2 and 3 to step 1 and mix well.
6. Add item 2 and mix again.
7. In a separate vessel, add and mix item 7 to 9. Add to step 6 and make up volume.
8. Fill.

Dornase-Alpha Inhalation Solution

Each Pulmozyme single-use ampule will deliver 2.5 mL of the solution to the nebulizer bowl. The aqueous solution contains 1.0 mg/mL dornase alfa, 0.15 mg/mL calcium chloride dihydrate, and 8.77 mg/mL sodium chloride. The solution contains no preservative. The nominal pH of the solution is 6.3.

Doxercalciferol Capsules

Doxercalciferol, the active ingredient in Hectorol, is a synthetic vitamin D analog that undergoes metabolic activation in vivo to form 1(alpha),25-dihydroxyvitamin D_2 (1(alpha),25-$(OH)_2$D2), a naturally occurring biologically active form of vitamin D_2. Hectorol is available as soft gelatin capsules containing 2.5 μg doxercalciferol. Each capsule also contains fractionated triglyceride of coconut oil, ethanol, and butylated hydroxyanisole. The capsule shells contain gelatin, glycerin, titanium dioxide, and D&C yellow No. 10.

Dyphylline, Guaifenesin Elixir

Each 15 mL (one tablespoonful) of elixir contains dyphylline 100 mg, guaifenesin 100 mg, alcohol (by volume) 17%, citric acid, FD&C yellow No. 6, flavor (artificial), purified water, saccharin sodium, sodium citrate, and sucrose.

Electrolyte Lavage Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
60.00	1	Polyethylene glycol 3350	60.00
1.46	2	Sodium chloride	1.46
0.75	3	Potassium chloride	0.75
1.68	4	Sodium bicarbonate	1.68
5.68	5	Sodium sulfate	5.68
0.81	6	Flavor	0.81

Manufacturing Directions

The values given above pertain to solution on reconstitution of one flavor pack. When dissolved in sufficient water to make 4 L, the final solution contains 125 mEq/L sodium, 10 mEq/L potassium, 20 mEq/L bicarbonate, 80 mEq/L sulfate, 35 mEq/L chloride, and 18 mEq/L polyethylene glycol 3350. The reconstituted solution is isoosmotic and has a mild, salty taste. Colyte flavor packs are available in citrus berry, lemon lime, cherry, and pineapple. This preparation can be used without the Colyte flavor packs and is administered orally or via a nasogastric tube. Each citrus berry flavor pack (3.22 g) contains hydroxypropyl methylcellulose 2910, citrus berry powder, saccharin sodium, and colloidal silicon dioxide. Each lemon lime flavor pack (3.22 g) contains lemon-lime NTA powder, hydroxypropyl methylcellulose 2910, Prosweet® powder natural, saccharin sodium, and colloidal silicon dioxide. Each cherry flavor pack (3.22 g) contains hydroxypropyl methylcellulose 2910, artificial cherry powder, saccharin sodium, and colloidal silicon dioxide. Each pineapple flavor pack (3.22 g) contains hydroxypropyl methylcellulose 2910, pineapple flavor powder, Magnasweet, saccharin sodium, and colloidal silicon dioxide.

Eplerenone Solution

Bill of Materials			
Scale (mg/L) or mL/L	Item	Material Name	Quantity mg or mL/L
2.50 mg	1	Eplerenone	2.50 mg/L
200 mL	2	Ethanol	200 mL
100 mL	3	Propylene glycol	100 mL
100 mL	4	Glycerol 70%	100 mL
QS	5	Water	QS

Erythromycin Drops

Bill of Materials			
Scale (mg/2.5 mL)	Item	Material Name	Qty/kg (g)
	1	Sodium carboxymethyl cellulose	0.41
	2	Dye red FD&C No. 3	0.13
	3	Sucrose	796.81
	4	Sodium citrate dihydrate	52.60
	5	Sodium carboxy methyl cellulose	13.10
	6	Magnesium aluminum silicate type IB Veegum F	7.90
	7	Water purified	66 mL
100.00	8	Erythromycin USE erythromycin ethylsuccinate citrate, washed (850 μg/mg)	123.50
	9	Flavor	3.94

Manufacturing Directions

Erythromycin ethylsuccinate (item 9) is factored in based on the potency used in the Bill of Materials. Excess of up to 5% erythromycin may be included. The weight of sugar (item 3) is adjusted to compensate for potency variation and excess of the erythromycin ethylsuccinate to maintain the standard quantity at 1000 g.

1. Dissolve the sodium carboxymethylcellulose (item 1) and the dye (if used) in 50 mL hot purified water. Stir until the sodium carboxymethylcellulose is completely in solution. Allow to cool before using.
2. Screen the sucrose through a 2-mm aperture screen into a mixer.
3. Mill the remaining ingredients, with the exception of the flavor, through a 1-B band (1.27-mm aperture or similar) or 0 band (686 micron aperture or similar) with impact forward at high speed, or screen through a 840-micron aperture screen.
4. Load the milled or screened ingredients into the mixer with the screened sucrose and dry blend for not less than 5 minutes.
5. Mass with the solution from step 1 and QS using purified water, if necessary. Mixer must not be stopped and the sides must be scraped down several times during the massing operation to minimize the presence of white particles in the final granulation. Do not allow massed granules to stand.
6. Screen the wet mass through a 16-mm aperture mesh (hammer mill) or a 4-mm aperture screen (oscillating granulator) and spread evenly onto trays.
7. Dry granules in an oven at between 49°C and 55°C to NMT 1.0% loss on drying (15 minutes Brabender, or equivalent, at 105°C), or loss on drying at 60°C at 5 mm of mercury for 3 hours.
8. Screen the cooled, dried granules through a 1.19-mm aperture screen and grind coarse through 2-AA band (1.98-mm aperture, or similar), medium speed, knives forward, or screen through a 1.4-mm aperture screen on an oscillating granulator. Protect granules from excessive exposure to moisture.
9. Screen the flavor through a 600-micron aperture screen with an equal portion of granulation.
10. Fill into suitable approved bottles at the theoretical fill weight.

Erythromycin Topical Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
500.00	1	Polyethylene glycol 400	100.00
20.00	2	Erythromycin, USE erythromycin base, 15% excess	25.55
0.32	3	Acetone	65.40 mL
77% (v/v)	4	Alcohol	840.00 mL
QS	5	Nitrogen gas	QS

Manufacturing Directions

Product is sensitive to moisture. Every effort should be made to avoid exposure or incorporation of moisture into the product because the stability of the final product is affected. Check mixing tank to make sure it is clean and dry. Mixing tank must be purged with nitrogen gas, as directed, at the start of and during manufacture to replace most of the air in the mixing tank and to reduce the possibility of fire or explosion if there should be a spark.

Transfer and filling hose lines must be approved for use with solvents.

1. Charge polyethylene glycol 400 to a suitable nitrogen-purged tank; keep nitrogen cover and purging on.
2. Add and mix acetone.
3. Add item 2 (quantity adjusted for potency) and mix.
4. Turn the agitator, sample, and adjust volume.

Estradiol Nasal Spray

Charge 2.6 g of estradiol into a pressure-addition vessel and dissolve with stirring in 405.6 g of ethanol in which 0.26 g of oleic acid has previously been dissolved. After sealing and evacuation thereof, 6.7 kg of HFA 134a that has previously been aerated with carbon dioxide and adjusted to a pressure of at most 6.5 bar (20°C) in another pressure-addition vessel is added with stirring. The formulation obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Ethchlorvynol Gelatin Capsule (200 mg)

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 capsules (g)
200.00	1	Ethchlorvynol	200.00
150.00	2	Polyethylene glycol 400	150.00
211.00	3	Gelatin colored opaque	211.00
–	4	Acetone, approximate[a]	86.00

[a]Used for cleaning purposes only and not present in final product.

Manufacturing Directions

Polyethylene glycol should be weighed into clean, dry, light-resistant containers and sealed under nitrogen protection. Bulk container should be flushed with nitrogen and resealed.

1. Mix ethchlorvynol, polyethylene glycol 400, and glycerin (if used) in an open stainless steel drum until uniform.
2. Cover with loose-fitting polyethylene cover, permitting gas to escape. Fumes will discolor metal. Retest if held for more than 1 month before encapsulating.
3. Mix gelatin to uniform consistency with minimal introduction of air. Encapsulate using the drug mixture into 1000 capsules using gelatin mass red opaque and 6.6-m size die roll.
4. Dry 3 days in a drying room at 20°C to 22°C and 22% to 33% relative humidity or lower.
5. Inspect and remove culls. Optionally, wash with acetone or rinse twice with methylene chloride if used in place of acetone.
6. Finishing: Fill.

Eucalyptus and Mint Emulsion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
427.50	1	Distilled water	427.50
375.00	2	Eucalyptamint	375.00
70.00	3	Sodium stearoyl lactylate (Pationic® SSL)	70.00
35.00	4	PEG-20 hydrogenated lanolin (Supersat ANS4)	35.00
17.50	5	Ritasynt IP	17.50
80.00	6	Cetearyl alcohol, polysorbate 60, PEG-15 stearate, and steareth-20 (Ritachol 1000)	80.00

Manufacturing Directions

1. Heat item 1 to 71°C.
2. Combine rest of the ingredients in another container and heat to 71°C.
3. Slowly add water at 71°C and mix for 1 hour.
4. Cool the mixture to 35°C to 45°C and fill.

Eucalyptol Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
80.00	1	Eucalyptol	80.00
40.00	2	Cremophor RH 40	40.00
QS	3	Preservative	QS
QS	4	Water	QS to 1 L

Manufacturing Directions

Mix eucalyptol and Cremophor at 65°C, stir well, and slowly add the warm solution of item 3 to produce a clear or slightly opalescent, colorless liquid.

Eucalyptol Solution (8%)

Formulation

I. Eucalyptol, 8 g; Cremophor RH 40 [1], 4 g;
II. Preservative, QS; water, add 100 mL

Manufacturing Directions

Mix eucalyptol and Cremophor at 65°C, stir well, and add slowly the warm solution II.

Fentanyl Citrate Nasal Spray

1. Charge 2.6 g of fentanyl citrate into a pressure addition vessel and dissolve with stirring in 405.6 g of ethanol in which 0.26 g of oleic acid has previously been dissolved.
2. After sealing and evacuation thereof, 6.7 kg of HFA 134a, which has previously been aerated with carbon dioxide and adjusted to a pressure of at most 6.5 bar (20°C) in another pressure addition vessel, is added with stirring.
3. The formulation obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Ferrous Sulfate Oral Solution

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
75.00[a]	1	Ferrous sulfate	125.00
294.00	2	Sucrose	490.00
147.00	3	Maltitol solution (Lycasin 80/55)	245.00
0.30	4	Citric acid (monohydrate)	0.50
0.90	5	Citric acid (monohydrate)	1.50
0.060	6	FD&C yellow No. 6 (sunset yellow FCF)	1.00
3.120	7	Guarana flavor 12144–33	5.20
0.33	8	Potassium sorbate	0.55
0.30	9	Saccharin sodium	0.50
–	10	Water purified	QS to 1 L

[a]Equivalent to 15 mg iron (Fe).

Manufacturing Directions

Bubble nitrogen throughout the process. Check and record pH of item 10 (limit: 5.0–6.5).

1. Collect 166.67 g of item 10 in mixer.
2. Heat to 90°C to 95°C for 10 minutes.
3. Add item 8. Stir to dissolve to a clear solution.
4. Add item 2. Stir to dissolve to a clear solution.
5. Add item 3. Stir for 10 minutes and cool to 30°C to 35°C.
6. Dissolve item 4 in 10 g of item 10 (30–35°C) and add to first step.
7. Dissolve item 9 in 10 g of item 10 (30–35°C) and add to first step.
8. Dissolve item 5 in 273.33 g of item 10 (30–35°C). Then add item 1 to the clear solution and dissolve slowly without aeration.
9. Add to mixer at first step.
10. Dissolve item 6 in 10 g of item 10 (25–30°C) and add to first step.
11. Add item 7 to first step. Mix at low speed for 10 minutes.
12. Make volume up to 1 L with item 10.
13. Check and record pH. Target pH: 2.20 (limit: between 1.95 and 5.15).
14. Filter the drops with recirculation.
15. Transfer the filtered drops in storage vessel under nitrogen blanket.
16. Use nitrogen blanket in the tank throughout the storage and filling period.

Ferrous Sulfate Oral Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
200.000[a]	1	Ferrous sulfate	40.000
3350.000	2	Sucrose	670.000
750.000	3	Maltitol solution (Lycasin 80/55)	150.000
4.166	4	Citric acid (monohydrate)	833.200
8.334	5	Citric acid (monohydrate)	1.667
0.500	6	Color	0.100
15.500	7	Flavor	3.100
–	8	Water purified	QS to 1 L

[a]Equivalent to 40 mg elemental iron.

Manufacturing Directions

Bubble nitrogen throughout the process.

1. Heat 300 g of item 8 to 95°C.
2. Add item 2 while stirring at low speed.
3. Dissolve to clear solution by stirring at 95°C.
4. Add item 3. Stir at low speed and cool to 25°C to 30°C.
5. Dissolve item 4 in 17 g of item 8 and add to first step.
6. Dissolve item 5 in 180 g of item 8 in a separate stainless steel container. Then add item 1 to the clear solution and dissolve slowly without aeration.
7. Add to first step.
8. Dissolve item 6 in 16 g of item 8 and add to first step.
9. Add item 7 to first step. Mix at low speed for 10 minutes.
10. Make volume up to 1 L with item 8. Check and record pH (limit: between 2 and 5). Filter the syrup at 1.5 bar.
11. Recirculate approximately 100 to 150 mL of syrup.
12. Use nitrogen blanket in the tank throughout the storage period.

Fluconazole Oral Suspension

Diflucan for oral suspension contains 350 or 1400 mg of fluconazole and the following inactive ingredients: sucrose, sodium citrate dihydrate, citric acid anhydrous, sodium benzoate, titanium dioxide, colloidal silicon dioxide, xanthan gum, and natural orange flavor. After reconstitution with 24 mL of distilled water or purified water, each milliliter of reconstituted suspension contains 10 or 40 mg of fluconazole.

Flunisolide Spray

Nasarel is a metered-dose manual-pump spray unit containing 0.025% w/w flunisolide in an aqueous medium containing benzalkonium chloride, butylated hydroxytoluene, citric acid, EDTA, polyethylene glycol 400, polysorbate 20, propylene glycol, sodium citrate dihydrate, sorbitol, and purified water. Sodium hydroxide or hydrochloric acid may be added to adjust the pH to approximately 5.2. It contains no fluorocarbons. Each 25-mL spray bottle contains 6.25 mg of flunisolide.

Fluocinonide Topical Solution

Lidex topical solution contains fluocinonide 0.5 mg/mL in a solution of alcohol (35%), citric acid, diisopropyl adipate, and propylene glycol. In this formulation, the active ingredient is totally in solution.

Fluorouracil Solution

Efudex solution consists of 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris(hydroxymethyl)aminomethane, hydroxypropylcellulose, parabens (methyl and propyl), and disodium edetate.

Fluorouracil Topical Solution

Fluoroplex 1% topical solution contains fluorouracil 1%, propylene glycol, sodium hydroxide or hydrochloric acid to adjust the pH, and purified water.

Fluticasone Suspension Spray

Manufacturing Directions

1. 2 g of fluticasone propionate and 0.02 g delta-tocopherol are weighed into a pressure-addition vessel.
2. After sealing and evacuation of the addition vessel, 1.5 kg of HFA 134a that has previously been aerated with carbon dioxide and adjusted to a pressure of 4.5 bar (20°C) in another pressure addition vessel is added with stirring.
3. The suspension obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Furosemide Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
5.00	1	Furosemide, 5% excess	1.05
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
1500.00	4	Sorbitol 70%	300.00
500.00	5	Glycerin	100.00
500.00	6	Propylene glycol	100.00
0.50	7	FD&C yellow No. 6	0.10
2.50	8	Orange flavor	0.50
QS	9	Sodium hydroxide	0.44
QS	10	Water purified	QS to 1 L

Manufacturing Directions

1. Charge 20% of item 10 to a suitable stainless steel jacketed vessel.
2. Add items 2 and 3 and heat to 90°C to 95°C to dissolve. Cool to 40°C after complete dissolution.
3. In a separate vessel, charge items 4, 5, and 6 and mix well.
4. Dissolve item 9 in a portion of item 10 in a separate vessel.
5. Add item 1 to step 4 and mix well.
6. In a separate vessel, dissolve item 7 in a portion of item 10.
7. Add to step 6.
8. Add step 2 to step 7.
9. Add item 8 and mix well.
10. Fill.

Ferrous Sulfate Oral Solution

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
75.00	1	Ferrous sulfate[a]	125.00
294.00	2X	Sucrose	490.00
147.00	3	Maltitol solution (Lycasin® 80/55)	245.00
0.30	4	Citric acid (monohydrate)	0.50
0.90	5	Citric acid (monohydrate)	1.50
0.06	6	FD&C yellow dye No. 6 (sunset yellow FCF)	1.00
3.12	7	Guarana flavor 12144–33	5.20
0.33	8	Potassium sorbate	0.55
0.30	9	Saccharin sodium	0.50
–	10	Purified water	QS to 1 L

[a]Equivalent to 15 mg iron (Fe).

Manufacturing Directions

1. Bubble nitrogen throughout the process.
2. Check and record pH of the purified water (limit: 5.0–6.5).
3. Collect 166.67 g of purified water in mixer.
4. Heat to 90°C to 95°C for 10 minutes.
5. Add item 8 and stir to dissolve to a clear solution.
6. Add item 2 and stir to dissolve to a clear solution.
7. Add item 3 and stir for 10 minutes and cool to 30°C to 35°C.
8. Dissolve item 4 in 10 g of purified water (30–35°C) and add to first step.
9. Dissolve item 9 in 10 g of purified water (30–35°C) and add to first step.
10. Dissolve item 5 in 273.33 g of purified water (30–35°C).
11. Then add item 1 to the clear solution and dissolve slowly without aeration.
12. Add to mixer.
13. Dissolve item 6 in 10 g of purified water (25–30°C) and add to first step.
14. Add item 7 to first step.
15. Mix at low speed for 10 minutes.
16. Bring volume up to 1 L with purified water.
17. Check and record pH (target: 2.2, limit: 1.95–5.15).
18. Filter the drops with recirculation.
19. Transfer the filtered drops to a storage vessel under an N_2 blanket.
20. Use the nitrogen blanket in the tank throughout the storage and filling period.

Ferrous Sulfate Oral Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
200.00	1	Ferrous sulfate[a]	40.00
3350.00	2	Sucrose	670.00
750.00	3	Maltitol solution (Lycasin® 80/55)	150.00
4.16	4	Citric acid (monohydrate)	833.20
8.33	5	Citric acid (monohydrate)	1.66
0.50	6	Color	0.10
15.50	7	Flavor	3.10
–	8	Purified water	QS to 1 L

[a]Equivalent to 40 mg elemental iron.

Manufacturing Directions

1. Bubble nitrogen throughout the process.
2. Heat 300 g of purified water to 95°C.
3. Add item 2 while stirring at low speed.
4. Dissolve to clear solution by stirring at 95°C.
5. Add item 3.
6. Stir at low speed and cool to 25°C to 30°C.
7. Dissolve item 4 in 17 g of item 8 and add to the first step.
8. Dissolve item 5 in 180 g of purified water in a separate stainless steel container.
9. Then add item 1 to the clear solution and dissolve slowly without aeration.
10. Add to first step.
11. Dissolve item 6 in 16 g of purified water and add to the first step.
12. Add item 7 to the first step.
13. Mix at low speed for 10 minutes.
14. Bring volume up to 1 L with purified water.
15. Check and record pH (limit: 2–5).
16. Filter the syrup at 1.5 bar.
17. Recirculate approximately 100 to 150 mL of syrup.
18. Use a nitrogen blanket in the tank throughout the storage period.

Fir Needle Oil Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
30.00	1	Fir needle oil (Frey & Lau)	30.00
50.00	2	Camphora	50.00
60.00	3	Cremophor RH 40	60.00
403.00	4	Ethanol (96%)	403.00
457.00	5	Water	457.00

Manufacturing Directions

1. Mix the active ingredients with Cremophor RH 40 and heat to 50°C to 60°C.
2. Add the ethanol to the well-stirred solution, then slowly add the warm water to produce a clear or slightly opalescent liquid.
3. The amount of Cremophor RH 40 required depends on the type of fir needle oil.

Foot Bath

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
200.00	1	Polysorbate 20	200.00
2.50	2	Menthol	2.50
10.00	3	α-Bisabolol	10.00
20.00	4	Disodium undecylenamido MEA-sulfosuccinate	20.00
20.00	5	Perfume (menthol compatible)	20.00
QS	6	Deionized water	QS to 1 L
QS	7	Preservative, color	QS

Manufacturing Directions

1. Predissolve menthol, alpha-bisabolol, and perfume in Polysorbate 20.
2. Add mixture to the water phase while stirring.
3. Stir until homogeneous and then fill.

Gabapentin Oral Solution

Gabapentin solution contains 250 mg/5 mL of gabapentin. The inactive ingredients for the oral solution are glycerin, xylitol, purified water, and artificial cool strawberry anise flavor.

Galantamine Hydrobromide Oral Solution

Reminyl is available as a 4 mg/mL galantamine hydrobromide oral solution. The inactive ingredients for this solution are methyl parahydroxybenzoate, propylparahydroxybenzoate, sodium saccharin, sodium hydroxide, and purified water.

Glucose, Fructose, and Phosphoric Acid Antiemetic Solution

Emetrol is an oral solution containing balanced amounts of dextrose (glucose) and levulose (fructose) and phosphoric acid with controlled hydrogen ion concentration. Available in original lemon-mint or cherry flavor. Each 5-mL teaspoonful contains dextrose (glucose), 1.87 g; levulose (fructose), 1.87 g; phosphoric acid, 21.5 mg; glycerin; methyl paraben; purified water; D&C yellow No. 10; and natural lemon-mint flavor in lemon-mint Emetrol and FD&C red No. 40 and artificial cherry flavor in cherry Emetrol.

Glycol Foam, Nonaqueous

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Polawax A31	4.00
710.00	2	Propylene glycol	71.00
150.00	3	Ethanol DEB100	15.00

Manufacturing Directions

1. Dissolve Polawax in propylene glycol/ethanol.
2. Pack into containers and pressurize.
3. Ethanol may be omitted if desired.
4. In aerosol pack, 90% concentrate and 10% propellant 12/114 may be used.
5. Propylene glycol is a suitable vehicle for glycol-soluble medicaments.
6. The above formulation provides a mousse for such a system.

Gramicidin Opthalmic Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
130.00	1	Gramicidin	130.00
1.00	2	Cremophor RH 40	1.00
10.00	3	Alcohol	10.00
QS	4	Preservatives	QS
QS	5	Water purified	QS to 1 L

Manufacturing Directions

1. Charge items 1 and 2 in a suitable mixing and jacketed vessel; heat to 65°C and mix.
2. Cool to room temperature.
3. In a separate vessel, add and mix items 3 to 5.
4. Add to step 2. Mix and fill.

Guaifenesin, Pseudoephedrine, Carbinoxamine, and Chlophedianol Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
20.00	1	Guaifenesin	20.00
400.00	2	Sucrose	400.00
240.00	3	Glucose liquid	240.00
120.00	4	Sorbitol solution	120.00
3.00	5	Saccharin sodium powder dihydrate	3.00
2.50	6	Sodium benzoate powder	2.50
30.00	7	Pseudoephedrine hydrochloride	30.00
1.00	8	Carbinoxamine maleate	1.00
6.60	9	Chlophedianol hydrochloride	6.60
105.00	10	Dye red E123 (Amaranth)	105.00 mg
3.75	11	Dye blue FD&C No. 1	3.75 mg
QS	12	Acid hydrochloric	QS
50.00	13	Menthol crystals	50.0 mg
2.75	14	Flavors	2.75
65.00	15	Oil orange terpeneless No. 54125	65.00 mg
5.66	16	Alcohol 190 proof (10% ex)	5.66
0.52 g	17	Filter aid HyFlo	0.52
420.00 g	18	Water purified, distilled approximate	420.00

Manufacturing Directions

1. Charge 260 mL purified water into a suitable tank.
2. Begin heating water to 70°C to 80°C while adding guaifenesin and sucrose with stirring.
3. Continue stirring to dissolve ingredients.
4. Remove heat and add glucose liquid and sorbitol to solution from step 3 with stirring.
5. Add saccharin sodium, sodium benzoate, pseudoephedrine hydrochloride, carbinoxamine maleate, and chlophedianol hydrochloride to solution from step 4. Stir well to dissolve all ingredients.
6. Dissolve dye red E123 and FD&C No. 1 in 10 mL warm, purified water.
7. Add dye solution to solution from step 6 with stirring. Cool solution to 30°C to 35°C.
8. QS to 975 mL using purified water and mix well.
9. Adjust to pH 4.25 (range 4.0–4.5) with hydrochloric acid (ca. 0.65 g/L of drops).
10. Stir well after each addition of acid. Dissolve menthol, flavors, and orange oil in alcohol; add mixture to solution from step above with good stirring.
11. Stir the solution slowly for 2 hours.
12. Allow to stand overnight to cool and remove entrapped air.
13. QS to 1 L with purified water and stir well.
14. Add filter aid HyFlo to solution and mix well.
15. Recirculate through filter press or equivalent until sparkling clean.

Guaifenesin Pseudoephedrine, Carbinoxamine, and Chlophedianol Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
20.00	1	Guaifenesin	20.000
400.00	2	Sucrose	400.000
240.00	3	Glucose liquid	240.000
120.00	4	Sorbitol solution	120.000
3.00	5	Saccharin sodium	3.000
2.50	6	Sodium benzoate (powder)	2.500
30.00	7	Pseudoephedrine hydrochloride	30.000
1.00	8	Carbinoxamine maleate	1.000
6.60	9	Chlophedianol hydrochloride	6.600
105.00	10	Dye red E123 (Amaranth)	0.105
3.75	11	Dye blue FD&C No. 1	3.750 mg
QS	12	Acid, hydrochloric	QS
50.00	13	Menthol crystals	50.000 mg
2.75	14	Flavors	2.750
65.00	15	Orange oil terpeneless	65.000 mg
5.66	16	Alcohol (190 proof)	5.664
GS	17	HyFlo filter aid	0.526
QS	18	Purified water	~420.000

Manufacturing Directions

1. Charge 260 mL purified water into a suitable tank.
2. Begin heating water to 70°C to 80°C while adding guaifenesin and sucrose with stirring.
3. Continue stirring to dissolve ingredients.
4. Remove heat, add glucose liquid and sorbitol to solution from step above with stirring.
5. Add saccharin sodium, sodium benzoate, pseudoephedrine hydrochloride, carbinoxamine maleate, and chlophedianol hydrochloride to solution from preceding step.
6. Stir well to dissolve all ingredients.
7. Dissolve dye red E123 and dye blue FD&C No. 1 in 10 mL warm purified water.
8. Add dye solution to solution from preceding step with stirring.
9. Cool solution to 30°C to 35°C.
10. QS to 975 mL using purified water, mix well.
11. Adjust to pH 4.25 (range: 4.0–4.5) with hydrochloric acid (~0.65 g/L of drops).
12. Stir well after each addition of acid.
13. Dissolve menthol, flavors, and orange oil in alcohol; add mixture to solution from previous step with good stirring.
14. Stir the solution slowly for 2 hours.
15. Allow to stand overnight to cool and remove entrapped air.
16. QS to 1 L with purified water and stir well.
17. Add HyFlo filter aid to solution and mix well.
18. Recirculate through filter press or equivalent until sparkling clean.

Haloperidol Oral Liquid

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
2.00	1	Haloperidol	2.00
11.00	2	Lactic acid	11.00
0.20	3	Propyl paraben	0.20
1.90	4	Methyl paraben	1.90
QS	5	Sodium hydroxide for pH adjustment, approximate	0.24
QS	6	Water purified, approximate	990.00 mL
QS	7	Nitrogen gas	QS
QS	8	Lactic acid	QS

Manufacturing Directions

1. Charge approximately 700 mL of water into a suitable mixing tank. Add and dissolve lactic acid with stirring; while mixing, add haloperidol. Mix until complete solution (approximately 15 minutes).
2. Charge 240 mL of water into a separate container and heat to boiling. Add and dissolve methyl and propyl parabens. Mix until complete solution. Add this solution to step 1 solution.
3. Check pH. If necessary, adjust to pH 2.75 (range: 2.5–3.0) with 2% sodium hydroxide. Continue mixing for 10 minutes after addition of sodium hydroxide. Record pH and amount of sodium hydroxide added. Lactic acid (No. 8) may also be used to adjust pH.
4. QS to 1 L with water and mix well.
5. Filter solution through 8-micron membrane filter (or similar) into a suitable container, under nitrogen protection.
6. Fill under nitrogen.

Heparin Nasal Spray

Charge 5 g of heparin into a pressure-addition vessel and suspend with stirring 50 g of ethanol in which 0.25 g of lecithin have previously been dissolved. After sealing and evacuation thereof, 1.5 kg of HFA 227 that has previously been aerated with carbon dioxide and adjusted to a pressure of 4.5 bar (20°C) in another pressure addition vessel is added with stirring and homogenized. The suspension obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Hydrocodone Bitartrate Elixir

Each 5 mL contains hydrocodone bitartrate 2.5 mg, acetaminophen 167 mg, and 7% alcohol. In addition, the liquid contains the following inactive ingredients: citric acid anhydrous, ethyl maltol, glycerin, methyl paraben, propylene glycol, propyl paraben, purified water, saccharin sodium, sorbitol solution, sucrose, and D&C yellow No. 10 and FD&C yellow No. 6 as coloring and natural and artificial flavoring.

Hydrocodone Polistirex Extended-Release Suspension

Each teaspoonful (5 mL) of Tussionex Pennkinetic extended-release suspension contains hydrocodone polistirex equivalent to 10 mg of hydrocodone bitartrate and chlorpheniramine polistirex equivalent to 8 mg of chlorpheniramine maleate Tussionex. Inactive ingredients: ascorbic acid, D&C yellow No. 10, ethylcellulose, FD&C yellow No. 6, flavor, high fructose corn syrup, methyl paraben, polyethylene glycol 3350, polysorbate 80, pregelatinized starch, propylene glycol, propyl paraben, purified water, sucrose, vegetable oil, and xanthan gum.

Hydromorphone Hydrochloride Oral Liquid

Hydromorphone hydrochloride, a hydrogenated ketone of morphine, is a narcotic analgesic. Each 5 mL (one teaspoon) contains 5 mg of hydromorphone hydrochloride. In addition, other ingredients include purified water, methylparaben, propyl paraben, sucrose, and glycerin. It may contain traces of sodium bisulfite.

Hydroxyzine Pamoate Oral Suspension

Hydroxyzine pamoate 25 mg/5 mL; inert ingredients for the oral suspension formulation are carboxymethylcellulose sodium, lemon flavor, propylene glycol, sorbic acid, sorbitol solution, and water.

Hyoscine Butylbromide Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
5.00	1	Hyoscine butylbromide	1.00
3300.00	2	Sugar	660.00
5.00	3	Methyl paraben	1.00
1.50	4	Propyl paraben	0.30
962.50	5	Sorbitol 70%	19.30
10.00	6	Sodium saccharin	2.00
35.00	7	Sodium chloride	7.00
0.70	8	Citric acid monohydrate	0.14
0.75	9	Sodium citrate	0.15
10.00	10	Flavor	2.00
5.00	11	Flavor	1.00
5.00	12	Flavor	1.00
QS	13	Water purified	QS to 1 L

Manufacturing Directions

1. In a suitable stainless steel container, charge 300 mL item 13 and heat to 90° to 95°C.
2. Add and dissolve items 3 and 4.
3. Add item 2 and dissolve.
4. Add item 5 and dissolve. Cool to room temperature
5. In 10 mL item 13, add and dissolve items 6 and 7 and add to step 4.
6. In 10 mL item 13, add and dissolve item 8 and add to step 4.
7. In 10 mL item 13, add and dissolve item 7 and add to step 4.
8. In 20 mL item 13, add and dissolve item 1 and add to step 4.
9. Add flavors.
10. Make up volume and fill.

Hyoscyamine Sulfate Elixir

Levsin elixir contains 0.125 mg hyoscyamine sulfate per 5 mL with 20% alcohol for oral administration. Levsin elixir also contains, as inactive ingredients, FD&C red No. 40, FD&C yellow No. 6, flavor, glycerin, purified water, sorbitol solution, and sucrose.

Ibuprofen Topical Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
QS	1	Vehicle (pluronic P105 63.16%, ethanol 18.95%, water 17.89%)	QS to 1 L
50.00	2	Ibuprofen	50.00

Manufacturing Directions

1. Screen the ibuprofen to reduce the particle size.
2. Add the ibuprofen into a clean vessel.
3. Add ethanol to the vessel.
4. Subsequently add the poloxamer and water to the vessel.
5. Mix until uniform.

Ibuprofen Pediatric Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
100.00	1	Ibuprofen, low-density[a]	20.00
3000.00	2	Sucrose	600.00
10.00	3	Sodium benzoate	2.00
5.00	4	Saccharin sodium	1.00
5.00	5	Edetate disodium (sodium EDTA)	1.00
500.00	6	Glycerin (glycerol)	100.00
500.00	7	Sorbitol (70% solution)	100.00
10.00	8	Xanthan gum (Keltrol-F)	2.00
20.00	9	Microcrystalline cellulose (Avicel™ RC591)	4.00
5.00	10	Polysorbate 80 (Tween 80)	1.00
8.50	11	Citric acid	1.70
1.35	12	FD&C red No. 40	0.27
7.50	13	Mixed fruits flavor	1.50
5.00	14	Strawberry flavor	1.00
QS	15	Purified water	QS to 1 L

[a]Meets USP criteria with the following additional requirements: 100% particle size below 50 μm and tapped density of 0.3 to 0.4 g/mL.

Manufacturing Directions

1. Heat 302 g of item 15 to 90°C and dissolve item 2 while mixing in mixer.
2. Cool to approximately 50°C.
3. Add items 3, 5, 4, 11, and 7 to mixer while mixing and dissolve.
4. Filter the syrup through Seitz Supra 2600 filters in clean stainless steel tank.
5. In a clean stainless steel vessel, dissolve item 10 in 35 g of item 15 (40°C).
6. Add item 1 slowly while mixing with stirrer.
7. Mix for 30 minutes to make uniform dispersion. *Caution*: Avoid excessive foaming.
8. Disperse items 8 and 9 in item 6 in a clean and dry stainless steel container using stirrer.
9. Add 75 g of hot item 15 (70–90°C) at once while mixing.
10. Mix for 20 minutes to make a homogeneous smooth mucilage.
11. Add approximately 500 g syrup, ibuprofen dispersion, and mucilage to the mixer.
12. Rinse the containers of ibuprofen dispersion and mucilage with 50 g of item 15 (40°C).
13. Add the rinsings to the mixer.
14. Set the mixer: temperature, 25°C; speed, 18 rpm; and manual mode vacuum at 0.5 bar.
15. Mix for 3 minutes at low homogenizer speed.
16. Mix for 2 minutes at homogenizer high speed. Check the suspension for uniformity of dispersion.
17. Homogenize for additional 3 minutes at high speed, if required.
18. Add the balance of the syrup (approximately 507.6 g) from previous step to the mixer.
19. In a separate container, dissolve item 12 in 6 g of cooled item 15 (40°C) and transfer to the mixer.
20. Add items 13 and 14 to the mixer.
21. Set the mixer: temperature, 25°C; speed, 18 rpm; manual mode vacuum at 0.5 bar.
22. Mix for 15 minutes.
23. Mix for 5 minutes at homogenizer low speed.
24. Mix for 5 minutes at homogenizer high speed.
25. Check the suspension for uniformity.
26. Adjust the final volume to 1 L by using purified water.

Iron Infant Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.18	1	Propyl paraben	0.18
0.022	2	Methyl paraben	0.02
1000.00	3	Sorbitol solution	1.00 kg
4.00	4	Citric acid (hydrous powder)	4.00
125.00	5	Iron sulfate	125.00
0.106	6	Sodium metabisulfite	0.10
0.50	7	Guarana flavor (artificial)	0.50
20.00	8	Alcohol (ethanol)	900.14
0.14	9	Dye	0.14
QS	9	Sodium hydroxide	QS
QS	10	Citric acid (powder)	1 QS
QS	11	Purified water	QS to 1 L
QS	12	HyFlo filter aid	1.00
QS	13	Liquid nitrogen	QS
QS	14	Carbon dioxide gas	QS

Manufacturing Directions

The product is susceptible to oxidation. No effort should be spared to protect it from atmospheric air. Maintain CO_2 or nitrogen atmosphere where indicated. The product must be manufactured and held in a glass-lined or stainless steel tank. Product waiting to be filled should either be in a closed tank with a CO_2 atmosphere or in an open tank covered with polyethylene sheeting taped tightly with a constant slow stream of CO_2 gas flowing into the tank headspace. Avoid vortex formation throughout processing.

1. Charge 144 mL of purified water into a mixing tank.
2. Heat to 95°C to 100°C and add parabens with strong agitation.
3. Add sorbitol solution and citric acid (item 4) while mixing.
4. Bring solution to 90°C while mixing.
5. Cool the solution while mixing to 60°C to 65°C and hold at this temperature with CO_2 or nitrogen gas bubbling into it.
6. CO_2 gas protection is continued for the remainder of the manufacturing process.
7. Add ferrous sulfate and dissolve while mixing, holding at 60°C to 65°C.
8. Cool to 25°C with mixing.
9. Add sodium metabisulfite and dissolve while mixing.
10. Avoid vortex formation.
11. Dissolve dye in 2 mL of freshly boiled purified water and add to the tank. Mix.
12. Dissolve the guarana flavor in alcohol, add to the tank, and mix.
13. Check pH (range: 1.8–2.2). Adjust if necessary, with a solution of 10% sodium hydroxide or a solution of 10% citric acid.
14. Make up to volume with freshly boiled purified water and mix.
15. Readjust to volume if necessary with freshly boiled purified water and mix.
16. Add HyFlo filter aid and mix. Filter through press until clear.
17. Bubble CO_2 or nitrogen gas into the clear filtrate for 5 minutes, then seal tank and hold product under CO_2 or nitrogen protection.

Iron Polystyrene and Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
125.00	1	Glycerin	125.00
1.40	2	Methyl paraben	1.40
0.16	3	Propyl paraben	0.16
79.61	4	Sorbitol; use sorbitol solution	364.33
3.30	5	Xanthan gum	3.30
10.00	6	Sucrose (granulated)	100.00
0.20	7	Saccharin (insoluble)	2.00
105.00	8	Elemental iron; use iron polystyrene sulfonate	530.31
50.00	9	Ascorbic acid, USP (35% excess)	61.95
0.10	10	Flavor	1.00 mL
0.10	11	Flavor (artificial guarana)	1.00 mL
QS	12	Sodium hydroxide	12. 1.0
QS	13	Dye	2.00
9.50	14	Distilled purified water	~95.00 mL
10.00	15	Sorbitol solution	~10.00

Manufacturing Directions

1. Add glycerin (item 1) to the tank.
2. Commence heating with agitation.
3. Add and disperse parabens.
4. Continue heating to 70°C to 80°C and mix until solution is complete.
5. Force cool to 30°C, then add and disperse xanthan gum (item 5).
6. Add sorbitol solution (item 4) and 80 mL of purified water (item 14) and heat with mixing to 60°C to 70°C until the xanthan gum is fully dissolved.
7. Add and disperse saccharin and sugar (items 6 and 7).
8. Mix at 60°C to 70°C until dispersion is complete.
9. Force cool to 25°C to 30°C with continuous mixing.
10. Commence N_2 gas protection and maintain for the remainder of the manufacturing process.
11. Add and disperse ascorbic acid.
12. Continue mixing for 30 minutes at 25°C to 30°C.
13. *Note*: Use suitable SS high-powered stirrer.
14. Mix the iron polystyrene sulfonate milled slurry in the original epoxy-lined drums under N_2 gas protection until uniform.
15. Add the slurry to the main batch and mix for 30 minutes at 25°C to 30°C.
16. *Note*: Avoid scraping the epoxy lining of the steel drum while mixing and use a plastic or rubber scraper to assist in complete transfer of the mixed slurry. Add and disperse the flavors. Mix well.
17. Check and record pH. Adjust pH using a 20% sodium hydroxide solution (1 g in 5 mL water) to a value of 3 (range: 2.8–3.2).
18. Dissolve the dye in 5 to 7 mL of water at 40°C to 45°C by stirring for 10 minutes.
19. Add this solution to the main batch through a 420-μm screen with mixing.
20. Rinse container with 2 to 3 mL water at 40°C to 45°C and add to bulk through a 420-μm screen.
21. Continue to mix under vacuum until mixture is uniform.
22. Pass the suspension through the colloid mill at a gap setting of 100 to 150 μm.
23. Adjust the flow rate such that the temperature rise of the suspension does not exceed 10°C.
24. Collect the milled suspension in a stainless steel jacketed tank with vacuum.
25. Mix at 25°C to 30°C under vacuum until a uniform suspension is achieved.
26. Flush the bulk suspension with nitrogen and seal.
27. Hold at 25°C to 30°C.

Ibuprofen Pediatric Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
100.00	1	Ibuprofen low density (100% particle size below 50 microns, tapped density is 0.3–0.4 g/mL)	20.00
3000.00	2	Sucrose	600.00
10.00	3	Sodium benzoate	2.00
5.00	4	Saccharin sodium	1.00
5.00	5	Edetate disodium (sodium EDTA)	1.00
500.00	6	Glycerin (glycerol)	100.00
500.00	7	Sorbitol (70% solution)	100.00
10.00	8	Xanthan gum (Keltrol-F)	2.00
20.00	9	Microcrystalline cellulose (Avicel RC 591)	4.00
5.00	10	Polysorbate 80 (Tween 80)	1.00
8.50	11	Citric acid	1.70
1.35	12	FD&C red No. 40	0.27
7.50	13	Mixed fruits flavor	1.50
5.00	14	Strawberry flavor	1.00
–	15	Water purified	QS to 1 L

Manufacturing Directions

1. Heat 302 g of item 15 to 90°C and dissolve item 2 while mixing in mixer.
2. Cool to approximately 50°C.
3. Add items 3, 5, 4, 7, and 11 to mixer while mixing and dissolve.
4. Filter the syrup through Seitz Supra 2600 filters in clean stainless steel tank.
5. In a clean stainless steel vessel, dissolve item 10 in 35 g of item 15 (40°C).
6. Add item 1 slowly while mixing with stirrer.
7. Mix for 30 minutes to make uniform dispersion. Avoid excessive foaming.
8. Disperse items 8 and 9 in item 6 in a clean and dry stainless steel container using stirrer. Add 75 g of hot item 15 (70–90°C) at once while mixing.
9. Mix for 20 minutes to make homogeneous smooth mucilage.
10. Add approximately 500 g syrup, ibuprofen dispersion, and mucilage to the mixer.
11. Rinse the containers of ibuprofen dispersion and mucilage with 50 g of item 15 (40°C).
12. Add the rinsings to the mixer. Set the mixer: temperature, 25°C; mixer speed, 18 rpm; manual mode vacuum, 0.5 bar.
13. Mix for 3 minutes at low homogenizer speed.
14. Mix for 2 minutes at homogenizer high speed. Check the suspension for uniformity of dispersion.
15. Homogenize for additional 3 minutes at high speed, if required.
16. Add the balance syrup approximately 507.6 g from step above to the mixer.
17. In a separate container, dissolve item 12 in 6 g of cooled item 15 (40°C) and transfer to the mixer.
18. Add the items 13 and 14 to the mixer. Set the mixer: temperature, 25°C; mixer speed, 18 rpm; manual mode vacuum, 0.5 bar. Mix for 15 minutes.
19. Mix for 5 minutes at homogenizer low speed.
20. Mix for 5 minutes at homogenizer high speed.
21. Check the suspension for uniformity.
22. Adjust the final volume to 1 L by using purified water.

Ibuprofen Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
20.00	1	Ibuprofen	20.00
200.00	2	Cremophor RH 40	200.00
QS	3	Preservatives	QS
QS	4	Water purified	QS to 1 L

Manufacturing Directions

1. In a suitable stainless steel jacketed vessel, add and suspend item 1 in item 2 by heating it to 60°C.
2. In a separate vessel, add items 3 and 4 and heat to 90°C to 95°C to dissolve preservatives and add to step 1.
3. Mix and fill.

Ibuprofen Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
40.00	1	Ibuprofen	40.00
250.00	2	Sucrose	250.00
80.00	3	Kollidon CL-M	80.00
20.00	4	Kollidon 90F	20.00
20.00	5	Sodium citrate	20.00
QS	6	Water purified	QS to 1 L

Manufacturing Directions

1. Charge items 2 and 4 to 6 (40%) in a suitable mixer.
2. Add and suspend item 3.
3. Add and disperse item 1. Homogenize if necessary.
4. Bring to volume with item 6. Mix and fill.

Ibuprofen Suspension, Sugar Free

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
40.00	1	Ibuprofen	40.00
10.00	2	Cremophor RH 40	100.00
50.00	3	Lutron F 68	50.00
QS	4	Preservatives	QS
QS	5	Water purified	QS to 1 L

Manufacturing Directions

1. Dissolve Lutrol F 68 and the preservatives in purified water.
2. In a separate vessel, add and mix items 1 and 2.
3. Add to step 1.
4. Homogenize if necessary.
5. Bring to volume with item 5. Mix and fill.

Ibuprofen and Domperidone Maleate Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
200.00	1	Ibuprofen	40.00
20.00	2	Domperidone maleate	4.00
2.50	3	Colloidal cellulose	0.50
15.00	4	Glycerin	3.00
10.00	5	Sorbitol	2.00
1.00	6	Kaolin	0.20
1.00	7	Polysorbate 80	0.20
QS	8	Water	QS

Manufacturing Directions

1. Item 7 is added to the water followed by the addition of glycerin with stirring.
2. The domperidone and ibuprofen are then added and also the colloidal cellulose, sorbitol, and kaolin (as thickeners) with continued stirring until a satisfactory suspension is formed.

Insulin Inhalation Spray

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Insulin	10.00
9.00	2	Brij 98	9.00
10.00	3	Sodium lauryl sulfate	10.00
200.00	4	Alcohol, anhydrous	200.00
QS	5	HFA 134a (1,1,1,2-tetrafluoroethane)	QS to 1 L

Manufacturing Directions

1. Weigh insulin in a clean glass container and dissolve in acid buffer and titrate to a pH of 7 with Tris buffer.
2. Add Brij 98 and sodium lauryl sulfate to the insulin solution to form a homogenous solution.
3. Lyophilize and suspend dried particles in a nonaqueous suspension medium of ethanol and then charge with hydrofluoroalkane (HFA) 134a.
4. Fill the formulation in a pressure-resistant container fitted with a metering valve.

Ipratropium Bromide Inhalation Solution

Atrovent inhalation solution is administered by oral inhalation with the aid of a nebulizer. It contains ipratropium bromide 0.02% (anhydrous basis) in a sterile, isotonic saline solution, pH adjusted to 3.4 (3–4) with hydrochloric acid.

Ipratropium Bromide Nasal Spray

Atrovent (ipratropium bromide) nasal spray 0.03% is a metered-dose manual-pump spray unit that delivers 21 μg (70 μL) ipratropium bromide per spray on an anhydrous basis in an isotonic, aqueous solution with pH adjusted to 4.7. It also contains benzalkonium chloride, EDTA, sodium chloride, sodium hydroxide, hydrochloric acid, and purified water. Each bottle contains 165 or 345 sprays.

Manufacturing Directions

1. 2.25 g of micronized ipratropium bromide and 11.25 g of micronized salbutamol are weighed into a pressure-addition vessel.
2. After sealing and evacuation thereof, 10.5 kg of HFA 227 that has previously been aerated with carbon dioxide and adjusted to a pressure of 6.25 bar (20°C) in another pressure addition vessel is added.
3. After homogenization of this mixture, the suspension obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Iron Polystyrene and Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
125.00	1	Glycerin	125.000
1.40	2	Methyl paraben	1.400
0.16	3	Propyl paraben	0.160
79.61	4	Sorbitol solution	364.330
3.30	5	Xanthan gum	3.300
10.00	6	Sucrose	100.000
0.20	7	Saccharin	2.000
105.00	8	Elemental iron USE iron polystyrene sulfonate	530.310
50.00	9	Acid ascorbic, 35% excess	61.950
0.10 v/v	10	Flavor	1.000 mL
0.10 v/v	11	Flavor guarana artificial	1.000 mL
QS	12	Sodium hydroxide	12. 1.0
QS	13	Dye	2.000
9.50	14	Water purified	95.000 mL
10.00	15	Sorbitol solution, approximate	10.000

Manufacturing Directions

1. Add glycerin (item 1) to the tank. Commence heating with agitation.
2. Add and disperse parabens. Continue heating to 70°C to 80°C and mix until solution is complete.
3. Force cool to 30°C then add and disperse xanthan gum (item 5).
4. Add sorbitol solution (item 4) and 80 mL of purified water (item 14) and heat with mixing to 60°C to 70°C until the xanthan gum is fully dissolved.
5. Add and disperse saccharin and sugar (items 7 and 6).
6. Mix at 60°C to 70°C until dispersion is complete.
7. Force cool to 25°C to 30°C with continuous mixing.
8. Commence N_2 gas protection and maintain for the remainder of the manufacturing process.
9. Add and disperse ascorbic acid. Continue mixing for 30 minutes at 25°C to 30°C. Use suitable stainless steel high-powered stirrer.
10. Mix the iron polystyrene sulfonate milled slurry, in the original epoxy lined drums, under N_2 gas protection until uniform.
11. Add the slurry to the main batch and mix for 30 minutes at 25°C to 30°C. Avoid scraping the epoxy lining of the steel drum while mixing and use a plastic or rubber scraper to assist in complete transfer of the mixed slurry.
12. Add and disperse the flavors. Mix well.
13. Check and record pH. Adjust pH using a 20% sodium hydroxide solution (1 g in 5 mL water) to a pH of 3 (range: 2.8–3.2).
14. Dissolve the dye in 5 to 7 mL of water at 40°C to 45°C by stirring for 10 minutes.
15. Add this solution to the main batch through a 420-micron aperture screen with mixing.
16. Rinse container with 2 to 3 mL water at 40°C to 45°C and add to bulk through a 420-micron screen.
17. Continue to mix under vacuum until uniform.
18. Pass suspension through the colloid mill at a gap setting of 100 to 150 micrometers.
19. Adjust flow rate such that the temperature rise of the suspension does not exceed 10°C.
20. Collect the milled suspension in a stainless steel-jacketed tank with vacuum. Mix at 25°C to 30°C under vacuum until a uniform suspension is achieved.
21. Flush the bulk suspension with N_2 and seal. Hold at 25°C to 30°C.

Isoproterenol Sulfate and Calcium Iodide Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
1.569	1	Glucose liquid	311.60
269.500	2	Glycerin	53.90
150.000	3	Calcium iodide anhydrous, USE calcium iodide solution 27%	111.11
5.000	4	Ascorbic acid	1.00
2.428	5	Sucrose	485.30
4.000	6	Saccharin sodium	0.80
5.000	7	Sodium cyclamate	1.00
6.550	8	Flavor honey	1.31
1.660	9	Flavor mint	0.33
0.260	10	Alcohol 190 proof	51.53
3.000	11	Isoproterenol sulfate	0.60
0.250	12	Dye yellow	0.05
1.250	13	Caramel	0.25
QS	14	Water purified	QS to 1 L

Manufacturing Directions

1. Charge in a stainless steel tank items 1, 2, 5, 6, 7, 10 and 90% of item 14. Mix well; heat if necessary.
2. In a separate vessel, add and dissolve items 4, 8, 9, 12, and 13 in item 14; mix well and add to step 1.
3. Add remaining items, mix, bring to volume. Fill.

Isotretinoin Capsules

Isotretinoin, a retinoid, is available in 10-, 20-, and 40-soft gelatin capsules for oral administration. Each capsule also contains beeswax, butylated hydroxyanisole, EDTA, hydrogenated soybean oil flakes, hydrogenated vegetable oil, and soybean oil. Gelatin capsules contain glycerin and parabens (methyl and propyl), with the following dye systems: 10 mg, iron oxide (red) and titanium dioxide; 20 mg, FD&C red No. 3, FD&C blue No. 1, and titanium dioxide; 40 mg, FD&C yellow No. 6, D&C yellow No. 10, and titanium dioxide. Chemically, isotretinoin is 13-cis-retinoic acid and is related to both retinoic acid and retinol (vitamin A). It is a yellow-orange to orange crystalline powder with a molecular weight of 300.44.

Itraconazole Oral Solution

Itraconazole oral solution contains 10 mg of itraconazole per milliliter, solubilized by hydroxypropyl-(beta)-cyclo-dextrin (400 mg/mL) as a molecular inclusion complex. The solution is clear and yellowish in color with a target pH of 2. Other ingredients are hydrochloric acid, propylene glycol, purified water, sodium hydroxide, sodium saccharin, sorbitol, cherry flavor 1, cherry flavor 2, and caramel flavor.

Kaolin, Pectin, and Aluminum Hydroxide Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
147.600	1	Sodium methyl paraben	4.92
6.720	2	Sodium propyl paraben	224.00
36.000	3	Magnesium aluminum silicate type IA	1.20
5832.000	4	Kaolin (powder)	194.40
130.000	5	Pectin	4.33
120.000	6	Sodium CMC (premium, low-viscosity)	4.00
210.000	7	Cyclamate calcium	7.00
21.00	8	Saccharin calcium (powder)	0.70
15.375	9	Flavor	0.51
1.234	10	Flavor	41.13
QS	11	Distilled purified water (approx.)	QS
QS	12	Citric acid (anhydrous powder)	QS
QS	13	Water purified, distilled	QS
QS	14	Acid citric anhydrous powder	QS
63.300	15	Aluminum hydroxide	12.72

Manufacturing Directions

1. Charge 600 mL of water into a suitable jacketed mixing tank.
2. Add methyl paraben and propyl paraben to the tank and heat to 90°C to 95°C.
3. Cool to 70°C, add the magnesium aluminum silicate, and mix for 30 minutes or until evenly dispersed.
4. Hold temperature at 70°C.
5. Add kaolin with constant mixing at 70°C until evenly dispersed.
6. Add pectin and mix for 2 hours, maintaining the temperature of 70°C.
7. Add sodium CMC premium low viscosity and mix for at least 30 minutes, maintaining the temperature at 70°C. Cool to 60°C and hold at this temperature.
8. Add aluminum hydroxide gel and mix under vacuum.
9. Add in order cyclamate calcium and saccharin calcium and mix thoroughly for 20 minutes. While mixing, cool to room temperature and allow standing overnight to hydrate.
10. After overnight standing (minimum 12 hours), mix for 30 minutes.
11. Add and mix flavors. Check and record pH (range: 4.5–7.5). If pH is more than 7.5, adjust with a 60% solution of citric acid to the desired pH.
12. Add water to 1 L and mix thoroughly for 3 hours.
13. Strain product through muslin cloth into holding tanks and cover.

Kaolin–Pectin Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
147.60	1	Sodium methyl paraben	4.92
6.72	2	Sodium propyl paraben	0.224
36.00	3	Magnesium aluminum silicate type IA (Veegum)	1.20
5.832 g	4	Kaolin powder	194.40
130.00	5	Pectin	4.33
120.00	6	Sodium CMC premium low viscosity	4.00
210.00	7	Cyclamate calcium	7.00
21.00	8	Saccharin calcium powder	0.70
15.37	9	Flavor	0.51
1.23	10	Flavor	41.13
QS	11	Water purified approximate	QS
QS	12	Acid citric anhydrous powder	QS

Manufacturing Directions

1. Charge 600 mL of water into a suitable jacketed mixing tank.
2. Add the methyl paraben and propyl paraben to the tank and heat to 90°C to 95°C.
3. Cool to 70°C, add the magnesium aluminum silicate, and mix for 30 minutes or until evenly dispersed.
4. Hold temperature at 70°C.
5. Add kaolin with constant mixing at 70°C until evenly dispersed.
6. Add pectin and mix for 2 hours, maintaining the temperature of 70°C.
7. Add the sodium CMC premium low viscosity and mix for at least 30 minutes, maintaining the temperature at 70°C.
8. Cool to 60°C and hold at this temperature. Add in order cyclamate calcium and saccharin calcium and mix thoroughly for 20 minutes.
9. While mixing, cool to room temperature and allow standing overnight to hydrate. After overnight standing (minimum 12 hours), mix for 30 minutes.
10. Mix while adding the flavors.
11. Check and record pH (range: 4.5–7.5). If pH is above 7.5, adjust with a 60% solution of citric acid to the desired pH.
12. Add water to 1 L and mix thoroughly for 3 hours. Strain product through muslin cloth into holding tanks and cover.

Kaolin–Pectin Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
147.60	1	Sodium methyl paraben	4.920
6.72	2	Sodium propyl paraben	0.220
36.00	3	Magnesium aluminum silicate Type IA (Veegum)	1.200
486.60	4	Kaolin powder	0.190
43.40	5	Pectin	4.330
120.00	6	Sodium CMC premium low viscosity	4.000
210.00	7	Cyclamate calcium	7.000
21.00	8	Saccharin calcium	0.700
15.37	9	Flavor	0.510
1.23	10	Flavor	0.041

Manufacturing Directions

1. Charge 600 mL of water into a suitable jacketed mixing tank.
2. Add the methyl paraben and propyl paraben to the tank and heat to 90°C to 95°C.
3. Cool to 70°C, add the magnesium aluminum silicate, and mix for 30 minutes or until evenly dispersed.
4. Hold temperature at 70°C.
5. Add kaolin with constant mixing at 70°C until evenly dispersed.
6. Add pectin, and mix for 2 hours, maintaining a temperature of 70°C.
7. Add the premium low-viscosity sodium CMC and mix for at least 30 minutes, maintaining a temperature of 70°C.
8. Cool to 60°C and hold at this temperature.
9. Add, in order, cyclamate calcium and saccharin calcium and mix thoroughly for 20 minutes.
10. While mixing, cool to room temperature and allow to stand overnight to hydrate.
11. After overnight standing (minimum 12 hours), mix for 30 minutes.
12. Add flavors while mixing.
13. Check and record pH (range: 4.5–7.5). If pH is more than 7.5, adjust with a 60% solution of citric acid to the desired pH.
14. Add water to 1 L and mix thoroughly for 3 hours.
15. Strain product through muslin cloth into holding tanks and cover.

Ketoprofen Topical Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
QS	1	Vehicle (pluronic F 127 56.12%, ethanol 30.61, water 13.27%)	QS to 1 L
20.00	2	Ketoprofen	20.00
QS	3	Perfumes	QS

Manufacturing Directions

1. Screen the ketoprofen to reduce the particle size.
2. Add the ketoprofen into a clean vessel.
3. Add ethanol to the vessel.
4. Subsequently add poloxamer and water to the vessel.
5. Mix until uniform.

Ketotifen Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.20	1	Ketotifen hydrogen fumarate	0.27
0.10	2	Flavor	0.10
0.17	3	Propyl paraben	0.17
0.33	4	Methyl paraben	0.33
2.10	5	Citric acid anhydrous	2.10
3.20	6	Disodium hydrogen phosphate anhydrous	3.20
20.00	7	Ethanol	20.00
300.00	8	Sucrose	300.00
350.00	9	Sorbitol	350.00
QS	10	Water purified	QS to 1 L

Manufacturing Directions

1. Take 1.5 L of purified water and heat to 90°C to 95°C, allow to cool down to 30°C, and bubble with nitrogen gas. Keep for batch preparation.
2. Dissolve the parabens in 1 L in a separate vessel and stir until the solution is completely clear. Add citric acid, disodium hydrogen phosphate anhydrous, sucrose, and sorbitol and stir slowly to dissolve until clear solution is obtained. Cool to room temperature.
3. In a separate container, dissolve ketotifen hydrogen fumarate in ethanol until clear.
4. Add the flavor to the alcoholic solution of ketotifen and dissolve.
5. Add the alcoholic mixture slowly to the syrup while stirring at room temperature avoiding entrapment of air.
6. Pass the syrup through 100-mesh screen and then through filter press until sparkling clear.

Lamivudine Oral Solution

Epivir oral solution is for oral administration. One milliliter of Epivir oral solution contains 10 mg lamivudine (10 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methyl paraben, propylene glycol, propyl paraben, sodium citrate (dihydrate), and sucrose.

One milliliter of Epivir-HBV oral solution contains 5 mg of lamivudine (5 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methyl paraben, propylene glycol, propyl paraben, sodium citrate (dihydrate), and sucrose.

Levalbuterol Hydrochloride Inhalation Solution

Xopenex (levalbuterol HCl) inhalation solution is supplied in unit-dose vials and requires no dilution before administration by nebulization. Each 3-mL unit-dose vial contains either 0.63 mg of levalbuterol (as 0.73 mg of levalbuterol HCl) or 1.25 mg of levalbuterol (as 1.44 mg of levalbuterol HCl), sodium chloride to adjust tonicity, and sulfuric acid to adjust the pH to 4.0 (3.3–4.5).

Levocarnitine Oral Solution

Each 118-mL container of Carnitor (levocarnitine) oral solution contains 1 g of levocarnitine/10 mL. It also contains artificial cherry flavor, D,L-malic acid, purified water, and sucrose syrup. Methyl paraben and propyl paraben are added as preservatives. The pH is approximately 5.

Linezolid for Oral Suspension

Zyvox for oral suspension is supplied as an orange-flavored granule/powder for constitution into a suspension for oral administration. Following constitution, each 5 mL contains 100 mg of linezolid. Inactive ingredients are sucrose, citric acid, sodium citrate, microcrystalline cellulose and carboxymethylcellulose sodium, aspartame, xanthan gum, mannitol, sodium benzoate, colloidal silicon dioxide, sodium chloride, and flavors.

Lithium Carbonate Solution

Each 5 mL of syrup for oral administration contains lithium ion (Li +) 8 mEq (equivalent to amount of lithium in 300 mg of lithium carbonate), alcohol 0.3% v/v.

Lithium Citrate Syrup

Each 5 mL of syrup for oral administration contains lithium ion 8 mEq (equivalent to amount of lithium in 300 mg of lithium carbonate), alcohol 0.3% v/v. Lithium citrate syrup is a palatable oral dosage form of lithium ion. Lithium citrate is prepared in solution from lithium hydroxide and citric acid in a ratio approximately dilithium citrate.

Lomustine Nasal Spray

Charge 112.5 g of micronized lomustine into a pressure-addition vessel. After sealing and evacuation thereof, 10.5 kg of HFA 227 that has been aerated with carbon dioxide and adjusted to a pressure of 4.5 bar (20°C) in another pressure addition vessel in which 312 g of ethanol has been initially introduced is added. After homogenization of this mixture, the formulation obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Loracarbef for Oral Suspension

After reconstitution, each 5 mL of Lorabid for oral suspension contains loracarbef equivalent to 100 (0.286 mmol) or 200 mg (0.57 mmol) anhydrous loracarbef activity. The suspensions also contain cellulose, FD&C red No. 40, flavors, methyl paraben, propyl paraben, simethicone emulsion, sodium carboxymethylcellulose, sucrose, and xanthan gum.

Loratadine Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
5.00	1	Loratadine	1.00
3000.00	2	Sucrose	600.00
10.00	3	Sodium benzoate	2.00
2.50	4	Saccharin sodium	0.50
12.50	5	Citric acid (monohydrate)	2.50
250.00	6	Glycerin (glycerol)	50.00
765.00	7	Propylene glycol	153.00
6.87	8	Hydrochloric acid 37% (concentrated)	1.51
6.25	9	All fruit flavor	1.25
1.50	10	Raspberry flavor	0.30
–	11	Water purified	QS to 1 L

Manufacturing Directions

Hydrochloric acid (concentrated) is very corrosive. Care should be taken during handling. Rubber gloves and protective goggles should be worn during dispensing and manufacturing.

1. Add 380 g of item 11 to a stainless steel manufacturing vessel and heat to 90°C to 95°C.
2. Add item 2 while mixing at slow speed at a temperature of 90°C to 95°C. Cool to 50°C.
3. Add items 3 to 6 in order while mixing at low speed at 50°C. Mix for 15 minutes at low speed. Cool to 30°C.
4. Take 13.53 g of item 11 in a stainless steel container. Add item 8 carefully. Add hydrochloric acid solution quantity 13.675 g to the manufacturing vessel. Adjust the pH between 2.3 and 2.4. If required, add the additional quantity and record. Discard the remaining quantity. Mix for 5 minutes.
5. Dissolve item 1 in 145 g of item 7 in a stainless steel drum while stirring. Add to the manufacturing vessel.
6. Rinse the stainless steel drum with 8 g of item 7. Transfer to manufacturing vessel.
7. Add items 9 and 10 in to manufacturing vessel. Mix for 5 minutes at low speed.
8. Make up the volume to 1 L with item 11.
9. Filter and fill.

Mafenide Acetate Topical Solution

Sulfamylon for 5% topical solution is provided in packets containing 50 g of sterile mafenide acetate to be reconstituted in 1000 mL of sterile water for irrigation or 0.9% sodium chloride irrigation. After mixing, the solution contains 5% w/v of mafenide acetate. The solution is an antimicrobial preparation suitable for topical administration.

Magaldrate Instant Powder for Dry Syrup

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
800.00	1	Magaldrate	800.00
640.00	2	Kollidon CL-M	640.00
200.00	3	Sorbitol, crystalline	200.00
40.00	4	Orange flavor	40.00
40.00	5	Kollidon 90F	40.00
4.00	6	Coconut flavor	4.00
4.00	7	Banana flavor	4.00
0.80	8	Saccharine sodium	0.80
QS	9	Water	~ 280 mL

Manufacturing Directions

1. Granulate mixture 1 to 4 with solution of items 5 to 9 and pass through a 0.8-mm sieve to obtain free-flowing granules.
2. Fill 2 g in sachets or 20 g in a 100-mL flask. Instant granules in sachets: Suspend 2 g (1 sachet) in a glass of water (800 mg magaldrate).

Magaldrate Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Magaldrate USP	100.00
80.00	2	Kollidon® CL-M	80.00
20.00	3	Kollidon® 90F	20.00
10.00	4	Orange flavor	10.00
0.50	5	Coconut flavor	0.50
0.80	6	Banana flavor	0.80
0.20	7	Saccharine sodium	0.20
QS	8	Preservatives	QS
QS	9	Water	QS to 1 L

Manufacturing Directions

1. Dissolve or suspend all the solids in water under aseptic conditions; pH should be approximately 9.

Magaldrate with Simethicone Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
QS	1	Distilled purified water	285.00 mL
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
5.00	4	Benzoic acid	1.00
3.75	5	Saccharin sodium (dihydrate powder)	0.75
400.00	6	Magaldrate (wet cake; 18–20%)	400.00
1.00 g	7	Sorbitol solution (70%)	260.00
12.50	8	Silicon dioxide (colloidal) (International)	2.50
QS	9	Citric acid (hydrous powder)	QS
200.00	10	Dimethyl polysiloxane emulsion (30%)	40.00
0.005 mL	11	Flavor	1.00 mL
1.26 g	12	Glycerin	252.00
25.00 g	13	Potassium citrate monohydrate	5.00
13.30	14	Xanthan gum	2.66

Manufacturing Directions

This product is highly prone to microbial contamination. All equipment coming into contact with the product should be treated with a freshly prepared sodium hypochlorite solution (100 ppm), made with freshly boiled and cooled down water on the day of use. Bottles and caps should also be so treated. Freshly boiled and cooled deionized water should be used for rinsing.

1. Charge 285 mL purified water into a suitable jacketed tank and heat to 90°C to 95°C.
2. Add and dissolve parabens, benzoic acid, saccharin sodium, and potassium citrate.
3. While maintaining temperature at 85°C to 90°C, add, in small quantities, half the quantity of magaldrate cake or powder, if used, and disperse well.
4. Adjust speed of the agitator and homogenizer to ensure effective mixing and to maintain free mobility of the suspension. Add sorbitol solution and mix well.
5. Raise the temperature, if necessary, maintaining temperature at 85°C to 90°C.
6. Add in small quantities the remaining half of the magaldrate cake or powder and disperse well.
7. Mix for 1 hour and then remove heat. (Adjust speed of the agitator and homogenizer to maintain the mobility of suspension.) Separately blend colloidal silicon dioxide with xanthan gum and disperse the blend in glycerin, with constant mixing.
8. While maintaining temperature at 85°C to 95°C, add and disperse the suspension from the previous step to the main tank and mix well.
9. Avoid lump formation at any stage.

10. Cool to room temperature.
11. Add dimethyl polysiloxane emulsion and mix well.
12. Add flavor and mix well.
13. Dissolve citric acid in twice the quantity of purified water and adjust pH if necessary.
14. Check and record pH (range: 7.5–8.0). Add purified water to volume and mix well for a minimum of 30 minutes.
15. Filter through a 180-μm aperture nylon cloth and store in a suitable tank.

Magaldrate with Simethicone Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
QS	1	Water purified	QS to 1 L
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
5.00	4	Acid benzoic	1.00
3.75	5	Saccharin sodium powder dihydrate	0.75
2.00 g	6	Magaldrate wet cake (18 to 20%)	400.00
1.00 g	7	Sorbitol solution	260.00
12.50	8	Silicon dioxide colloidal (international)	2.50
QS	9	Acid citric powder hydrous	QS
200.00	10	Dimethyl polysiloxane emulsion (30%)	40.00
0.005 mL	11	Flavor	1.000 mL
1.26 g	12	Glycerin	252.00
25.00 g	13	Potassium citrate monohydrate	5.00
13.30	14	Xanthan gum	2.66

Manufacturing Directions

This product is highly prone to microbial contamination. All equipment coming into contact with the product should be treated with a freshly prepared sodium hypochlorite solution (100 ppm) made with freshly boiled and cooled town water on the day of use. Bottles and caps should also be so treated. Freshly boiled and cooled purified water should be used for rinsing.

1. Charge 285 mL purified water into a suitable jacketed tank and heat to 90°C to 95°C.
2. Add and dissolve parabens, acid benzoic, saccharin sodium, and potassium citrate.
3. While maintaining temperature at 85°C to 90°C, add, in small quantities, half the quantity of magaldrate cake or powder, if used, and disperse well. (Adjust the speed of agitator and of the homogenizer to ensure effective mixing and to maintain free mobility of the suspension.)
4. Add sorbitol solution and mix well. Raise the temperature, if necessary, maintaining temperature at 85°C to 90°C.
5. Add, in small quantities, the remaining half of magaldrate cake or powder and disperse well. Mix for 1 hour and then remove heat. (Adjust the speed of the agitator and of the homogenizer to maintain the mobility of suspension.)
6. Separately blend silicon dioxide colloidal with xanthan gum and disperse the blend in glycerin with constant mixing.
7. While maintaining temperature at 85°C to 95°C, add and disperse the suspension from previous step to the main tank and mix well. Avoid lump formation at any stage. Cool to room temperature.
8. Add dimethyl polysiloxane emulsion and mix well.
9. Add flavor and mix well. Dissolve acid citric in twice the quantity of purified water and adjust pH if necessary. Check and record pH (range: 7.5–8.0).
10. Add purified water to volume and mix well for a minimum of 30 minutes.
11. Filter through a 180-micron aperture nylon cloth and store in a suitable tank.

Mebendazole Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
102.00	1	Mebendazole[a]	20.40
10.00	2	Methyl paraben	2.00
1.00	3	Propyl paraben	0.20
750.00	4	Propylene glycol	150.00
8.25	5	Sodium citrate	1.65
7.50	6	Saccharin sodium	1.50
0.55	7	Citric acid (monohydrate)	0.11
52.50	8	Microcrystalline cellulose	10.50
25.00	9	Carboxymethylcellulose sodium	5.00
7.50	10	Polysorbate 80	1.50
12.50	11	All fruits flavor	2.50
–	12	Water purified	QS to 1 L

[a]2 mg/5 mL mebendazole added as an extra to compensate the loss on drying and assay of the material.

Manufacturing Directions

1. Load 300 g of item 12 (25–30°C) in mixer. In it dissolve items 5, 6, and 7 while stirring at a speed of 18 rpm.
2. Dissolve items 2 and 3 in 30 g of item 4 (45°C) in a stainless steel container while stirring by stirrer.
3. Cool to 25°C to 30°C.
4. Add the paraben solution into step 1 while mixing.
5. Disperse item 8 in 200 g of item 12 (25–30°C) in a stainless steel container while stirring by stirrer. Keep aside for 1 hour for complete hydration.
6. Disperse item 9 in 100 g of item 12 (70°C) in a stainless steel container while stirring by stirrer.
7. Cool to 25°C to 30°C. Keep aside for 1 hour for complete gelation. Cooling is necessary for gelation.
8. Dissolve item 10 in 20 g of item 12 (50°C) in a stainless steel container while stirring by stirrer.
9. Cool to 30°C. Add 120 g of item 4 while mixing.
10. Disperse item 1 while mixing. Keep aside for complete levigation.
11. Add the Avicel dispersion and sodium CMC dispersion from step 3 and step 4 into mixer in step 1. Mix and homogenize at mixer speed 18 rpm, homogenizer low speed, and vacuum 0.4 to 0.6 bar for 10 minutes.
12. Add the mebendazole dispersion from step 5 into mixer in step 1. Mix and homogenize at mixer speed 18 rpm, homogenizer low speed, and vacuum 0.4 to 0.6 bar for 10 minutes.
13. Add item 11 into step 6. Make up the volume up to 1 L with item 12. Mix at a speed of 18 rpm for 5 minutes.
14. Check the suspension for homogeneity. Transfer the suspension through 630-micron sieve to stainless steel storage tank, previously sanitized by 70% ethanol.

Mebendazole Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
20.00	1	Mebendazole	20.00
30.00	2	Lutrol F 127	30.00
1.80	3	Methyl paraben	1.80
0.20	4	Propyl paraben	0.20
QS	5	Water purified	QS

Manufacturing Directions

1. Charge 80% of item 5 in a stainless steel jacketed vessel. Heat to 90°C to 95°C.
2. Add items 3 and 4 and stir to dissolve.
3. Cool to 40°C and add item 2. Stir to dissolve completely.
4. Add item 1 and mix well. Homogenize if necessary.

Megestrol Acetate Oral Suspension

Megace oral suspension is supplied as an oral suspension containing 40 mg of micronized megestrol acetate per milliliter. Megace oral suspension contains the following inactive ingredients: alcohol (maximum of 0.06% v/v from flavor), citric acid, lemon-lime flavor, polyethylene glycol, polysorbate 80, purified water, sodium benzoate, sodium citrate, sucrose, and xanthan gum.

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
40.00	1	Megestrol acetate	40.00
100.00	2	Glycerin	100.00
100.00	3	Sorbitol	100.00
0.30	4	Polysorbate 90	0.30
2.20	5	Xanthan gum	2.20
2.00	6	Sodium benzoate	2.00
0.60	7	Sodium citrate	0.60
50.00	8	Sucrose	50.00
0.80	9	Lemon flavor	0.80
QS	10	Water purified	QS to 1 L

Manufacturing Directions

1. Charge glycerol, sorbitol, and polysorbate in a suitable container. Mix well.
2. Charge xanthan gum in a separate vessel with item 10 and allow overnight hydration.
3. Add sodium citrates, sucrose, sodium benzoate, and flavor to step 1 and then add step 2 to step 1.
4. Pass the gum slurry through a screen.
5. Add megestrol acetate and pass then suspension through a colloid mill or homogenizer to provide a uniform oral suspension.

Menthol and Benzocaine Solution

Bill of Materials			
Scale (mg/mg)	Item	Material Name	Qty/kg (g)
QS	1	Vehicle (pluronic F 108 56.79%, ethanol 21.69%, water 21.52%)	QS to 1 kg
10.00	2	Menthol	10.00
20.00	3	Benzocaine	20.00
0.05	4	Eucalyptus oil	0.05
1.00	5	Sodium saccharin	1.00
0.50	6	Monoammonium glycyrrhizinate	0.50
QS	7	Flavors and colors	QS

Manufacturing Directions

1. Mill and screen the menthol and benzocaine to reduce the product particle size.
2. Add the menthol, benzocaine, sodium saccharin, and monoammonium glycyrrhizinate into a clean vessel.
3. Add eucalyptus oil and ethanol to the vessel.
4. Subsequently add the poloxamer and water to the vessel.
5. Mix until uniform.

Menthol Mouthwash

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Menthol	10.00
10.00	2	Eucalyptus oil	10.00
40.00	3	Cremophor RH 40	40.00
4.50	4	Saccharin sodium	4.50
2.00	5	Sodium citrate	2.00
5.00	6	Citric acid	5.00
50.00	7	Lutrol F 127	50.00
67.00	8	Ethanol 96%	67.00
QS	9	Sicovit colorant	QS
801.00	10	Water	801.00

Manufacturing Directions

1. Mix components 1 to 3 and heat to approximately 60°C.
2. Prepare solution of items 4 to 10, heat to approximately 60°C, and add it slowly to the well-stirred mixture of items 1 to 3.
3. Clear, colored liquids having a fresh mint taste are the desired result.

Mesalamine Rectal Suspension Enema

The active ingredient in rectal suspension enema, a disposable (60 mL) unit, is mesalamine, also known as 5-aminosalicylic acid. Each rectal suspension enema unit contains 4 g of mesalamine. In addition to mesalamine, the preparation contains the inactive ingredients carbomer 934P, EDTA, potassium acetate, potassium metabisulfite, purified water, and xanthan gum. Sodium benzoate is added as a preservative. The disposable unit consists of an applicator tip protected by a polyethylene cover and lubricated with white petrolatum. The unit has a one-way valve to prevent backflow of the dispensed product.

Mesalamine Rectal Suspension

Each rectal suspension enema unit contains 4 g of mesalamine. In addition to mesalamine, the preparation contains the inactive ingredients carbomer 934P, EDTA, potassium acetate, potassium metabisulfite, purified water, and xanthan gum. Sodium benzoate is added as a preservative.

Metformin Liquid

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Metformin hydrochloride	100.00
400.00	2	Xylitol	400.00
5.00	3	Potassium bicarbonate	5.00
1.20	4	Potassium sorbate	1.20
2.75	5	Sodium saccharin	2.75
0.004 mL	6	Hydrochloric acid	4.00 mL
2.75	7	Wild cherry flavor	2.75
QS	8	Water purified	QS to 1 L

Manufacturing Directions

1. Under continuous stirring, add potassium bicarbonate and metformin hydrochloride to purified water and dissolve to get a clear solution.
2. Add hydrochloric acid solution as a dilute solution (approximately one molar) to the mixture of the previous step. This results in carbon dioxide gas formation (effervescent gas).
3. Add xylitol at a temperature of NMT 31°C and stir to get a clear solution.
4. Continue stirring and add artificial cherry flavor and saccharin.
5. Adjust the pH to a range of 4.6 to 4.9 using dilute solution of hydrochloric acid (if required).
6. Make up the volume and filter through clarifying grade filter and fill in approved container.

Metoclopramide Oral Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
4.00	1	Metoclopramide HCl, 10% excess	4.40
0.76	2	Saccharin sodium	0.76
1.00	3	Sorbic acid	1.00
1.48	4	Sodium metabisulfite (sodium disufite)	1.48
0.10	5	Polyoxyl 35 castor oil (Cremophor EL)	0.10
5.20	6	Sodium citrate	5.20
8.52	7	Citric acid (monohydrate)	8.52
–	8	Water purified	QS to 1 L

Manufacturing Directions

1. Load 80 g of item 8 to the mixer and heat to 90°C to 95°C.
2. Dissolve items 2 and 3 while stirring. Mix for 15 minutes at high speed to get clear solution.
3. Cool the temperature to 25°C.
4. Transfer the solution to drops manufacturing vessel.
5. Add item 5 to the drops manufacturing vessel at step 4, while stirring to dissolve.
6. Add 8 g of item 8 (25°C) in a separate container and dissolve items 6 and 7 using stirrer and transfer to the drops manufacturing vessel at step 5.
7. Add item 4 to the drops manufacturing vessel at step 6 while mixing.
8. Add 5 g of item 8 (25°C) in a separate container and dissolve item 1 using stirrer.
9. Transfer this solution to the drops manufacturing vessel at step 7 while mixing.
10. Check and record the pH (limit: 3.4–3.6).
11. Adjust the pH if required using 5% aqueous solution of citric acid or sodium citrate.
12. Make up the volume up to 1 L with item 8 (25°C).
13. Assemble the membrane filter of 0.2 micron. Filter the solution and collect the filtrate in clean HDPE containers.

Metoclopramide Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
30.00	1	Hydroxyethyl cellulose	6.00
4.00	2	Methyl paraben	0.80
1.00	3	Propyl paraben	0.20
5.00	4	Sorbic acid	1.00
14.25	5	Citric acid (monohydrate)	2.85
4.60	6	Sodium citrate	0.92
7.50	7	Saccharin sodium	1.50
5.00	8	Metoclopramide HCl (14% excess)	1.14
40.00	9	Alcohol (ethanol 95%)	8.00
25.00	10	Propylene glycol	5.00
6.50	11	Flavor	1.30
10.00	12	Caramel	2.00
0.50	13	Flavor	0.10
–	14	Water purified	QS to 1 L

Manufacturing Directions

1. Add 200 g of item 14 to the mixer and heat to 90°C.
2. Sprinkle item 1 slowly while mixing at 20 rpm in manual mode. Check that item 1 is dispersed completely without forming lumps.
3. Start the homogenizer at high speed with recirculation, vacuum 0.4 bar.
4. Homogenize for 15 minutes at high speed. Cool to approximately 60°C.
5. Add 200 g of item 14 in a storage container.
6. Transfer the homogenized mucilage to the storage container (step 5).
7. Add 500 g of item 14 to the syrup vessel and heat to 90°C.
8. Add items 2, 3, and 4 to the syrup vessel and mix at high speed for 15 minutes to dissolve. Start cooling until temperature reaches at 50°C to 60°C.
9. Withdraw a portion of the solution and check that it is clear and colorless.
10. Transfer the mucilage to the syrup vessel and mix at high speed for 15 minutes. Start cooling and cool to 30°C.
11. Add 20 g of item 4 (25°C) in a separate container, dissolve items 5 and 6 by using stirrer, and add solution to the manufacturing vessel.
12. Add 10 g of item 14 (25°C) in a separate container, dissolve item 7 by using stirrer, and add solution to the manufacturing vessel.
13. Withdraw a portion of the solution and check that it is clear and colorless.
14. Add 10 g of item 14 (25°C) in a separate container, dissolve item 8 by using stirrer, and add solution to the manufacturing vessel.
15. Rinse the container with 5 g of item 14 (25°C) cooled and transfer the rinsing to the syrup vessel. Mix at high speed for 20 minutes.
16. Withdraw a portion of the solution and check that it is clear and colorless.
17. Mix items 9 and 10 in a clean stainless steel container. Add items 11, 12, and 13 and mix well manually.
18. Transfer the solution to the manufacturing vessel and mix for 15 minutes at high speed.
19. Make up the volume to 1 L with item 14 (25°C) and, finally, mix for 20 minutes at high speed.
20. Check and record the color and pH (limit: 2.9–3.1). Color should be clear to faint yellow.
21. Suspend 1 g of the filter aid in 40 g of cooled item 14 (25°C) and stir well. Allow the filter aid to settle. Decant off the water.
22. Transfer the washed filter aid to the syrup vessel while mixing. Mix for 30 minutes at high speed.
23. Assemble the filter press.
24. Wash the filters using approximately 250 L purified water (25°C) by passing through filters at 0.2 bar.
25. Filter the syrup at 1 bar. Recirculate approximately 100 to 150 mL syrup.
26. Transfer the filtered syrup to the storage vessel.

Metronidazole Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
125.00	1	Metronidazole (use metronidazole benzoate)	40.20
7.50	2	Methyl paraben	1.50
1.00	3	Propyl paraben	0.20
2500.00	4	Sucrose	500.00
7.50	5	Saccharin sodium	1.50
8.75	6	Sodium phosphate monobasic	1.75
8.75	7	Sodium phosphate dibasic	1.75
40.00	8	Magnesium aluminium silicate	8.00
30.00	9	Microcrystalline cellulose	6.00
650.00	10	Propylene glycol	130.00
7.50	11	Lemon flavor	1.50
7.50	12	Bergamot flavor	1.50
–	13	Water purified	QS to 1 L

Note: For 200 mg/5 mL strength use 64.400 g of metronidazole benzoate.

Manufacturing Directions

1. Disperse item 1 in item 10 in a stainless steel vessel, using stirrer. Make smooth slurry and keep aside for use later.
2. Add 186 g of item 13 to a vessel and heat to 90°C to 95°C. Dissolve items 2 and 3 while mixing.
3. Add and dissolve item 4 while mixing at a temperature of 90°C to 95°C.
4. Cool down to 50°C to 55°C.
5. In a stainless steel container, dissolve item 5 in 4 g of item 13 and add to the vessel while mixing.
6. Filter the syrup. Collect the syrup in stainless steel tank.
7. Disperse item 8 in 120 g of hot item 13 (70–75°C) in stainless steel vessel, using stirrer. Keep on stirring for 30 minutes. Transfer the dispersion into mixer by vacuum.
8. Mix and homogenize at temperature 70°C to 80°C, mixer speed 18 rpm, homogenizer at high speed, and vacuum 0.4 to 0.6 bar for 10 minutes.
9. Cool down to 25°C to 30°C.
10. Disperse item 9 in 120 g of item 13 in stainless steel vessel, using stirrer. Keep on stirring for 30 minutes to make smooth dispersion.
11. Transfer the filtered syrup from step 7 and transfer Avicel mucilage from step 4 to mixer. Set the mixer to 25°C to 30°C, 18 rpm, high speed and vacuum 0.4 to 0.6 bar.
12. Mix and homogenize for 10 minutes.
13. Dissolve items 6 and 7 in 12 g of item 13 and add to mixer while mixing.
14. Add metronidazole benzoate and propylene glycol dispersion (step 1) to mixer.
15. Rinse the drug container with 10 g of item 13 and add the rinsing to mixer to avoid loss.
16. Add items 11 and 12 to mixer. Make up the volume to 1 L with item 13.
17. Mix and homogenize for 20 minutes at high speed, vacuum 0.4 to 0.6 bar. Check the suspension for homogeneity. Transfer the suspension through 630-micron sieve to stainless steel storage tank, previously sanitized by 70% ethanol.
18. Do not store the bulk suspension more than 48 hours in the storage tank without stirring. Before filling, stir not less than 30 minutes for uniform dispersion to avoid problem of content uniformity.

Mineral and Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
6.65	1	Hypophosphorous acid	6.655
16.47	2	Calcium hypophosphite	16.47
31.68	3	Calcium lactate (powder)	31.68
1.00	4	Methyl paraben	1.00
0.20	5	Propyl paraben	0.20
1.00	6	Benzoic acid	1.00
150.00	7	Sucrose (granular)	150.00
5.20	8	Ferrous gluconate	5.20
2.00	9	Niacinamide (5% excess)	2.10
0.328	10	Riboflavin-5-phosphate sodium	0.33
1.00	11	D-Pantothenyl alcohol (dexpanthenol; 20% excess)	1.20
0.60 μg	12	Vitamin B_{12} (cyanocobalamin) (35% excess)	0.81 mg
0.20	13	Pyridoxine hydrochloride	0.20
0.30	14	Thiamine hydrochloride (regular powder) (55% excess)	0.46
4.782	15	Flavor, raspberry blend	4.78
1.945	16	Flavor, chocolate	1.945
0.642	17	Orange oil (terpeneless, No. 54125)	0.64
0.21	18	Lime oil, distilled	0.215
4.28	19	Alcohol	4.28
2.50	20	Saccharin sodium	2.50
10.00	21	Ascorbic acid (white powder/EP) (45% excess)	14.50
3.00	22	Caramel (acid proof)	3.00
2.00	23	Anhydrous citric acid	2.00
10.0 μg	24	Butylated hydroxyanisole (BHA)	10.00 mg
3.39	25	Corn oil	3.39
0.40	26	Vitamin A palmitate (1.5 MM U/g) (40% excess)	0.56
0.08	27	Viosterol in corn oil (syn. oleovitamin D; 1000 mg/g) (40% excess)	0.112
1.5 G	28	Acacia (special grade)	1.50
0.127	29	Sodium lauryl sulfate (acetone-washed)	0.127
171.00	30	Deionized, purified water	~171
QS	31	Glucose liquid (corn syrup)	QS to 1 L

Manufacturing Directions

Do not expose this preparation during manufacturing to direct sunlight. Riboflavin is sensitive to light.

1. Add 83.7 mL purified water to a stainless steel jacketed tank.
2. Add calcium hypophosphite, calcium lactate, the parabens, and benzoic acid.
3. Heat mixture to 60°C with agitation.
4. Shut off mixer and wash tank until free of all powders with 25.9 mL purified water.
5. Heat to and maintain a maximum temperature of 100°C until solution is complete. Do not agitate. Avoid loss of water through evaporation; cover opening of tank.
6. After solution occurs, take sample from bottom of tank and examine for clarity. Solution must be clear.
7. Add hypophosphorous acid (if used) with mixing.
8. Turn off heat, add 222 g glucose, and start agitator. (*Caution*: Use CO_2 cover throughout; wherever water is used, it should be CO_2-saturated water.) Dissolve ferrous gluconate in 7.4 mL water CO_2-saturated by heating.
9. Add 278 g glucose with mixing. Add and dissolve sugar.
10. Allow solution to cool to 35°C and mix well.

11. To 29.6 mL water add and dissolve nicotinamide, riboflavin, D-pantothenyl alcohol, vitamin B_{12}, pyridoxine, and thiamine. Mix until solution is complete and add to tank. Dissolve by heat, if necessary.
12. Charge raspberry blend flavor and chocolate flavor into tank; charge saccharin into tank and mix until dissolved.
13. Charge ascorbic acid into tank. Mix well.
14. Charge caramel into tank and mix well.
15. Dissolve citric acid in 3 mL water and add.
16. Heat corn oil to 50°C to 60°C and add and dissolve BHA. Ensure the BHA is completely dissolved before continuing.
17. Cool to room temperature. While cooling oil mixture, saturate with CO_2 and maintain heavy CO_2 coverage for balance of operation.
18. Set aside a small amount of this mixture as a rinse for the vitamin A and viosterol containers in step above.
19. Add vitamin A palmitate and viosterol to the cool corn oil mixture, rinsing the containers with the oil reserved above.
20. Add the rinse to the bulk. Mix well.
21. Add the acacia to the oil mixture with good mixing.
22. Dissolve sodium lauryl sulfate in 3 mL CO_2-saturated purified water. To avoid excessive foaming, do not bubble CO_2 gas through the water/sodium lauryl sulfate solution.
23. Add the sodium lauryl sulfate solution to the oil mixture and stir to a thick creamy emulsion.
24. Add 7.56 g glucose to the emulsion with mixing.
25. Blend 13.33 mL CO_2-saturated purified water with 77.04 g glucose and add emulsion with stirring.
26. Recycle primary emulsion back into holding tank while setting mill.
27. Homogenize until all oil globules are less than 8 μm in diameter using colloid mill with a very fine setting. Do not change mill setting after removing sample unless samples are unacceptable.
28. Add primary emulsion to syrup solution with mixing; add glucose QS to 965 mL and mix well. Allow to stand overnight to vent entrapped air.
29. Adjust the volume to 1 L using glucose or glucose and CO_2-saturated water.
30. Strain through 149-μm aperture or similar screen into clean reserve tank and recheck volume.

Minoxidil Solution

Minoxidil 5% w/v; alcohol, 30% v/v; propylene glycol, 50% v/v; and purified water.

Mint–Menthol Mouthwash

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
20.00	1	Mint oil	20.00
0.40	2	Menthol	0.40
0.90	3	Eucalyptus oil	0.90
10.00	4	Alpha-bisabolol (BASF)	10.00
0.60	5	Thymian oil	0.60
40.00	6	Cremophor RH 40	40.00
4.50	7	Saccharin sodium	4.50
2.00	8	Sodium citrate	2.00
5.00	9	Citric acid	5.00
0.20	10	Sodium fluoride	0.20
50.00	11	Glycerol	50.00
50.00	12	Lutrol F 127	50.00
0.60	13	Salicylic acid	0.60
1.00	14	Benzoic acid	1.00
175.00	15	Sorbitol, crystalline	175.00
216.00	16	Ethanol 96%	216.00
QS	17	Sicovit colorant	QS
QS	18	Water	48.4

Manufacturing Directions

1. Mix components 1 to 6 and heat to approximately 60°C.
2. Prepare solution of items 7 to 18, heat to approximately 60°C.
3. Add this solution slowly to the well-stirred mixture of items 1 to 6. The result is a clear, colored liquid having a fresh mint taste.

Mint–Menthol Mouthwash

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
20.00	1	Mint oil	20.00
0.40	2	Menthol	0.40
0.90	3	Eucalyptus oil	0.90
10.00	4	α-Bisabolol (BASF)	10.00
0.60	5	Thymian oil	0.60
40.00	6	Cremophor RH 40	40.00
4.50	7	Saccharin sodium	4.50
2.00	8	Sodium citrate	2.00
5.00	9	Citric acid	5.00
0.20	10	Sodium fluoride	0.20
50.00	11	Glycerol	50.00
50.00	12	Lutrol F 127	50.00
0.60	13	Salicylic acid	0.60
1.00	14	Benzoic acid	1.00
175.00	15	Sorbitol, crystalline	175.00
216.00	16	Ethanol 96%	216.00
QS	17	Sicovit colorant	QS
QS	18	Water	48.40

Manufacturing Directions

1. Mix items 1 to 6 and heat to approximately 60°C.
2. Prepare solution of items 7 to 18, heat it to approximately 60°C, and add it slowly to the well-stirred mixture of items 1 to 6.
3. Clear, colored liquids have a fresh mint taste.

Mint Oil Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
35.00	1	Peppermint oil	35.00
138.00	2	Cremophor RH 40	138.00
520.00	3	Ethanol 96%	520.00
QS	4	Water	307.00

Manufacturing Directions

1. Mix the peppermint oil with Cremophor RH 40, stir well, and slowly add ethanol and water.
2. Clear, colorless liquid is of low viscosity.

Mint Oil Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
35.00	1	Peppermint oil	35.00
138.00	2	Cremophor RH 40	138.00
520.00	3	Ethanol 96%	520.00
307.00	4	Water	307.00

Manufacturing Directions

1. Mix peppermint oil with Cremophor RH 40 and stir well.
2. Slowly add ethanol and water. A clear, colorless liquid of low viscosity is the result.

Mometasone Furoate Nasal Spray

Nasonex nasal spray, 50 μg, is a metered-dose manual-pump spray unit containing an aqueous suspension of mometasone furoate monohydrate equivalent to 0.05% w/w mometasone furoate, calculated on the anhydrous basis, in an aqueous medium containing glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, sodium citrate, 0.25% w/w phenylethyl alcohol, citric acid, benzalkonium chloride, and polysorbate 80. The pH is between 4.3 and 4.9.

Monosulfiram Solution

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
25.00	1	Monosulfiram	250.00
10.00	2	Dispersol	100.00
QS	3	Methylated spirit	QS to 1 kg

Manufacturing Directions

1. Liquefy item 1 by warming to 40°C.
2. Charge item 3 in a suitable dry stainless steel mixing vessel.
3. Add item 2 to step 2 and then add item 1 with constant stirring until clear solution obtained.
4. Filter through a suitable clarifying filter.

Multivitamin and Calcium Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/100 g (mg)
0.10	1	Vitamin A palmitate	10.00
0.50 μg	2	Vitamin D 40 mio IU/g	0.05
1.00	3	Vitamin E acetate, BASF	100.00
0.02	4	Butylhydroxytoluene	2.00
45.00	5	Cremophor RH 40	4.50 g
100.00	6	Water	10.00 g
450.00	7	Saccharose	45.00 g
2.00	8	Methyl paraben	200.00
0.80	9	Citric acid	80.00
96.00	10	Glycerol	9.60 g
0.70	11	Calcium gluconate	70.00
250.00	12	Water	25.00 g
0.15	13	Thiamine hydrochloride, BASF	15.00
0.15	14	Riboflavin 5′-phosphate sodium	15.00
0.55	15	Nicotinamide	55.00
0.15	16	Pyridoxine hydrochloride	15.00
3.00	17	Ascorbic acid, crystalline	300.00
1.00	18	Sorbic acid	100.00
50.00	19	Propylene glycol (Pharma)	5.00 g

Manufacturing Directions

1. Heat items 1 to 5 and item 6 separately to approximately 60°C and mix slowly, stirring well to obtain a clear solution.
2. Dissolve items 7 to 9 in the hot solution of items 10 to 12 to obtain a clear solution.
3. Mix all the solutions upon cooling and add solutions of items 13 to 19; adjust the pH value to 4.0 to 4.1.
4. Pass during 10 minutes nitrogen through the solution and fill in bottles under nitrogen cover.

Multivitamin and Mineral Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
6.65	1	Hypophosphorous acid (50% pure)	6.655
16.47	2	Calcium hypophosphite	16.47
31.68	3	Calcium lactate (powder)	31.68
1.00	4	Methyl paraben	1.00
0.20	5	Propyl paraben	200.00 mg
1.00	6	Acid benzoic	1.00
150.00	7	Sucrose	150.00
5.20	8	Ferrous gluconate	5.20
2.00	9	Niacinamide (white powder) (5% excess)	2.10
0.32	10	Riboflavin-5-phosphate sodium	328.77 mg
1.00	11	D-Pantothenyl alcohol (dexpanthenol; 20% excess)	1.20
0.00060	12	Vitamin B_{12} (cyanocobalamin; 35% excess)	810.00 μg
0.20	13	Pyridoxine hydrochloride	200.00 mg
0.30	14	Thiamine hydrochloride (powder, regular) (55% excess)	465.00 mg
4.78	15	Flavor, raspberry blend	4.782
1.94	16	Flavor, chocolate	1.945
0.64	17	Orange oil, terpeneless No. 54125	642.00 mg
0.21	18	Lime oil (distilled)	214.975 mg
4.28	19	Alcohol (ethanol, 190 proof)	4.28
2.50	20	Saccharin sodium	2.50
10.00	21	Acid ascorbic (45% excess)	14.50
3.00	22	Caramel (acid proof)	3.00
2.00	23	Anhydrous citric acid	2.00
0.0010	24	Butylated hydroxyanisole (BHA)	10.0 mg
3.39	25	Corn oil	3.39
0.56	26	Vitamin A palmitate (1.5 MM UA/g) (40% excess)	560.00 mg
0.08	27	Viosterol in corn oil (syn. oleovitamin D; 1000 mD/g; D_3 in arachis oil) (40% excess)	112.00 mg
1.50	28	Acacia	1.50
0.12	29	Sodium lauryl sulfate (acetone washed)	127.41 mg
171.00	30	Purified water	~171
QS	31	Glucose liquid	QS to 1 L

Manufacturing Directions

Do not expose this preparation during manufacturing to direct sunlight. Riboflavin is sensitive to light.

1. Add 83.7 mL of purified water to a stainless steel jacketed tank.
2. Add calcium hypophosphite, calcium lactate, parabens, and benzoic acid.
3. Heat mixture to 60°C with agitation.
4. Shut off mixer and wash tank free of all powders with 25.9 mL purified water.
5. Heat to and maintain a maximum temperature of 100°C until solution is complete. Do not agitate. Avoid loss of water through evaporation. Cover opening of tank. After solution occurs, take sample from bottom of tank and examine for clarity. Solution must be clear.
6. Add acid hypophosphorous (if used) with mixing.
7. Turn off heat and add 222 g glucose and start agitator. (*Caution*: Use CO_2 cover throughout; wherever water is used, it should be CO_2-saturated water.) Dissolve ferrous gluconate in 7.4 mL water CO_2 saturated by heating.
8. Add 278 g glucose with mixing. Add and dissolve sugar.
9. Allow solution to cool to 35°C and mix well.
10. To 29.6 mL water, add and dissolve nicotinamide, riboflavin, D-pantothenyl alcohol, vitamin B_{12}, pyridoxine, and thiamine.
11. Mix until solution is complete and add to tank. Dissolve by heat, if necessary.

12. Charge raspberry blend flavor and chocolate flavor into tank.
13. Charge saccharin into tank and mix until dissolved.
14. Charge ascorbic acid into tank and mix well.
15. Charge caramel into tank and mix well.
16. Dissolve citric acid in 3 mL water and add this solution to above.
17. Heat corn oil to 50°C to 60°C and add and dissolve BHA. Ensure the BHA is completely dissolved before continuing.
18. Cool to room temperature. While cooling oil mixture, saturate with CO_2 and maintain heavy CO_2 coverage for balance of operation.
19. Set aside a small amount of this mixture as a rinse for the vitamin A and viosterol containers in previous step.
20. Add vitamin A palmitate and viosterol to the cool corn oil mixture, rinsing the containers with the oil reserved earlier.
21. Add the rinse to the bulk and mix well.
22. Add the acacia to the oil mixture with good mixing.
23. Dissolve sodium lauryl sulfate in 3 mL CO_2-saturated purified water. To avoid excessive foaming, do not bubble CO_2 gas through the water/sodium lauryl sulfate solution.
24. Add the sodium lauryl sulfate solution to the oil mixture and stir to a thick creamy emulsion.
25. Add 7.56 g glucose to the emulsion with mixing.
26. Blend 13.33 mL CO_2-saturated purified water with 77.04 g glucose and add emulsion with stirring.
27. Recycle primary emulsion back into the holding tank while setting mill.
28. Homogenize until all oil globules are less than 8 μm in diameter using colloid mill with a very fine setting. After setting mill, sample. Do not change mill setting after removing sample unless samples are unacceptable.
29. Add primary emulsion to syrup solution with mixing; add glucose QS to 965 mL and mix well.
30. Allow to stand overnight to vent entrapped air. Adjust the volume to 1 L using glucose or glucose and CO_2-saturated water.
31. Strain through 149-μm aperture or similar screen into clean reserve tank and recheck volume.

Multivitamin Drops

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
13600 IU	1	Vitamin A palmitate (1.7 MM IU/g)	8.00
5200 IU	2	Vitamin D3 (40 MM IU/g)	0.13
5.00	3	Vitamin E acetate	5.00
150.0	4	Cremophor EL (or Cremophor RH 40)	150.00
2.00	5	Parabens (Methyl and propyl)	2.00
525.00	6	Water purified	525.00
4.00	7	Thiamine hydrochloride	4.00
2.00	8	Riboflavin 5-phosphate sodium	2.00
2.00	9	Pyridoxine hydrochloride	2.00
2.00	10	Nicotinamide	2.00
0.20	11	Sodium bisulfite	0.20
200.00	12	Propylene glycol	200.00
QS	13	Water purified	10.00
QS	14	Hydrochloric acid	QS

Manufacturing Directions

1. Heat mixture of items 1 to 4 to approximately 60°C; stir strongly and slowly add solution of items 5 and 6 (60°C).
2. To the obtained clear solution, add solution of items 7 to 13.
3. Adjust the pH with item 14 to approximately 4 and QS to volume.

Multivitamin Infant Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1125 IU	1	Vitamin A palmitate (1.7 mm IU/g) (50% excess)	1.324
416 IU	2	Vitamin D (40 mm IU/g) (cholecalciferol, 25% excess)	0.013
5.00	3	Vitamin E (oily; α-tocopheryl acetate)	5.00
52.50	4	Ascorbic acid (50% excess)	52.50
0.375	5	Thiamine hydrochloride (50% excess)	0.75
0.40	6	Pyridoxine hydrochloride	0.40
8.00	7	Nicotinamide	8.00
0.00125	8	Cyanocobalamine (50% excess)	0.0025
0.82	9	Riboflavin sodium phosphate (5% excess as riboflavin)	0.865
2.50	10	Poloxyl 20 cetostearyl ether (Cetomacrogol 1000)	2.50
12.50	11	Polysorbate 80 (Tween 80)	12.50
0.50	12	Edetate disodium (sodium EDTA)	0.50
3.75	13	Sodium hydroxide	3.75
0.25	14	Saccharin sodium	0.25
300.00	15	Glycerin (glycerol)	300.00
500.00	16	Sorbitol (70% solution)	500.00
50.00	17	Propylene glycol	50.00
1.50	18	Flavor	1.50
3.00	19	Flavor	3.00
1.50	20	Flavor	1.50
–	21	Purified water	QS to 1 L

Manufacturing Directions

The product is a microemulsion and thermolabile. The temperature of solution must not exceed 25°C at the time of processing. Store bulk at temperature 15°C to 20°C under nitrogen protection to avoid discoloration and precipitation. Period of storage should not exceed 48 hours prior to filling in the bottle.

1. Check and record pH of item 21 (limit: 5.0–6.5) and collect 250 g of it in manufacturing vessel. Heat to 90°C to 95°C for 10 minutes, then cool to 20°C to 25°C.
2. Bubble nitrogen gas into cooled item 21 for 20 minutes.
3. Load 200 g of item 21 from first step to the manufacturing vessel.
4. Bubble nitrogen gas during all stages of the process.
5. Charge items 4 to 9 and 12 to 14 one by one to the manufacturing vessel while mixing.
6. Check that all materials are dissolved completely. Solution should be clear.
7. Add item 11 in a separate stainless steel container and heat to 45°C.
8. Mix items 1, 2, 3, and 10 one by one.
9. Mix for 1 hour at slow speed.
10. Add oil phase preparation to the aqueous phase at a rate of 2 mL/min while mixing; keep on bubbling nitrogen gas throughout the process.
11. Add items 15 and 16 to the manufacturing vessel one by one while mixing.
12. Keep on bubbling nitrogen gas throughout the process.
13. Add items 18 to 20 in item 17 and add to the manufacturing vessel while mixing.
14. Adjust the volume to 1 L using nitrogen-bubbled item 21.
15. Mix for 10 minutes at slow speed without aeration.
16. Check pH (limit: 3.7–4.5).
17. Filter the product at 1.5 bar.
18. Recirculate approximately 100 to 150 mL of product.
19. Transfer the filtered product to the storage vessel under a nitrogen blanket.

Multivitamin Infant Drops

Bill of Materials			
Scale (mg/0.6 mL)	Item	Material Name	Qty/L
675.00	1	Glycerin, USP (96%)	675.00 g
10.00	2	Nicotinamide niacinamide (white powder) (5% excess)	17.50 g
2.74	3	Riboflavin-5′-phosphate sodium (0% excess)	2.74 g
0.50	4	Methyl paraben (powder)	500.00 mg
1.00	5	Benzoic acid	1.00 g
2.10	6	Saccharin sodium (powder)	2.10 g
1.50	7	Thiamine HCl (45% excess)	3.625 g
0.60	8	Pyridoxine HCl	833.34 mg
50.00	9	Ascorbic acid (white powder) (20% excess)	100.00 g
0.257	10	Orange oil terpeneless No. 54125	257.789 mg
0.095	11	Alcohol (ethanol)	95.50 mg
80.00	12	Polysorbate 80	80.00 g
0.186	13	Butylated hydroxyanisole	186.92 mg
400 IU	14	Vitamin D viosterol in corn oil (oleovitamin D) (25% excess)	833.34 mg
5000 IU	15	Vitamin A; use vitamin A palmitate (1500000 AU/g) (50% excess[a])	16.66 g
QS	16	Purified water	329 g
QS	17	Carbon dioxide gas	QS

[a]Excess includes 20% manufacturing loss and 30% stability excess.

Manufacturing Directions

Use carbon dioxide cover at all time and use stainless steel 316 or higher resistant equipment.

1. Add 300 mL of purified water and the glycerin into a suitable jacketed tank. Start mixing.
2. Add, in this order, nicotinamide, riboflavin-5-phosphate sodium, Aspetoform M, benzoic acid, and saccharin sodium.
3. Continue mixing for balance of process.
4. Heat to 90°C to 100°C to dissolve ingredients.
5. In a separate tank, boil at least 15 mL of purified water for at least 15 minutes.
6. Cool while bubbling CO_2 gas into it and hold at 30°C or lower for use later for making up the volume.
7. Start cooling the main tank. When the temperature reaches 50°C to 60°C, start bubbling CO_2 gas through the solution from the bottom of the tank.
8. Continue cooling to 25°C. Continue the CO_2 gas protection for the balance of the process.
9. Add and dissolve thiamine HCl, pyridoxine HCl, and ascorbic acid.
10. Dissolve orange oil in alcohol and add.
11. Load approximately 5.25 g of polysorbate 80 into a separate stainless steel container.
12. Heat to 50°C to 60°C; add the butylated hydroxyanisole and dissolve with mixing. Remove heat.
13. Add remaining polysorbate 80 into the container, setting aside a sufficient quantity for rinsing the vitamin containers.
14. Bubble in CO_2 gas while mixing slowly. Stop mixing.
15. Add viosterol and vitamin A palmitate.
16. Rinse bottles with remaining polysorbate 80 and drain.
17. Mix slowly for at least 30 minutes or longer, if necessary, to provide a clear solution. Continue to bubble CO_2 gas for the entire mixing period.
18. Change CO_2 gas protection on main mixing tank to the top to prevent excessive foaming upon addition of polysorbate 80 solution.
19. Add polysorbate 80 solution to the main tank from the bottom of the tank to the top to prevent excessive foaming. Stop mixing.
20. If the volume is less than 1000 mL, adjust the volume with CO_2-saturated purified water made above to 1000 mL; mix for at least 1 hour.
21. In a separate tank, boil at least 115 mL of purified water for at least 15 minutes.
22. Cool while bubbling CO_2 gas into it, and hold at 30°C or lower for use later. Stop mixing.
23. Allow to stand for at least 4 hours to eliminate entrapped CO_2 gas.
24. Readjust volume to 1000 mL with CO_2-saturated purified water; mix for at least 1 hour. Stop mixing.
25. Filter through lint-free paper and do not use filter aids.
26. Recirculate product back to mixing tank until clear.
27. Flush storage tank with CO_2 gas and continue CO_2 gas protection until product has been filled.
28. Average intake dose is 0.60 mL.

Multivitamin Mineral Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
6.65	1	Acid hypophosphorous (50% pure)	6.65
16.47	2	Calcium hypophosphite	16.47
31.68	3	Calcium lactate (powder)	31.68
1.00	4	Methyl paraben	1.00
0.20	5	Propyl paraben	200.00 mg
1.00	6	Benzoic acid	1.00
150.00	7	Sucrose (granular)	150.00
5.20	8	Ferrous gluconate	5.20
2.00	9	Niacinamide (5% excess)	2.10
0.32	10	Riboflavin-5-phosphate sodium	328.77 mg
1.00	11	D-Pantothenyl alcohol (dexpanthenol) (20% excess)	1.20
0.60	12	Vitamin B_{12} (cyanocobalamin) (35% excess)	810.00 μg
0.20	13	Pyridoxine hydrochloride	200.00 mg
0.30	14	Thiamine hydrochloride (regular powder) (55% excess)	465.00 mg
4.78	15	Flavor	4.78
1.94	16	Flavor	1.94
0.64	17	Orange oil, terpeneless	642.00 mg
0.21	18	Lime oil, distilled	214.97 mg
4.28	19	Alcohol (190 proof)	4.28
2.50	20	Saccharin sodium	2.50
14.50	21	Acid ascorbic (white powder/EP) (45% excess)	14.50
3.00	22	Caramel (acid proof)	3.00
2.00	23	Anhydrous citric acid (powder/EP)	2.00
0.01	24	Butylated hydroxyanisole (BHA)	10.00 mg
3.39	25	Corn oil	3.39
0.40	26	Vitamin A palmitate (TN, 1.5 MM UA/g) (40% excess)	560.00 mg
0.08	27	Viosterol in corn oil (syn. oleovitamin D; 1000 mD/g; D_3 in arachis oil) (40% excess)	112.00 mg
1.50	28	Acacia	1.50
0.12	29	Sodium lauryl sulfate (acetone washed)	127.41 mg
171.00	30	Deionized, purified water	171.00
QS	31	Glucose liquid	QS to 1 L

Manufacturing Directions

Do not expose this preparation during manufacturing to direct sunlight. Riboflavin is sensitive to light.

1. Add 83.7 mL of purified water to a stainless steel jacketed tank.
2. Add calcium hypophosphite, calcium lactate, parabens, and benzoic acid.
3. Heat mixture to 60°C with agitation.
4. Shut off mixer and wash tank free of all powders with 25.9 mL purified water.
5. Heat mixture to and maintain a maximum temperature of 100°C until solution is complete. Do not agitate. Avoid loss of water through evaporation. Cover opening of tank.
6. After solution occurs, take sample from bottom of tank and examine for clarity. Solution must be clear.
7. Add acid hypophosphorous (if used) with mixing.
8. Turn off heat and add 222 g glucose and start agitator. (*Caution*: Use CO_2 cover throughout; wherever water is used, it should be CO_2-saturated water.) Dissolve ferrous gluconate in 7.4 mL water CO_2 saturated by heating.
9. Add 278 g glucose with mixing. Add and dissolve sugar.
10. Allow solution to cool to 35°C and mix well.

11. To 29.6 mL water, add and dissolve nicotinamide, riboflavin, D-pantothenyl alcohol, vitamin B_{12}, pyridoxine, and thiamine. Mix until solution is complete and add to tank. Dissolve by heat, if necessary.
12. Charge flavors into tank.
13. Charge saccharin into tank and mix until dissolved.
14. Charge ascorbic acid into tank and mix well.
15. Charge caramel into tank and mix well, Dissolve citric acid in 3 mL water and add to above.
16. Heat corn oil to 50°C to 60°C and add and dissolve BHA. Ensure the BHA is completely dissolved before continuing.
17. Cool to room temperature. While cooling oil mixture, saturate with CO_2 and maintain heavy CO_2 coverage for balance of operation.
18. Set aside a small amount of this mixture as a rinse for the vitamin A and viosterol containers above.
19. Add vitamin A palmitate TN and viosterol to the cool corn oil mixture, rinsing the containers with the oil reserved above.
20. Add the rinse to the bulk. Mix well.
21. Add the acacia to the oil mixture with good mixing.
22. Dissolve sodium lauryl sulfate in 3 mL CO_2-saturated purified water.
23. To avoid excessive foaming, do not bubble CO_2 gas through the water/sodium lauryl sulfate solution.
24. Add the sodium lauryl sulfate solution to the oil mixture and stir to a thick creamy emulsion.
25. Add 7.56 g glucose to the emulsion with mixing.
26. Blend 13.33 mL CO_2-saturated purified water with 77.04 g glucose and add emulsion with stirring.
27. Recycle primary emulsion back into holding tank while setting mill.
28. Homogenize until all oil globules are less than 8 μm in diameter using colloid mill with a very fine setting.
29. Add primary emulsion to syrup solution with mixing; add glucose QS to 965 mL and mix well.
30. Allow to stand overnight to vent entrapped air.
31. Adjust the volume to 1 L using glucose or glucose and CO_2-saturated water.
32. Strain through 149-μm aperture or similar screen into clean reserve tank and recheck volume.
33. Seal tank under heavy CO_2 until filled.

Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/100 mL
170.00 IU	1	Vitamin A palmitate (1.7 million IU/g)	10.00
2.00 IU	2	Vitamin D (40 million IU/g)	0.05
1.00	3	Vitamin E acetate	100.00
0.02	4	Butylhydroxytoluene	2.00
45.00	5	Cremophor RH 40	4.50 g
100.00	6	Water	10.00 g
450.00	7	Saccharose	45.00 g
2.00	8	Methyl paraben	200.00
0.08	9	Citric acid	80.00
9.60	10	Glycerol	9.60 g
250.00	11	Water	25.00 g
0.15	12	Thiamine hydrochloride	15.00
0.15	13	Riboflavin 5′-phosphate sodium	15.00
0.55	14	Nicotinamide	55.00
0.15	15	Pyridoxine hydrochloride	15.00
3.00	16	Ascorbic acid (crystalline)	300.00
1.00	17	Sorbic acid	100.00
5.00	18	Propylene glycol (pharma)	5.00 g

Manufacturing Directions

1. Mix items 1 through 5 and heat to 60°C.
2. Separately heat item 2 to approximately 60°C.
3. Mix these two solutions slowly, stirring well to obtain a clear solution.
4. Dissolve items 7 to 9 in the hot solution of items 10 and 11 to obtain a clear solution.
5. Add to solution above.
6. Add items 12 to 18 and adjust the pH to 4.0 to 4.2.
7. Pass nitrogen through the solution for 10 minutes and fill under nitrogen cover. Provides 1 to 2 RDA/20 mL.

Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/100 mL (mg)
0.17	1	Vitamin A palmitate (1.7 MM IU/g)	17.00
0.001	2	Vitamin D_3 (40 MM IU/g)	0.10
0.01	3	Butylhydroxytoluene	1.00
30.00	4	Cremophor RH 40	3.00 g
1.00	5	Parabens	100.00
170.00	6	Water	17.00 g
0.50	7	Thiamine hydrochloride	50.00
0.20	8	Riboflavin phosphate sodium	20.00
0.20	9	Pyridoxine hydrochloride	20.00
2.50	10	Ascorbic acid (crystalline)	250.00
50.00	11	Water	5.00 g
–	12	Sugar syrup	Add 100 mL

Manufacturing Directions

1. Heat mixture of items 1 to 4 to approximately 65°C.
2. Stir well and very slowly add item 6 to warm solution (65°C).
3. Mix with solution of items 7 to 11 and add item 12 to make up the volume. *Note*: Parabens are generally a 1:10 ratio of methyl and propyl paraben.

Multivitamin with Fluoride Infant Drops

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
8.00	1	Niacin; use niacinamide (5% excess)	8.332
0.60	2	Riboflavin, USP; use riboflavin-5′–phosphate sodium (2% excess)	0.83
0.50	3	Methyl paraben	0.50
1.00	4	Benzoic acid	1.00
5000 IU	5	Vitamin E; use D-α-tocopheryl PEG-1000 succinate (20% excess)	13.826
400 IU	6	Vitamin D; use viosterol in corn oil (syn. oleovitamin D) (25% excess)	0.522
1500 IU (0.45)	7	Vitamin A palmitate (synthetic A palmitate, 1 MM U/g), USP	1.44
35.00	8	Ascorbic acid (white powder), USP (33% excess)	46.55
0.50	9	Thiamine hydrochloride (44% excess)	0.72
0.40	10	Pyridoxine; use pyridoxine hydrochloride	0.486
0.25	11	Fluoride; use sodium fluoride (powder)	0.5526
4.013	12	Caramel (acid proof)	4.013
0.257	13	Orange oil terpeneless	0.257
QS	14	Alcohol (ethanol; 190 proof)	10.00 mL
QS	15	Distilled purified water	QS
QS	16	Acid hydrochloric	QS
QS	17	Sodium hydroxide	QS
QS	18	Carbon dioxide gas	QS

Manufacturing Directions

Use only stainless steel tanks and minimize vortex formation to prevent aeration. Product attacks glass, so avoid contact with glass.

1. Charge 350 mL of purified water into the stainless steel jacketed main tank.
2. Start mixing.
3. Add, in this order, niacinamide, riboflavin, sodium fluoride, methyl paraben, and benzoic acid.
4. Rinse the interior walls of the tank with approximately 16 mL purified water.
5. Continue mixing for the balance of the process.
6. Heat the main tank to 95°C to dissolve ingredients.
7. When the solution is complete, cool below 85°C (range: 80–90°C).
8. The main tank will have to be heated to 85°C for this step.
9. Add vitamin E to another tank, if necessary, by heating vitamin E container.
10. Melt vitamin E in the tank.
11. Add viosterol and vitamin A and heat to 60°C to 65°C with mixing.
12. Start bubbling in CO_2.
13. Mix slowly for 10 minutes or longer to produce a clear solution.
14. Start CO_2 gas protection on the main mixing tank and continue for the balance of the process.
15. With the main batch at 85°C to 90°C, add the solution of vitamins E, D, and A at 60°C to 65°C with mixing.
16. The addition may cause the temperature of the main batch to drop below the specified range, so readjust to 85°C to 90°C.
17. Mix and maintain at this temperature until solution is complete, after which cool to below 30°C.
18. Add the glycerin with mixing.
19. Adjust the temperature to 25°C ± 5°C and maintain at this temperature before proceeding.
20. Add and dissolve with mixing, in this order, ascorbic acid, thiamine, pyridoxine, and caramel.
21. Rinse the caramel container with approximately 3 mL of water and add the rinsings.
22. Rinse the tank inner walls and mixer shaft with approximately 3 mL water.
23. Dissolve the orange oil with mixing in the alcohol and add to solution above.
24. Continue mixing for at least 30 minutes to ensure a homogeneous product.
25. Stop mixing and take pH (range: 3.1–3.3). If necessary, adjust with 10% sodium hydroxide or 10% hydrochloric acid, prepared by adding 1 mL hydrochloric acid (reagent-grade) with 3.3 mL purified water. Mix.
26. Stop mixing and allow to stand for at least 4 hours to eliminate entrapped CO_2 gas.
27. In a properly cleaned separate tank, boil at least 65 mL of purified water for at least 15 minutes.
28. Cool while bubbling CO_2 into it and hold at 30°C.
29. Adjust pH to the range of 3.1 to 3.3.
30. Filter using a lint-free paper; do not use filter aids.
31. Recirculate product back to main mixing tank until clear.
32. Flush a storage tank with CO_2 for at least 10 minutes with the CO_2 valve completely open.
33. Filter product into this storage tank.
34. Fill under CO_2 cover.

Multivitamin Drops

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
8.00	1	Vitamin A palmitate 1.7 mm U/g (BASF)	8.00
0.130	2	Vitamin D_3 40 mm U/g	0.130
5.00	3	Vitamin E acetate (BASF)	5.00
150.0	4	Cremophor EL (or Cremophor RH 40)	150.00
2.00	5	Parabens	2.00
525.00	6	Water	525.00
4.00	7	Thiamine hydrochloride (BASF)	4.00
2.00	8	Riboflavin 5-phosphate sodium	2.00
2.00	9	Pyridoxine hydrochloride (BASF)	2.00
2.00	10	Nicotinamide	2.00
0.20	11	Sodium bisulfite	0.20
200.00	12	Propylene glycol	200.00
QS	13	Water	10.00 g
QS	14	Hydrochloric acid	QS

Manufacturing Directions

1. Heat mixture of items 1 to 4 to approximately 60°C and stir strongly.
2. Slowly add solution of items 5 and 6 at 60°C.
3. To the obtained clear solution, add solution of items 7 to 13.
4. Adjust the pH, with item 14, to approximately 4.
5. Bring to volume.

Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/100 mL (g)
0.170	1	Vitamin A palmitate 1.7 MM U/g (BASF)	17.0 mg
0.001	2	Vitamin D3 40 MM U/g	0.1 mg
0.010	3	Butylhydroxytoluene	1.0 mg
30.000	4	Cremophor RH 40	3.00
1.000	5	Parabens	0.10
170.000	6	Water	17.00
0.500	7	Thiamine hydrochloride (BASF)	0.05
0.200	8	Riboflavin phosphate sodium	0.02
0.200	9	Pyridoxine hydrochloride (BASF)	0.02
2.500	10	Ascorbic acid, crystalline (BASF)	0.25
50.000	11	Water	5
QS	12	Sugar syrup	QS to 100 mL

Manufacturing Directions

1. Heat mixture of items 1 to 4 to about 65°C and stir well.
2. Add very slowly item 6 to the warm solution (65°C).
3. Mix with solution of items 7 to 11 and add item 12 to make up the volume. Parabens are generally a 1:10 ratio of methyl and propyl paraben.

Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/100 mL (g)
170.00 U	1	Vitamin A palmitate 1.7 MMM U/g (BASF)	0.010
2.00 U	2	Vitamin D 40 MMM U/g	0.05 mg
1.00	3	Vitamin E acetate (BASF)	0.10
0.020	4	Butylhydroxytoluene	0.0020
45.0	5	Cremophor RH 40	4.50
100.00	6	Water	10.00
450.00	7	Saccharose	45.00
2.00	8	Methyl paraben	0.20
0.080	9	Citric acid	0.080
9.60	10	Glycerol	9.60
250.00	11	Water	25.00
0.150	12	Thiamine hydrochloride (BASF)	0.015
0.150	13	Riboflavin 5'-phosphate sodium	0.015
0.55	14	Nicotinamide	0.055
0.150	15	Pyridoxine hydrochloride (BASF)	0.015
3.00	16	Ascorbic acid, crystalline (BASF)	0.30
1.00	17	Sorbic acid	0.10
5.00	18	Propylene glycol	5.00

Manufacturing Directions

1. Heat items 1 to 5 and item 2 separately to approximately 60°C and mix slowly with stirring to obtain a clear solution.
2. Dissolve items 7 to 9 in the hot solution of items 10 and 11 to obtain a clear solution.
3. Mix the cool solutions and then add items 12 to 18 and adjust the pH value to 4.0 to 4.2.
4. Pass nitrogen for 10 min through the solution and fill under nitrogen cover. Provides 1 to 2 RDA/20 mL.

Multivitamin With Fluoride-Infant Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/1000 L (g)
8.00	1	Niacin, USE niacinamide, 5% excess	8.33
0.60	3	Riboflavin, USE riboflavin-5'-phosphate sodium 2% excess	0.84
0.50 g	5	Methyl paraben	0.50
1.00	6	Acid benzoic	1.00
5000 U	7	Vitamin E, USE D-alpha tocopheryl polyethylene glycol 1000 succinate, 20% excess	13.82
400 U	9	Vitamin D, USE viosterol in corn oil (synthetic oleovitamin D, 25% excess)	0.52
1500 U (0.45 mg)	11	Vitamin A palmitate synthetic A palmitate 1 mm	
U/g	1.44		
35.00	14	Acid, ascorbic white powder, 33% exc;	46.55
0.50	15	Thiamine hydrochloride, 44% excess	0.72
0.40	16	Pyridoxine, USE pyridoxine hydrochloride	0.48
0.25	18	Fluoride, USE sodium fluoride powder	0.55
4.01	20	Caramel acid proof	4.01
0.26	21	Oil Orange Terpeneless	0.25
0.00001 mL	22	Alcohol, ethanol, 190 proof	0.101 mL
QS	23	Water purified, distilled	QS
QS	24	Acid hydrochloric	QS
QS	25	Sodium hydroxide	QS
QS	26	Carbon dioxide gas	QS

Manufacturing Directions

Use only stainless steel tanks; minimize vortex formation to prevent aeration. Product attacks glass; avoid contact with glass.

1. Charge 350 mL of purified water into the stainless steel jacketed main tank.
2. Start mixing. Add, in order, niacinamide, riboflavin, sodium fluoride, methyl paraben, and benzoic acid.
3. Rinse the interior walls of tank with approximately 16 mL purified water.
4. Continue mixing for the balance of the process.
5. Heat the main tank to 95°C to dissolve ingredients. When the solution is complete, cool below 85°C (range 80–90°C).
6. Add vitamin E to another tank, if necessary, by heating vitamin E container. Melt vitamin E in the tank.
7. Add viosterol and vitamin A and heat to 60°C to 65°C with mixing.
8. Start bubbling in CO_2. Mix slowly for 10 minutes or longer to produce a clear solution. Start CO_2 gas protection on the main mixing tank and continue for the balance of the process.
9. With the main batch at 85°C to 90°C, add the solution of vitamins E, D, and A at 60°C to 65°C, with mixing. The addition may cause the temperature of the main batch to drop below the specified range; readjust to 85°C to 90°C.
10. Mix and maintain at this temperature until solution is complete, after which cool to below 30°C. Add the glycerin with mixing. Adjust the temperature to the 25°C to 5°C range and maintain at this temperature before proceeding.
11. Add and dissolve with mixing in the following order: ascorbic acid, thiamine, pyridoxine, and caramel. Rinse the caramel container with approximately 3 mL of water and add the rinsings.
12. Rinse the tank inner walls and mixer shaft with approximately 3 mL water.
13. Dissolve the orange oil with mixing in the alcohol and add to solution.
14. Continue mixing for at least 30 minutes to ensure a homogenous product.
15. Stop mixing, take pH (range: 3.1–3.3). If necessary, adjust with 10% sodium hydroxide or 10% hydrochloric acid (prepared by adding 1 mL hydrochloric acid, reagent grade, with 3.3 mL purified water). Mix.
16. Stop mixing and allow to stand for at least 4 hours to eliminate entrapped CO_2 gas.
17. In a separate tank, properly cleaned, boil at least 65 mL of purified water for at least 15 minutes, cool while bubbling CO_2 into it, and hold at 30°C and adjust pH in the range 3.1 to 3.3.
18. Filter using a lint-free paper; do not use filter aids.
19. Recirculate product back to main mixing tank until clear. Flush a storage tank with CO_2 for at least 10 minutes with the CO_2 valve completely open.
20. Filter product into this storage tank. Fill under carbon dioxide cover.

Nafarelin Acetate Nasal Solution

Synarel nasal solution contains nafarelin acetate (2 mg/mL, content expressed as nafarelin base) in a solution of benzalkonium chloride, glacial acetic acid, sodium ride, polysorbate 80, aroma, and water. The solution is isotonic with a pH of 7. It contains no chlorofluorocarbons.

Naproxen Suspension

Naprosyn (naproxen) suspension for oral administration contains 125 mg/5 mL of naproxen in a vehicle containing sucrose, magnesium aluminum silicate, sorbitol solution, and sodium chloride (30 mg/5 mL, 1.5 mEq), methyl paraben, fumaric acid, FD&C yellow No. 6, imitation pineapple flavor, imitation orange flavor, and purified water. The pH of the suspension ranges from 2.2 to 3.7.

Nevirapine Suspension

Viramune oral suspension is for oral administration. Each 5 mL of Viramune suspension contains 50 mg nevirapine (as nevirapine hemihydrate). The suspension also contains the following excipients: carbomer 934P, methyl paraben, propyl paraben, sorbitol, sucrose, polysorbate 80, sodium hydroxide, and water.

Nicotine Spray

Each 10-mL spray bottle contains 100 mg nicotine (10 mg/mL) in an inactive vehicle containing disodium phosphate, sodium dihydrogen phosphate, citric acid, methyl paraben, propyl paraben, EDTA, sodium chlorhydroxide, or hydrochloric acid (to adjust pH), sorbitol, and purified water.

Nimesulide Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Nimesulide	10.00
400.00	2	Sucrose	400.00
49.00	3	Propylene glycol	49.00
1.00	4	Methyl paraben	1.00
0.20	5	Propyl paraben	0.20
2.80	6	Sodium benzoate	2.80
0.20	7	Disodium edentate	0.20
0.50	8	Sodium citrate	0.50
0.10 mL	9	Sorbitol solution 70%	100 mL
4.00	10	Carboxymethyl cellulose sodium	4.00
2.00	11	Aerosil 200	2.00
3.30	12	Citric acid	3.30
1.00	13	Hydroxypropyl methyl cellulose	1.00
0.48	14	Simethicone emulsion	0.48
QS	15	Flavor	QS
QS	16	Water purified	QS to 1 L

Manufacturing Directions

1. In a suitable stainless steel container, heat item 16 to 70°C.
2. Add and dissolve sodium benzoate, disodium edentate, and sodium citrate.
3. Filter though a filter press.
4. Add sugar till completely dissolved.
5. Filter again through a filter press.
6. In a separate container, charge propylene glycol and sorbitol solution. Add carboxymethyl cellulose and aerosol homogenizes and store for a few hours.
7. Add and mix in step 5, hydroxypropylmethylcellulose and simethicone emulsion.
8. Add item 1 and make a slurry in step 6.
9. Add step 7 into step 4 and make up the volume with item 16.

Nimodipine Capsules

Each liquid-filled capsule contains 30 mg nimodipine in a vehicle of glycerin, peppermint oil, purified water, and polyethylene glycol 400. The soft gelatin capsule shell contains gelatin, glycerin, purified water, and titanium dioxide.

Nitroglycerin Lingual Spray

Nitrolingual pumpspray (nitroglycerin lingual spray 400 μg) is a metered-dose spray containing nitroglycerin. This product delivers nitroglycerin (400 μg per spray, 75 or 200 metered sprays) in the form of spray droplets onto or under the tongue. Inactive ingredients are medium-chain triglycerides, dehydrated alcohol, medium-chain partial glycerides, and peppermint oil.

Norephedrine Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
40.00	1	DL-Norephedrine hydrochloride	40.00
10.00	2	Parabens	10.00
50.00	3	Saccharin sodium	50.00
30.00	4	Kollidon 90F	30.00
500.00	5	Sorbitol solution	500.00
460.00	6	Water	460.00

Manufacturing Directions

1. Dissolve the parabens in the hot water (90–95°C).
2. Add the sorbitol, cool to room temperature, and dissolve the other components.
3. To prevent of discoloration of Kollidon in the solution during storage, 0.1% to 0.5% of cysteine could be added as antioxidant.
4. Flavors should be added to adjust the required taste.

Norephedrine Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
40.00	1	DL-norephedrine hydrochloride	40.00
4.00	2	Parabens	4.00
5.00	3	Saccharin sodium	5.00
3.00	4	Kollidon® 90F	3.00
500.00	5	Sorbitol solution	500.00
460.00	6	Water	460.00

Manufacturing Directions

1. Dissolve the parabens in the hot water, add the sorbitol, cool to room temperature, and dissolve the other components.
2. To prevent discoloration of Kollidon in the solution during storage, 0.1% to 0.5% cysteine could be added as an antioxidant.
3. Flavors should be added to adjust the taste, as needed.

Nystatin Oral Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
21.05	1	Nystatin microfine (particles size not less than 90% below 45 (im, 100% below 80 (im; based on potency of 5500 U/g anhydrous; adjust accordingly; 10% overage)	21.050
600.00	2	Sucrose	600.000
1.80	3	Methyl paraben	1.8000
0.20	4	Propyl paraben	0.2000
150.00	5	Sorbitol (70% solution)	150.000
5.00	6	Microcrystalline cellulose	5.000
10.00	7	Glycerin	10.000
2.00	8	Carboxymethylcellulose sodium	2.000
2.00	9	Polysorbate 80	2.000
50.00	10	Glycerin	50.000
2.50	11	Saccharin sodium	2.500
2.00	12	Flavor	2.000
30.00	13	Alcohol (ethanol 95%)	30.000
QS	14	Sodium hydroxide	0.174
QS	15	Hydrochloric acid (37%)	0.296
–	16	Water purified	QS to 1 L

Manufacturing Directions

1. Add 200 g of item 16 (90–95°C) into mixer and heat to 90°C to 95°C. Dissolve items 3 and 4 while mixing. Add and dissolve item 2 while mixing at a speed of 18 rpm.
2. Cool down to approximately 50°C to 55°C.
3. Filter the syrup. Collect the syrup in a clean stainless steel tank. Avoid any loss of syrup. Clean the mixer.
4. Transfer the sugar syrup from the stainless steel tank into the mixer.
5. Add 100 g of item 5 into mixer while mixing.
6. Disperse item 6 in the mixture of 50 g of item 16 (25–30°C) and 50 g of item 5 in a stainless steel drum while mixing with stirrer.
7. Disperse item 8 in item 7 in a stainless steel drum while mixing with stirrer. Add 30 g of item 16 (90°C) to the solution. Stir until it becomes clear. Cool to 30°C.
8. Transfer the dispersion from step 3 and 4 into mixer.
9. Mix and homogenize under vacuum 0.4 to 0.6 bar for 10 minutes.
10. Stop homogenizer and keep continuous mixing.
11. Dissolve item 9 in 50 g of item 16 (50°C) in a stainless steel container while mixing by stirrer.
12. Add item 10 into it. Disperse item 1 while stirring by stirrer. Cool to 30°C.
13. Add the drug dispersion into mixer while mixing.
14. Dissolve item 11 in 15 g of item 16 (25–30C) in a stainless steel container while stirring by stirrer. Add to mixer while mixing.
15. Add items 12 and 13 into mixer while mixing.
16. Homogenize high speed and vacuum 0.4 to 0.6 bar. Mix and homogenize for 10 minutes.
17. Dissolve item 14 in 7 g of item 16 in a stainless steel container. Add slowly into the mixer while mixing.
18. Dissolve item 15 carefully in 7 g of item 16 in a stainless steel container. Slowly add the required quantity into mixer to adjust the pH between 6.8 and 7.1.
19. Make up the volume with item 16, up to 1 L. Mix for 5 minutes.

Nystatin Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
22.50	1	Nystatin	22.50
57.50	2	Kollidon CL-M	57.50
20.00	3	Kollidon 90F	20.00
248.00	4	Sorbitol	248.00
5.00	5	Citric acid	5.00
QS	6	Water purified	QS to 1 L

Manufacturing Directions

1. Charge items 1, 2, and 4 in a suitable stainless steel vessel and suspend in item 6; mix well.
2. Add item 3 slowly while stirring and in small portions and then follow up with vigorous stirring to obtain smooth suspension. Homogenize if necessary.
3. Fill.

Ofloxacin Otic Solution

Floxin otic contains 0.3% (3 mg/mL) ofloxacin with benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 6.5 ± 0.5.

Ofloxacin Otic Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
3.00	1	Ofloxacin	3.00
QS	2	Vehicle (pluraflo 1220 45.48%, ethanol 5.05%, propylene glycol 41.23%, anhydrous glycerin 8.24)	QS to 1 L
QS	3	Perfumes	QS

Manufacturing Directions

1. Add propylene glycol, pluraflo, glycerin, and ethanol to a clean vessel.
2. While stirring, add ofloxacin. Stir until a clear solution is obtained.
3. Add perfume and mix until uniform.

Omeprazole Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
20.00	1	Omeprazole free base	20.00
QS	2	Vehicle (pluronic F127 34.07%, ethanol 10.43%, propylene glycol 42.18%)	1.00 L
1.00	3	Sodium metabisulfite	1.00
1.00	4	Disodium EDTA	1.00
2.50	5	Sodium saccharin	2.50
1.10	6	Monoammonium glycerhizzinate	1.10
3.50	7	Acesulfame	3.50
QS	8	Flavor	QS

Manufacturing Directions

1. Add propylene glycol and poloxamer to a clean vessel (main mix).
2. While stirring, heat the mixture as appropriate to sufficiently melt the poloxamer.
3. Once a uniform solution is obtained, remove from heat source and continue mixing.
4. In a separate vessel (alcohol premix), add alcohol, omeprazole base, and monoammonium glycerizzinate and mix until uniform. In another vessel (water premix), add water, EDTA, sodium saccharin, acesulfame, and sodium metabisulfite.
5. Mix until all materials are dissolved.
6. Add the alcohol containing premix to the main mixing vessel containing the poloxamer.
7. Mix until uniform.
8. While stirring, add the water containing premix to the main vessel and continue to mix until uniform.
9. Subsequently, add desired flavor component and mix until uniform.

Ondansetron Hydrochloride Dihydrate Oral Solution

Each 5 mL of Zofran oral solution contains 5 mg of ondansetron HCl dihydrate equivalent to 4 mg of ondansetron. Zofran oral solution contains the inactive ingredients citric acid anhydrous, purified water, sodium benzoate, sodium citrate, sorbitol, and strawberry flavor.

Orciprenaline Sulfate and Clobutinol Hydrochloride Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
10.00	1	Natrosol 250 M	2.00
5.00	2	Sodium benzoate	1.00
10.00	3	Saccharin sodium	2.00
35.00	4	Ammonium chloride	7.00
26.24	5	Citric acid	5.25
4.00	6	Sodium citrate	0.80
2500.00	7	Sorbitol 70%	500.00
500.00	8	Glycerin	100.00
5.00	9	Orciprenaline sulfate, 5% excess	1.05
20.00	10	Clobutinol hydrochloride	4.20
40.40	11	Alcohol	8.00
0.20	12	Anise oil	0.04
QS	13	Water purified	QS to 1 L

Manufacturing Directions

1. In a suitable stainless steel mixing vessel, charge 250 mL of item 13 and heat to 70°C to 75°C. Add item 1 and mix well; cool to room temperature.
2. In 10 mL of item 13, add and dissolve item 2 and 3 and add to step 2.
3. In 20 mL of item 13, add and dissolve item 4 and add to step above.
4. In a separate vessel, add items 50 mL of item 13 and item 8 and mix well; add to step 4.
5. In 50 mL of item 13, add item 10, mix well, and add to step 5.
6. In 50 mL of item 13, add item 9, mix well, and add to step 6.
7. Adjust pH to 3.1 to 3.2 using item 5.
8. Filter through 100-micron filter and then through filter pads.
9. Make up volume and fill.

Oxitropium and Formoterol Nasal Spray

1. Charge 4.5 g of micronized oxitropium bromide and 0.675 g of micronized formoterol fumarate into a pressure-addition vessel.
2. After sealing and evacuation thereof, 10.5 kg of HFA 227, which has previously been aerated with carbon dioxide and adjusted to a pressure of 6.25 bar (20°C) in another pressure addition vessel, is added.
3. After homogenization of this mixture, the suspension obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Oxycodone Hydrochloride Oral Concentrate Solution

Each 1 mL of Oxyfast concentrate solution contains oxycodone hydrochloride, 20 mg citric acid, FD&C yellow No. 10, sodium benzoate, sodium citrate, sodium saccharine, and water.

Oxymetazoline Hydrochloride Congestion Nasal Spray

Each milliliter of Afrin severe congestion nasal spray contains oxymetazoline hydrochloride 0.05%. It also contains benzalkonium chloride, benzyl alcohol, camphor, EDTA, eucalyptol, menthol, polysorbate 80, propylene glycol, sodium phosphate dibasic, sodium phosphate monobasic, and water.

Oxymetazoline Hydrochloride Nasal Solution

Bill of Materials			
Scale (g/100 mL)	Item	Material Name	Qty/L (g)
0.025	1	Oxymetazoline hydrochloride	0.25
0.03	2	Benzalkonium chloride (50% Solution)	0.30
0.05	3	Disodium edetate (sodium EDTA)	0.50
0.025	4	Sodium hydroxide (1N solution)	0.25
1.02	5	Monobasic sodium phosphate	10.20
2.80	6	Dibasic sodium phosphate	28.00
–	7	Water purified	QS to 1 L

Manufacturing Directions

Oxymetazoline hydrochloride is toxic. There is a risk of serious intoxication if inhaled or swallowed. This product is a colorless, odorless membrane-filtered solution. Thus, make sure that the receiving tank for the filtered solution is cleaned and free of any contamination.

1. Heat 1 kg of item 7 up to 85°C to 90°C in the manufacturing vessel. Hold the temperature at 85°C to 90°C for 30 minutes.
2. Cool item 7 to 30°C and transfer into mobile tank.
3. Add 900 g of cold item 7 (from step 2) into manufacturing vessel.
4. Dissolve items 1 to 6 one by one while mixing in manufacturing vessel containing cold item 7.
5. After completion of addition mix for 20 more minutes.
6. Make up the volume to 1 L with cold item 7 and, finally, mix for 20 minutes.
7. Check and record the pH (limit: 6.8 ± 0.1).
8. Filter the solution through Sartorius prefilter and membrane filter 0.2 μm into receiving tanks.

Oxymetazoline Moisturizing Nasal Spray

Each milliliter of Afrin extra moisturizing nasal spray contains oxymetazoline hydrochloride, 0.05%. It also contains benzalkonium chloride, EDTA, glycerin, polyethylene glycol, polyvinyl pyrrolidone, propylene glycol, sodium phosphate dibasic, sodium phosphate monobasic, and water.

Oxymetazoline Nasal Spray

Each milliliter of Afrin original nasal spray and pump mist contains oxymetazoline hydrochloride 0.05%. It also contains benzalkonium chloride, EDTA, polyethylene glycol, polyvinyl pyrrolidone, propylene glycol, sodium phosphate dibasic, sodium phosphate monobasic, and water.

Oxymetazoline Sinus Nasal Spray

Each milliliter of Afrin sinus nasal spray contains oxymetazoline hydrochloride 0.05%. It also contains benzalkonium chloride, benzyl alcohol, camphor, EDTA, eucalyptol, menthol, polysorbate 80, propylene glycol, sodium phosphate dibasic, sodium phosphate monobasic, and water.

Oxymetazoline Nasal Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
QS	1	Vehicle (pluronic F127 40.27%, ethanol 26.18%, water 33.55%)	QS to 1 L
0.50	2	Oxymetazoline	0.50
1.50	3	Tyloxapol	1.50
0.40	4	Dibasic sodium phosphate	0.40
1.30	5	Monobasic potassium phosphate	1.30
0.40	6	Benzalkonium chloride	0.40
2.60	7	Chlorhexidine gluconate	2.60
0.10	8	Disodium EDTA	0.10

Manufacturing Directions

1. Add the dibasic sodium phosphate, monobasic potassium phosphate, disodium EDTA, benzalkonium chloride, and oxymetazoline HCl to a clean vessel.
2. Add tyloxapol, chlorhexidine gluconate, and ethanol to the vessel.
3. Subsequently, add the poloxamer and water to the vessel.
4. Mix until uniform.

Peptide Topical Liquid

Formulation

Peptide such as thymic fraction 5, glycerin 44.5, propylene glycol 44.9, methyl nicotinate 0.1, water 50, polysorbate 80, 0.5% by weight.

Pheniramine Maleate Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
15.00	1	Pheniramine maleate	3.00
2980.00	2	Sugar	596.00
5.40	3	Methyl paraben	1.08
0.60	4	Propyl paraben	0.11
0.60	5	Citric acid monohydrate	0.11
1.50	6	Sodium citrate	0.30
3.50	7	Flavor	0.70
QS	8	Water purified	QS to 1 L

Manufacturing Directions

1. Charge 700 mL item 8 in a suitable mixing vessel and heat to 90°C to 95°C.
2. Add and mix item 2.
3. Add items 3 and 4 and mix to dissolve.
4. In separate vessels in approximately 100 mL item 8, add and dissolve items 5 to 7 and item 1 separately.
5. Add the two mixtures in step 3 to step 2 at room temperature.
6. Make up the volume.

Phenobarbital, Hyoscyamine Sulfate, Atropine Sulfate, and Scopolamine Hydrobromide Elixir

Each 5 mL (teaspoonful) of elixir (23% alcohol) contains phenobarbital 16.2 mg, hyoscyamine sulfate 0.1037 mg, atropine sulfate 0.0194 mg, and scopolamine hydrobromide 0.0065 mg; D&C yellow No. 10, FD&C blue No. 1, FD&C yellow No. 6, flavors, glucose, saccharin sodium, water.

Phenylephrine Tannate and Chlorpheniramine Tannate Pediatric Suspension

Rynatan® pediatric suspension is an antihistamine/nasal decongestant combination available for oral administration as a suspension. Each 5 mL (one teaspoonful) of the slate purple-colored, natural strawberry, artificial currant-flavored suspension contains phenylephrine tannate 5 mg, chlorpheniramine tannate 4.5 mg, benzoic acid, FD&C blue No. 1, FD&C red No. 3, FD&C red No. 40, FD&C yellow No. 5, flavors (natural and artificial), glycerin, kaolin, magnesium aluminum silicate, methylparaben, pectin, purified water, saccharin sodium, and sucrose.

Phenylephrine Tannate and Pyrilamine Tannate Suspension

RYNA-12 S suspension is an antihistamine/nasal decongestant combination available for oral administration as a suspension. Each 5 mL (one teaspoonful) of the pink-colored, natural strawberry, artificial currant-flavored suspension contains phenylephrine tannate 5 mg, pyrilamine tannate 30 mg, benzoic acid, FD&C red No. 3, flavors (natural and artificial), glycerin, kaolin, magnesium aluminum silicate, methyl paraben, pectin, purified water, saccharin sodium, and sucrose.

Phenylpropanolamine, Chlorpheniramine, Dextromethorphan, Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
150.00	1	Polyethylene glycol 400	150.00
21.66	2	Acetaminophen	21.66
0.075 mL	3	Glycerin	75.000 mL
0.35 mL	4	Sorbitol solution	350.000 mL
1.00	6	Acid, benzoic	1.00
1.75	7	Saccharin sodium, powder, dihydrate	1.75
0.91	8	Phenylpropanolamine hydrochloride	0.92
0.065	9	Chlorpheniramine maleate (10% excess)	0.073
0.66	10	Dextromethorphan hydrobromide	0.67
20.00	11	Sodium CMC premium low viscosity	0.02
70.00	12	Dye	0.070
6.00	13	Dye	0.006
5.00	14	Ascorbic acid, USE sodium ascorbate fine powder	5.62
0.50	15	Flavor orange	0.50
0.25	16	Flavor orange	0.25
QS	17	Carbon dioxide gas	QS
QS	18	Water purified	QS to 1 L

Manufacturing Directions

1. In a covered stainless steel container, heat 500 mL water to boiling. Boil for 30 minutes.
2. Turn off the heat and, while keeping the container covered, cool the water to 30°C while purging it with carbon dioxide.
3. Keep this water in a covered container blanketed with carbon dioxide gas and use where indicated.
4. Transfer to the main stainless steel mixing tank the polyethylene glycol 400, cover, start bubbling CO_2 gas, and then, while mixing, slowly heat to 60°C to 65°C. Maintain at this temperature.
5. While mixing, add and dissolve the acetaminophen. Maintain the temperature and CO_2 protection.
6. When all the acetaminophen has dissolved, add, while mixing, the glycerin and sorbitol.
7. Continue mixing while maintaining the temperature and CO_2 gas protection until used later. Do not allow the temperature to go above 65°C. During this mixing period, remove samples through the bottom valve of the mixing tank and inspect for clarity. Return samples to the mixing tank.
8. Continue mixing and sampling until absolutely clear.
9. In a separate stainless steel mixing tank, add 300 mL water, cover, and then heat to 90°C.
10. While maintaining at this temperature, start bubbling CO_2 gas and then, while mixing, add and dissolve successively the benzoic acid, saccharin sodium, and phenylpropanolamine hydrobromide.
11. Continue mixing until all have dissolved. Reduce the temperature to 60°C to 65°C while mixing. Do not force cool.
12. To the solution in the main mixing tank add, while mixing and bubbling CO_2 gas, the solution from step above. Rinse the container with two lots of 5 mL carbon dioxide-saturated water and add the rinsings to the batch while mixing.
13. Continue mixing for 15 minutes while maintaining the temperature at 60°C to 65°C and CO_2 gas protection.
14. While mixing the batch, sprinkle on the sodium CMC.
15. Continue mixing until all the sodium CMC has been dispersed. Check to be sure there are no undissolved lumps.
16. Add CO_2-saturated water from step above and mix while cooling the batch to 30°C. Dissolve the dyes in 10 mL carbon dioxide-saturated water then add to the batch with mixing.
17. Rinse the container with two lots of 5 mL the same water and add the rinsings to the batch. Mix until a homogenously colored batch is formed.
18. Stop bubbling in CO_2 gas but maintain CO_2 protection of the tank headspace. In a stainless steel container, dissolve the sodium ascorbate in 25 mL carbon dioxide-saturated water, taking care to minimize exposure of the solution to air or light.
19. Mix all solutions, add rinsings where necessary, and continue mixing for 15 minutes.
20. Add the flavors, complete the batch to 1 L with carbon dioxide-saturated water, and mix well for 1 hour.
21. Stop mixing, saturate the head space with CO_2, and leave overnight to release any entrapped air.

Phenylpropanolamine, Chlorpheniramine, Dextromethorphan, Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
150.00	1	PEG-400 (low color), NF	150.00
21.66	2	Acetaminophen, USP	21.66
0.075 mL	3	Glycerin, USP (96%)	75.00 mL
0.35 mL	4	Sorbitol; use sorbitol solution, USP	350.00 mL
1.00	5	Benzoic acid, USP	1.00
1.75	6	Saccharin sodium (dihydrate powder), USP	1.75
0.91	7	Phenylpropanolamine hydrochloride, USP	916.70 mg
0.06	8	Chlorpheniramine maleate, USP (plus 10% manufacturing)	73.30 mg
0.66	9	Dextromethorphan hydrobromide, USP	667.00 mg
20.00	10	Sodium CMC (premium low viscosity)	20.00
70.00	11	Dye	70.00 mg
6.00	12	Dye	6.00 mg
5.00	13	Ascorbic acid; use sodium ascorbate (fine powder)	5.62
0.50	14	Flavor, orange	500.00 mg
0.25	15	Flavor, orange	250.00 mg
QS	16	Carbon dioxide gas	QS
QS	17	Purified water, USP	QS to 1 L

Manufacturing Directions

Manufacture under complete CO_2 protection. Bubble the CO_2 gas through the solution from the bottom of the tank.

If excessive foaming occurs, change CO_2 gas protection from the bottom to the top of the tank. Minimize vortex formation while mixing to prevent aeration of the product.

1. In a covered stainless steel container, heat 500 mL of water to boiling. Boil for 30 minutes.
2. Turn off the heat; while keeping the container covered, cool the water to 30°C while purging the water with CO_2.
3. Keep this water in a covered container blanketed with CO_2 gas and use where indicated.
4. Transfer the PEG-400 to the main stainless steel mixing tank and cover.
5. Start bubbling CO_2 gas; while mixing, slowly heat to 60°C to 65°C. Maintain at this temperature.
6. While mixing, add and dissolve the acetaminophen. Maintain the temperature and CO_2 protection.
7. When all the acetaminophen has dissolved, add, while mixing, the glycerin and sorbitol.
8. Continue mixing while maintaining the temperature and CO_2 gas protection until mixture is used later.
9. Do not allow the temperature to go above 65°C.
10. During this mixing period, remove samples through the bottom valve of the mixing tank and inspect for clarity; return samples to the mixing tank. Continue mixing and sampling until absolutely clear.
11. In a separate stainless steel mixing tank, heat 300 mL of water, covered, to 90°C.
12. While maintaining at this temperature, start bubbling CO_2 gas.
13. While mixing, add and dissolve successively the benzoic acid, saccharin sodium, and phenylpropanolamine hydrobromide. Continue mixing until all have dissolved.
14. Reduce the temperature to 60°C to 65°C while mixing. Do not force-cool.
15. Add the solution from step above to the solution in the main mixing tank, while mixing and bubbling CO_2 gas.
16. Rinse the container with two lots of 5 mL of CO_2-saturated water and add the rinsings to the batch while mixing.
17. Continue mixing for 15 minutes while maintaining the temperature at 60°C to 65°C and under CO_2 gas protection.
18. While mixing the batch, sprinkle on the sodium CMC.
19. Continue mixing until all the sodium CMC has been dispersed.
20. Check on the absence of any undissolved lumps.
21. Add CO_2-saturated water from step 3 to 900 mL and mix while cooling the batch to 30°C.
22. Dissolve the dyes in 10 mL of CO_2-saturated water, then add to the batch with mixing.
23. Rinse the container with two lots of 5 mL of the same water and add the rinsings to the batch.
24. Mix until a homogenously colored batch is formed.
25. Stop bubbling in CO_2 gas but maintain CO_2 protection of the tank headspace.
26. In a stainless steel container, dissolve the sodium ascorbate in 25 mL of CO_2-saturated water, taking care to minimize exposure of the solution to air or light.
27. Mix all solutions, add rinsings where necessary, and continue mixing for 15 minutes.
28. Add the flavors, complete the batch to 1 L with CO_2-saturated water, and mix well for 1 hour.
29. Stop mixing, saturate the headspace with CO_2, and leave overnight to release any entrapped air.

Phenylpropanolamine Controlled-Release Capsules

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
33.00	1	Phenylpropanolamine	33.00
QS	2	Vehicle (pluraflo 1220 70.12%, ethanol 2.26%, anhydrous glycerin 16.35%)	QS to 1 L
1.00	3	Sodium metabisulfite	1.00
1.00	4	Disodium EDTA	1.00

Manufacturing Directions

1. Add alcohol, propylene glycol, EDTA, sodium metabisulfite, and phenylpropanolamine to a clean vessel and begin mixing.
2. Subsequently, add pluraflo and glycerin to the vessel.
3. Mix until uniform.
4. This liquid may be filled into hard gelatin capsules that are then banded to prevent leakage or it may be used as the fill for a soft elastic gelatin capsule. One capsule is made to contain 0.75 mL of the liquid and, taken 3 times daily, provides controlled release of the phenylpropanolamine active. After swallowing, the gelatin shell dissolves in the gastrointestinal tract and the liquid fill immediately transforms into a slow-dissolving gel that provides controlled release of the phenylpropanolamine.

Phenytoin Suspension

Each teaspoonful of suspension contains 125 mg phenytoin, with maximum alcohol content not greater than 0.6%. It also contains carboxymethylcellulose sodium; citric acid, anhydrous; flavors; glycerin; magnesium aluminum silicate; polysorbate 40; purified water; sodium benzoate; sucrose; vanillin; and FD&C yellow No. 6.

Phenytoin Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Phenytoin	50.00
80.00	2	Kollidon CL-M	80.00
10.00	3	Kollidon 90F	10.00
QS	4	Preservative	QS
QS	5	Water purified	QS to 1 L

Manufacturing Directions

1. Charge in a suitable stainless steel-jacketed vessel item 5 and heat to 90°C to 95°C.
2. Add and dissolve preservatives (e.g., parabens). Stir to complete solution.
3. Cool to 40°C.
4. Add item 3 and dissolve.
5. Add item 2 and suspend.
6. Add item 1 and suspend. Homogenize if necessary.
7. Fill.

Pipenzolate Methyl Bromide and Phenobarbital Drops

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
20.00	1	Pipenzolate methyl bromide	4.00
30.00	2	Phenobarbital	6.00
350.00	3	Alcohol	70.00
1000.00	4	Propylene glycol	200.00
450.00	5	Propylene glycol	90.00
33.00	6	Sodium saccharin	6.66
2500.00	7	Glycerin	500.00
5.00	8	Peppermint oil	1.00
1.65	9	Flavor	0.33
1.65	10	Flavor	0.33
0.20	11	Dye	0.04
10.00	12	Sodium citrate	2.00
17.70	13	Citric acid monohydrate	3.54
QS	14	Water purified	QS to 1 L

Manufacturing Directions

1. Charge 150 mL item 14 in a suitable stainless steel vessel and heat to 90°C for 1 hour and then cool to room temperature.
2. Add items 1, 6, 11, 12, and 13 and mix well.
3. In a separate vessel, charge items 4 and 7 and mix well for 10 minutes.
4. In a separate vessel, charge items 2, 3, 5, flavors, and item 7 and mix well.
5. Add step 4 to step 3 and mix well.
6. Add step 5 to step 1 and make up volume and mix well.
7. Fill.

Podofilox Solution

Condylox is the brand name of podofilox, an antimitotic drug that can be chemically synthesized or purified from the plant families *Coniferae* and *Berberidaceae* (e.g., species of Juniperus and Podophyllum). Condylox 0.5% solution is formulated for topical administration. Each milliliter of solution contains 5 mg of podofilox in a vehicle containing lactic acid and sodium lactate in alcohol 95%.

Polidocanol Wound Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	I. Polidocanol	5.00
50.00	2	Kollidon VA 64	50.00
50.00	3	Ethocel® 20	50.00
20.00	4	Lutrol E 400	20.00
675.00	5	Ethyl acetate	675.00
200.00	6	Isopropanol	200.00

Manufacturing Directions

1. Dissolve the items 1 to 4 in the solvent mixture of items 5 and 6.
2. Fill the solution into spray cans with the necessary quantity of propellant (e. g., propane/butane) or in a mechanical pump bottle.

Polidocanol Wound Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Polidocanol	5.00
50.00	2	Kollidon® VA 64	50.00
50.00	3	Ethocel® 20	50.00
20.00	4	Lutrol E 400	20.00
675.00	5	Ethyl acetate	675.00
200.00	6	Isopropanol	200.00

Manufacturing Directions

1. Dissolve items 1 to 4 in the solvent mixture of items 5 and 6.
2. Fill the solution into spray cans with the necessary quantity of propellant (e.g., propane/butane) or in a mechanical pump bottle.

Polyvinyl Pyrrolidone–Iodine Gargle Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Polyvinyl pyrrolidone–iodine, powder, 35% excess	13.500
10.00	2	Glycerin (96%)	10.000
QS	3	Water purified	QS to 1 L

Manufacturing Directions

Wear gloves and mask during all phases of manufacturing and filling. Do not keep the lid of the manufacturing or storage tank open unless necessary, as iodine may be liberated.

1. Add 600 mL purified water to a suitable stainless steel manufacturing tank.
2. Add polyvinyl pyrrolidone–iodine powder, slowly to first step (with continuous stirring).
3. Stir for 30 minutes or until a clear brown solution is obtained.
4. Add glycerin to the manufacturing tank. Stir until uniform solution is obtained.
5. Make up volume to 1 L with purified water and mix well for 5 minutes.
6. Check pH (range: 2–4). Filter the solution through a 100-mesh nylon cloth and transfer to a stainless steel storage tank.
7. Keep the storage tank tightly closed.

Polyvinyl Pyrrolidone–Iodine Gargle Solution Concentrate

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Polyvinyl pyrrolidone–Iodine 30/06	100.00
10.00	2	Propylene glycol (pharma)	10.00
90.00	3	Ethanol 96%	90.00
800.00	4	Water	800.00

Manufacturing Directions

1. Dissolve the polyvinyl pyrrolidone–iodine in the solvent mixture.
2. Brown transparent liquid: Dilute 10 mL the concentrate with approximately 100 mL water before use.

Polyvinyl Pyrrolidone–Iodine Liquid Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Polyvinyl pyrrolidone–Iodine 30/06	100.00
150.00	2	Kollidon VA 64	150.00
750.00	3	*N*-Propanol	750.00
750.00	4	Ethanol	750.00

Manufacturing Directions

1. Dissolve Kollidon VA 64 in the mixture of solvents.
2. Slowly add polyvinyl pyrrolidone–iodine to the well-stirred solution.
3. Fill in aerosol cans with propellants such as propane and butane or with manual valves.

Polyvinyl Pyrrolidone–Iodine Mouthwash

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.0	1	Polyvinyl pyrrolidone–Iodine	100.0
5.0	2	Sodium saccharin	5.0
2.0	3	Menthol	2.0
0.5	4	Oil aniseed	0.5
0.5	5	Eucalyptus oil	0.5
160.0	6	Polyethylene glycol 400	160.0
300.0	7	Ethanol	300.0
440.0	8	Water purified	440.0

Manufacturing Directions

1. Dissolve polyvinyl pyrrolidone–iodine powder and sodium saccharin in 440 g water to obtain a clear solution.
2. In a separate container, add alcohol and mix and dissolve aniseed oil, eucalyptus oil, menthol, and polyethylene glycol 400 to obtain a clear solution.
3. Add solution from step above and mix with stirring. Package in HDPE plastic bottles.

Polyvinyl Pyrrolidone–Iodine Mouthwash and Gargle Solution Concentrate

Bill of Materials			
Scale (mg/g)	**Item**	**Material Name**	**Qty/kg (g)**
75.00	1	Polyvinyl pyrrolidone–Iodine 30/06	75.00
5.00	2	Saccharin sodium	5.00
150.00	3	Water	150.00
2.00	4	Menthol	2.00
1.00	5	Anise oil + eucalyptus oil, 1+1	1.00
150.00	6	Lutrol E 400	150.00
500.00	7	Ethanol 96%	500.00

Manufacturing Directions

1. Dissolve polyvinyl pyrrolidone–iodine and saccharin in water and mix with solution of items 4 to 7.
2. A brown, transparent liquid having a fresh odor is formed.
3. Dilute 10 to 20 mL with a glass of water. A brown liquid is obtained having a fresh taste.

Polyvinyl Pyrrolidone–Iodine Scrub

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
75.00	1	Polyvinyl pyrrolidone–iodine, powder,	
40% excess	105.000		
250.00	2	Sodium lauryl sulfate	250.000
35.00	3	Lauric diethanolamide	35.000
QS	4	Water purified, distilled	QS to 1 L

Manufacturing Directions

1. Add 600 mL purified water to a suitable stainless steel manufacturing tank.
2. Add, by sprinkling, sodium lauryl sulfate in the manufacturing tank.
3. Continue to mix slowly under vacuum and begin to heat until product temperature is 70°C.
4. Continue to mix vigorously under vacuum at 65°C to 70°C for 15 minutes or until completely dissolved. Do not add detergent quickly, as a gel may form that is difficult to dissolve. Stop mixer, release vacuum, and open tank.
5. Add and disperse the previously broken lauric diethanolamide in the warmed solution in step above.
6. Maintain vacuum and then mix vigorously for 30 minutes at 65°C to 70°C or until completely dissolved.
7. Slowly cool under vacuum to room temperature with slow mixing. Do not force cool with cold water, otherwise the mixture will adhere to the walls of the manufacturing tank.
8. When temperature reaches 30°C, release vacuum and open tank.
9. While mixing slowly, add polyvinyl pyrrolidone–iodine in small portions.
10. Rinse the container of polyvinyl pyrrolidone–iodine with 150 mL purified water and add to the main tank. Do not keep the lid of the manufacturing or storage tank open unless necessary, as iodine may liberate.
11. Mix under vacuum until a clear, reddish-brown solution is obtained.
12. Make volume to 1 L with purified water and mix well under vacuum for at least 15 minutes to ensure product uniformity and to deaerate the product.
13. Stop mixing, release the vacuum, and open the tank.
14. Check and record pH (range: 3–6).
15. Filter the solution through 100-mesh nylon cloth.

Polyvinyl Pyrrolidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Polyvinyl pyrrolidone–iodine 30/06	100.00
0.230	2	Texapon K 12	0.230
1.40	3	Sodium biphosphate	1.40
0.30	4	Sodium citrate	0.30
20.80	5	Sodium hydroxide solution, 1 molar	20.80
10.00	6	Glycerol	10.00
864.20	7	Water	864.20

Manufacturing Directions

1. Dissolve Texapon K 12 in solution of items 3 to 7.
2. Slowly add polyvinyl pyrrolidone–iodine to the well-stirred solution. This creates a brown, transparent liquid having a pH of 4.5.

Polyvinyl Pyrrolidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Polyvinyl pyrrolidone–Iodine 30/06	100.00
10.00	2	Natrosol® HR 250	10.00
2.00	3	Lutrol F 127	2.00
32.00	4	Sodium hydroxide, 1 molar solution	32.00
856.00	5	Water	856.00

Manufacturing Directions

1. Dissolve Lutrol F 127 and then Natrosol in the water.
2. As soon as both are dissolved, slowly add the polyvinyl pyrrolidone–iodine to the well-stirred solution.
3. Adjust the pH with the sodium hydroxide solution to about 3.5.

Polyvinyl Pyrrolidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Tylose M 300	20.00
2.00	2	Texapon K 12	2.00
595.00	3	Citric acid solution 0.1 molar	595.00
283.00	4	Sodium biphosphate solution 0.2 molar	283.00

Manufacturing Directions

1. Dissolve Tylose M 300 in the mixture of the citric acid and sodium biphosphate solutions.
2. Add Texapon and slowly dissolve the polyvinyl pyrrolidone–iodine. This creates a brown, clear solution having a certain viscosity and a pH of 3 to 4.

Polyvinyl Pyrrolidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Polyvinyl pyrrolidone–iodine 30/06	100.00
3.00	2	Lutrol F 127	3.00
5.00	3	Lutrol E 400	5.00
432.00	4	Citric acid 0.1 molar solution	432.00
460.00	5	$Na2HPO_4 \cdot 12H_2O$ 0.2 molar solution	460.00

Manufacturing Directions

1. Dissolve the polyvinyl pyrrolidone–iodine (and Lutrol F 127) in the mixture of the buffer solutions (and Lutrol E 400).
2. A brown, clear solution is formed that has a low viscosity and a pH of about 4.5.
3. Items 2 and 3 can be deleted and compensated with item 5.

Polyvinyl Pyrrolidone–Iodine Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/1000 Tabs. (g)
100.00	1	Polyvinyl pyrrolidone–iodine powder, 35% excess	135.00
9.318	2	Acid, citric, anhydrous, powder	9.318
14.62	3	Sodium phosphate, dibasic, anhydrous	14.62
QS	4	Water purified, distilled	QS to 1 L

Manufacturing Directions

1. Add 600 mL purified water to a suitable stainless steel manufacturing tank. With gentle stirring, add citric acid into the purified water in the manufacturing tank.
2. Stir for 10 minutes or until completely dissolved. During this mixing period, remove samples from the bottom valve of the manufacturing tank and inspect for clarity.
3. Return samples to the manufacturing tank.
4. Continue mixing and sampling until the solution is completely clear.
5. With gentle stirring, add sodium phosphate, dibasic, into the solution. Stir for 10 minutes or until completely dissolved. During this mixing period, remove samples from the bottom valve of the manufacturing tank and inspect for clarity. Return samples to the manufacturing tank.
6. Continue mixing and sampling until the solution is completely clear. Make up volume to 1 L with purified water and mix well for 5 minutes.
7. Check and record pH (range: 4.8–5.2). Filter the solution through a 100-mesh nylon cloth.
8. Transfer into a suitable stainless steel storage tank and keep tightly closed. This solution should be freshly prepared and should not be stored for more than 24 hours.
9. Dissolve polyvinyl pyrrolidone–iodine in about 600 mL citric acid–phosphate buffer (pH 5) solution (made above) in a suitable stainless steel mixing tank.
10. Stir evenly for 10 minutes or until a clear, brown solution is obtained. Make up volume to 1 L with citric acid–phosphate buffer solution.
11. Mix well for 10 minutes.
12. Check and record pH (range: 3.0–4.5).
13. Filter the solution through a 100-mesh nylon cloth.
14. Transfer into a suitable stainless steel storage tank and keep tightly closed

Polyvinyl Pyrrolidone–Iodine Surgical Scrub

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
75.00	1	Polyvinyl pyrrolidone–Iodine 30/06	75.00
250.00	3	Lutensit AES	250.00
40.00	4	Monoamide 150 MAW	40.00
QS	6	Floral bouquet	QS
635.00	7	Water	635.00

Manufacturing Directions

1. Dissolve monoamide in hot water, cool to room temperature.
2. Dissolve polyvinyl pyrrolidone–iodine.
3. Add Lutensit to form a brown, clear viscous solution.

Polyvinyl Pyrrolidone–Iodine Surgical Scrub

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
75.00	1	Polyvinyl pyrrolidone–Iodine 30/06	75.00
250.00	2	Neutronyx S 60	250.00
40.00	3	Super amide L 9	40.00
QS	4	Floral bouquet	QS
635.00	5	Water	635.00

Manufacturing Directions

1. Dissolve Super Amide in hot water and then cool.
2. Dissolve polyvinyl pyrrolidone–iodine and add Neutronyx.
3. A brown, clear viscous solution is formed, with pH of about 3.4.

Polyvinyl Pyrrolidone–Iodine Vaginal Douche Concentrate

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Polyvinyl pyrrolidone-iodine 30/06	100.00
5.00	2	Lutrol E 400	5.00
3.00	3	Lutrol F 127	3.00
432.00	4	Citric acid, 0.1 molar solution	432.00
460.00	5	$Na_2HPO_4 \cdot 12H_2O$, 0.2 molar solution	460.00

Manufacturing Directions

1. Dissolve polyvinyl pyrrolidone–iodine and Lutrol F 127 in the mixture of the buffer solutions with Lutrol E 400.
2. A brown, clear solution is created having a low viscosity and a pH of about 4.3.

Polyvinyl Pyrrolidone–Iodine Viscous Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Polyvinyl pyrrolidone–Iodine 30/06	10.00
15.00	2	Natrosol HR 250	15.00
QS	3	Buffer	QS
QS	4	Water	975.00

Manufacturing Directions

1. Clear brown viscous liquid viscosity (Brookfield) of 7500 mPas is obtained.
2. Dissolve polyvinyl pyrrolidone–iodine and natrosol in the well-stirred water.

Polyvinylpyrrolidone–Iodine Mouthwash

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–Iodine	100.00
5.00	2	Saccharin sodium	5.00
2.00	3	Menthol	2.00
0.50	4	Aniseed oil	0.50
0.50	5	Eucalyptus oil	0.50
160.00	6	PEG-400	160.00
300.00	7	Ethanol	300.00
QS	8	Purified water	QS to 1 kg

Manufacturing Directions

1. Dissolve PVP–iodine powder and saccharin sodium in 440 g of water to obtain a clear solution.
2. In a separate container, add alcohol.
3. Mix and dissolve aniseed oil, eucalyptus oil, menthol, and PEG-400 to obtain a clear solution.
4. QS with water.
5. Add solution from step above and mix with stirring.
6. Package in HDPE plastic bottles.

Povidone–Iodine Concentrates for Broilers and Cattle

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
200.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	200.00
50.00	2	Texapon® K 12	50.00
50.00	3	Cremophor NP 14	50.00
73.00	4	Tartaric acid	73.00
43.00	5	Sulfuric acid, diluted	43.00
100.00	6	Ethanol 96%	100.00
QS	7	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve surfactant items 2 and 3 in solution of items 4 to 7 and slowly add PVP–iodine.
2. Brown, transparent liquids having a pH of about 1.
3. Dilute about 3 mL of the concentrate with 1 L of water prior to use.

Povidone–Iodine Foam Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	100.00
0.10	2	Cremophor A 25	0.10
QS	3	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve PVP–iodine in the solution of Cremophor A 25 in water.
2. Fill the aerosol cans with 90 parts of this solution and 10 parts of propane plus 1 part butane.

Povidone–Iodine Gargle

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Polyvinylpyrrolide-Iodine (powder) (35% excess)	13.50
10.00	2	Glycerin, USP (96%)	10.00
–	3	Purified water, USP	QS to1 L

Manufacturing Directions

Wear gloves and mask during all phases of manufacturing and filling. Do not keep the lid of the manufacturing or storage tank open, unless necessary, as iodine may be liberated.

1. Add 600 mL purified water to a suitable stainless steel manufacturing tank.
2. Slowly add povidone–iodine powder to the water (with continuous stirring).
3. Stir for 30 minutes or until a clear, brown solution is obtained.
4. Add glycerin to the manufacturing tank.
5. Stir until uniform solution is obtained.
6. Make up volume to 1 L with purified water and mix well for 5 minutes.
7. Check pH (range: 2.0–4.0).
8. Filter the solution through a 100-mesh nylon cloth and transfer to a stainless steel storage tank.
9. Keep the storage tank tightly closed.

Povidone–Iodine Gargle Solution Concentrate

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	100.00
10.00	2	Propylene glycol	10.00
90.00	3	Ethanol (96%)	90.00
800.00	4	Water	800.00

Manufacturing Directions

1. Dissolve the PVP–iodine in the solvent mixture to produce a brown transparent liquid.
2. Dilute 10 mL of the concentrate with approximately 100 mL of water prior to use.

Povidone–Iodine Liquid Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	100.00
150.00	2	Kollidon® VA 64	150.00
750.00	3	*N*-Propanol	750.00
750.00	4	Ethanol	750.00

Manufacturing Directions

1. Dissolve Kollidon VA 64 in the mixture of solvents and slowly add PVP–iodine to the well-stirred solution.
2. Fill in aerosol cans with propellants such as propane and butane or with manual valves.

Povidone–Iodine Mouthwash and Gargle Solution Concentrate

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
75.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	75.00
5.00	2	Saccharin sodium	5.00
150.00	3	Water	150.00
2.00	4	Menthol	2.00
1.00	5	Anise oil + eucalyptus oil (1+1)	1.00
150.00	6	Lutrol E 400	150.00
500.00	7	Ethanol (96%)	500.00

Manufacturing Directions

1. Dissolve PVP–iodine and saccharin in water and mix with solution of items 4 to 7.
2. Brown transparent liquid has a fresh odor.
3. Dilute 10 to 20 mL with a glass of water.
4. A brown liquid with a fresh taste is obtained.

Povidone–Iodine Powder Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
250.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	250.00
250.00	2	Maize PO_4 aerosol	250.00
15.00	3	Isopropyl myristate	15.00
100.00	4	Dow Corning® 344 fluid	100.00
500.00	5	Pentane	500.00
220.00	6	Propane + butane (1+3)	220.00

Manufacturing Directions

1. Suspend PVP–iodine and maize PO_4 aerosol in the liquid mixture of items 3 to 5.
2. Fill in aerosol cans with the propellants.

Povidone–Iodine Pump Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	10.00
100.00	2	Water	100.00
1.00	3	Potassium iodide	1.00
100.00	4	Xylitol	100.00
787.50	5	Propylene glycol	787.50
1.00	6	Menthol (crystalline)	1.00
0.50	7	Peppermint oil (double rectified)	0.50

Manufacturing Directions

1. Dissolve potassium iodide in water, warm up to 40°C, and dissolve xylitol.
2. At room temperature, dilute with propylene glycol, dissolve PVP–iodine, and add flavors to produce a clear, brown liquid with a sweet, refreshing taste.

Povidone–Iodine Shampoo

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
75.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	75.00
250.00	2	Neutronyx® S 60	250.00
40.00	3	Super Amide® L 9	40.00
5.0–7.0	4	Natrosol® 250 HR	5.0–7.0
–	5	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve Super Amide and Natrosol in hot water (about 60°C), then dissolve PVP–iodine.
2. After cooling, incorporate Neutronyx.
3. A brown, clear solution is obtained.
4. The viscosity can be changed by modification of the amount of Natrosol 250 HR.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Povidone–Iodine powder (35% excess)	135.00
9.318	2	Anhydrous citric acid (powder)	9.318
14.62	3	Anhydrous sodium phosphate (dibasic)	14.62
QS	4	Purified water	QS to 1 L

Manufacturing Directions

Wear gloves and mask during all phases of manufacturing and filling. Do not keep the lid of the manufacturing or storage tank open, unless necessary, as iodine may be liberated.

1. Citric acid–phosphate buffer solution (pH 5): Add 600 mL purified water to a suitable stainless steel manufacturing tank.
2. With gentle stirring add citric acid to the purified water in the manufacturing tank.
3. Stir for 10 minutes or until completely dissolved.
4. During this mixing period, remove samples from the bottom valve of the manufacturing tank and inspect for clarity.
5. Return samples to the manufacturing tank.
6. Continue mixing and sampling until the solution is completely clear.
7. With gentle stirring add dibasic sodium phosphate to the solution.
8. Stir for 10 minutes or until completely dissolved.
9. During this mixing period, remove samples from the bottom valve of the manufacturing tank and inspect for clarity.
10. Return samples to the manufacturing tank.
11. Continue mixing and sampling until the solution is completely clear.
12. Make up volume to 1 L with purified water and mix well for 5 minutes.
13. Check and record pH (range: 4.8–5.2).
14. Filter the solution through a 100-mesh nylon cloth.
15. Transfer into a suitable stainless steel storage tank and keep tightly closed.
16. This solution should be freshly prepared and should not be stored for more than 24 hours.
17. Preparation of solution: Dissolve povidone–iodine in approximately 600 mL of citric acid/phosphate buffer (pH 5) solution in a suitable stainless steel mixing tank.
18. Stir evenly for 10 minutes or until a clear brown solution is obtained.
19. Make up volume to 1 L with citric acid/phosphate buffer solution.
20. Mix well for 10 minutes.
21. Check and record pH (range: 3.0–4.5).
22. Filter the solution through a 100-mesh nylon cloth.
23. Transfer into a suitable stainless steel storage tank and keep it tightly closed.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	100.00
3.00	2	Lutrol F 127	3.00
5.00	3	Lutrol E 400	5.00
432.00	4	Citric acid (0.1-M solution)	432.00
460.00	5	$Na_2HPO_4 \cdot 12H_2O$ (0.2-M solution)	460.00

Manufacturing Directions

1. Dissolve the PVP–iodine (and Lutrol F 127) in the mixture of buffer solutions (and Lutrol E 400).
2. Brown clear solutions having a low viscosity and pH of approximately 4.5.
3. Items 2 and 3 can be deleted and compensated with item 5.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	100.00
0.23	2	Texapon® K 12	0.23
1.40	3	Sodium biphosphate	1.40
0.30	4	Sodium citrate	0.30
20.80	5	Sodium hydroxide (1-M solution)	20.80
10.00	6	Glycerol	10.00
QS	7	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve Texapon K 12 in solution of items 3 to 7 and slowly add PVP–iodine to the well-stirred solution.
2. The brown, transparent liquid has a pH of 4.5.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	100.00
10.00	2	Natrosol® HR 250	10.00
2.00	3	Lutrol F 127	2.00
32.00	4	Sodium hydroxide (1-M solution)	32.00
QS	5	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve Lutrol F 127 and then Natrosol in the water.
2. As soon as both are dissolved, slowly add the PVP–iodine to the well-stirred solution.
3. Adjust the pH with the sodium hydroxide solution to approximately 3.5.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Tylose® M 300	20.00
2.00	2	Texapon® K 12	2.00
595.00	3	Citric acid (0.1-M solution)	595.00
283.00	4	Sodium biphosphate (0.2-M solution)	283.00

Manufacturing Directions

1. Dissolve Tylose M 300 in the mixture of the citric acid and sodium biphosphate solutions.
2. Add Texapon and slowly dissolve the PVP–iodine.
3. The brown, clear solution has a pH of 3 to 4.

Povidone–Iodine Scrub

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
75.00	1	Polyvinylpyrrolidone–Iodine (powder) (40% excess)	105.00
250.00	2	Sodium lauryl sulfate	250.00
35.00	3	Lauric diethanolamide	35.00
–	4	Distilled purified water, USP	QS to 1 L

Manufacturing Directions

1. Add 600 mL purified water to a suitable stainless steel manufacturing tank.
2. Add, by sprinkling, the sodium lauryl sulfate to the manufacturing tank.
3. Continue to mix slowly under vacuum and begin to heat until product temperature is 70°C.
4. Continue to mix vigorously under vacuum at 65°C to 70°C for 15 minutes or until completely dissolved.
5. (*Note*: Do not add detergent quickly, as a gel may form that is difficult to dissolve.) Stop mixer, release vacuum, and open tank.
6. Add and disperse the previously broken lauric diethanolamide in the warmed solution from the step above.
7. Maintain vacuum and mix vigorously for 30 minutes at 65°C to 70°C or until completely dissolved.
8. Slowly cool under vacuum to room temperature with slow mixing. (*Note*: Do not force cool with cold water; otherwise, the mixture will adhere to the walls of the manufacturing tank.) When temperature reaches 30°C, release vacuum and open tank.
9. While mixing slowly, add povidone–iodine in small portions.
10. Rinse the container of povidone–iodine with 150 mL purified water and add to the main tank. (*Note*: Do not keep the lid of the manufacturing or storage tank open, unless necessary, as iodine may liberate.) Mix under vacuum until a clear reddish brown solution is obtained.
11. Make volume up to 1 L with purified water and mix well under vacuum for at least 15 minutes to ensure product uniformity and to deaerate the product.
12. Stop mixing, release the vacuum, then open the tank.
13. Check and record pH (range: 3–6).
14. Filter the solution through 100-mesh nylon cloth.

Povidone–Iodine Surgical Scrub

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
75.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	75.00
250.00	2	Neutronyx® S 60	250.00
40.00	3	Super Amide® L 9	40.00
QS	4	Floral bouquet	QS
QS	5	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve Super Amide in hot water, cool, dissolve PVP–iodine, and add Neutronyx to produce a brown, clear viscous solution with pH of approximately 3.4.

Povidone–Iodine Surgical Scrub

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
75.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	75.00
250.00	2	Lutensit® AES	250.00
40.00	3	Monoamide® 150 MAW	40.00
QS	4	Floral bouquet	QS
QS	5	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve Monoamide in hot water, cool, dissolve PVP–iodine, and add Lutensit to produce a brown, clear viscous solution.

Povidone–Iodine Vaginal Douche Concentrate

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	100.00
5.00	2	Lutrol E 400	5.00
3.00	3	Lutrol F 127	3.00
432.00	4	Citric acid (0.1-M solution)	432.00
460.00	5	$Na_2HPO_4 \cdot 12H_2O$ (0.2-M solution)	460.00

Manufacturing Directions

1. Dissolve PVP–iodine and Lutrol F 127 in the mixture of buffer solutions with Lutrol E 400.
2. The brown, clear solution has a low viscosity and pH of approximately 4.3.

Povidone–Iodine Viscous Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Polyvinylpyrrolidone (PVP)–Iodine 30/06	10.00
15.00	2	Natrosol® HR 250	15.00
QS	3	Buffer	QS
QS	4	Water	975.00

Manufacturing Directions

1. Dissolve PVP–iodine and Natrosol in the well-stirred buffered solution in water to produce a clear brown viscous liquid.
2. Viscosity (Brookfield) is 7500 mPa.

Prednisone Oral Solution

Each 5 mL oral solution contains prednisolone 5 mg and alcohol 5% or 30%. Inactive ingredients include alcohol, citric acid, disodium edetate, fructose, hydrochloric acid, maltol, peppermint oil, polysorbate 80, propylene glycol, saccharin sodium, sodium benzoate, vanilla flavor, and water. Prednisone 30% alcohol solution contains citric acid, poloxamer 188, propylene glycol, and water.

Prednisolone Sodium Phosphate Oral Solution

Pediapred (prednisolone sodium phosphate) oral solution is a dye-free, colorless to light-straw-colored, raspberry-flavored solution. Each 5 mL (teaspoonful) of Pediapred contains 6.7 mg prednisolone sodium phosphate (5 mg prednisolone base) in a palatable, aqueous vehicle.

Prednisolone Syrup

The syrup contains 15 or 5 mg prednisolone in each 5 mL. Benzoic acid 0.1% is added as a preservative. The syrup also contains alcohol 5%, citric acid, edetate disodium, glycerin, propylene glycol, purified water, sodium saccharin, sucrose, artificial wild cherry flavor, and FD&C blue No. 1 and red No. 40.

Progesterone Capsules

Progesterone capsules contain micronized progesterone for oral administration. Capsules are available in multiple strengths to afford dosage flexibility for optimum management. Capsules contain 100 or 200 mg micronized progesterone. The inactive ingredients for 100-mg capsules include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, D&C yellow No. 10, and FD&C red No. 40. The inactive ingredients for capsules 200 mg include peanut oil, gelatin, glycerin, lecithin, titanium dioxide, D&C yellow No. 10, and FD&C yellow No. 6.

Promethazine and Codeine Syrup

Each teaspoon (5 mL) of Phenergan VC with codeine contains 10 mg codeine phosphate (*Warning*:—this may be habit forming), 6.25 mg promethazine hydrochloride, and 5 mg phenylephrine hydrochloride in a flavored syrup base with a pH between 4.8 and 5.4; alcohol, 7%. The inactive ingredients present are artificial and natural flavors, citric acid, D&C red No. 33, FD&C yellow No. 6, glycerin, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients.

Promethazine and Dextromethorphan Syrup

Each teaspoon (5 mL) of Phenergan with dextromethorphan contains 6.25 mg promethazine hydrochloride and 15 mg dextromethorphan hydrobromide in a flavored syrup base with a pH between 4.7 and 5.2; alcohol, 7%. The inactive ingredients present are artificial and natural flavors, citric acid, D&C yellow 10, FD&C yellow 6, glycerin, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients.

Promethazine Hydrochloride Syrup

Each teaspoon (5 mL) of Phenergan syrup plain contains 6.25 mg promethazine hydrochloride in a flavored syrup base with a pH between 4.7 and 5.2; alcohol, 7%. The inactive ingredients present are artificial and natural flavors, citric acid, D&C red No. 33, D&C yellow No. 10, FD&C blue No. 1, FD&C yellow No. 6, glycerin, saccharin sodium, sodium benzoate, sodium citrate, sodium propionate, water, and other ingredients. Each teaspoon (5 mL) of Phenergan syrup fortis contains 25 mg promethazine hydrochloride in a flavored syrup base with a pH between 5.0 and 5.5; alcohol, 1.5%. The inactive ingredients present are artificial and natural flavors, citric acid, saccharin sodium, sodium benzoate, sodium propionate, water, and other ingredients.

Promethazine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1.00	1	Promethazine HCl (5% excess)	1.05
675.00	2	Sucrose	675.00
1.00	3	Citric acid (monohydrate)	1.00
2.40	4	Sodium citrate	2.40
0.50	5	Ascorbic acid	0.50
0.25	6	Sodium metabisulfite (sodium disulfite)	0.25
0.25	7	Anhydrous sodium sulfite	0.25
50.00	8	Alcohol (ethanol, 95%)	50.00
0.15	9	Flavor	0.15
0.30	10	Flavor	0.30
0.50	11	Polysorbate 80 (Tween 80)	0.50
0.15	12	Caramel color	0.15
QS	13	Purified water	QS to 1 L

Manufacturing Directions

Promethazine HCl undergoes thermal and photochemical oxidation. Protect from light, heat, and oxygen as practicable. Avoid vortex or overmixing to avoid air entrapment. Use nitrogen gas whenever necessary to expel air.

1. Add 400 g of item 13 to the manufacturing vessel and heat to 90°C to 95°C.
2. Add item 2 while mixing at slow speed.
3. After addition of item 2, mix for 30 minutes at high speed and a temperature of 90°C to 95°C.
4. Cool down to 30°C to 35°C while mixing at low speed.
5. Add items 3 and 4 to the manufacturing vessel while mixing and mix until dissolved.
6. Add items 6 and 7 to the manufacturing vessel while mixing and mix until dissolved.
7. Add item 5 to the manufacturing vessel while mixing and mix until dissolved.
8. Mix items 9 and 10 with items 8 and 11 in a separate container by using stirrer.
9. Mix for 10 minutes and add to the manufacturing vessel while mixing.
10. Add 8 g of cold purified water (25–30°C) to a separate container and dissolve item 12 by using stirrer.
11. Mix for 10 minutes and add to the manufacturing vessel while mixing.
12. Start flushing the syrup with nitrogen gas pressure at 20 to 40 psi.
13. Add 10 g of cold purified water (cooled and flushed with N_2 gas) in a separate container with lid.
14. Pass nitrogen gas at 20 to 40 psi pressure for 15 minutes.
15. Dissolve item 1 in nitrogen-flushed cold purified water (25–30°C) by using stirrer.
16. Mix for 10 minutes and add to the manufacturing vessel while mixing. Do not produce vortex.
17. Bring volume up to 1 L with nitrogen-flushed purified water.
18. Continue flushing nitrogen gas at 20 to 40 psi pressure for 30 minutes while mixing at slow speed.
19. Check and record the pH (limit: 4.5–5.5). If required, adjust pH with 10% citric acid or 10% sodium citrate solution.
20. Filter the syrup at 1.5 bar.
21. Recirculate approximately 20 to 30 mL syrup.
22. Transfer the filtered syrup to the storage vessel.
23. Flush with nitrogen gas and seal the tank.

Promethazine Rectal Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
QS	1	Pluronic L62	QS to 1 L
2.50	2	Promethazine hydrochloride	2.50

Manufacturing Directions

1. Mill and screen the promethazine HCl to reduce particle size.
2. Add the poloxamer and the promethazine HCl into a clean vessel.
3. Mix until uniform.

Promethazine Rectal Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
QS	1	Pluronic L62	QS to 1 L
10.00	2	Carbopol 974	10.00
2.50	3	Promethazine hydrochloride	2.50

Manufacturing Directions

1. Mill the promethazine HCl to reduce particle size.
2. Sieve the carbomer and promethazine HCl and add to a clean vessel.
3. Add the poloxamer. Mix until uniform.

Pseudoephedrine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
6.00	1	Pseudoephedrine HCl (3.0% excess)	6.18
600.00	2	Sucrose	600.00
100.00	3	Glycerin (glycerol)	100.00
100.00	4	Sorbitol (70% solution)	100.00
15.00	5	Propylene glycol	15.00
1.00	6	Methyl paraben	1.00
0.30	7	Propyl paraben	0.30
0.50	8	Saccharin sodium	0.50
0.02	9	Dye (if needed)	0.02
0.05	10	Menthol	0.05
0.13	11	Citric acid	0.13
1.15	12	Sodium citrate	1.15
QS	13	Purified water	QS to 1 L

Manufacturing Directions

1. Add 390 g of purified water to the manufacturing vessel and heat to 90°C to 95°C.
2. Add items 6 and 7 while mixing to dissolve at high speed.
3. Add item 2 while mixing at slow speed at a temperature of 90°C to 95°C.
4. Mix for 1 hour at high speed.
5. Cool down to 50°C while mixing at slow speed.
6. Dissolve items 8 and 12 in 10 g of item 13 and add to the manufacturing vessel while mixing at high speed.
7. Dissolve item 11 in 10 g of purified water and add to the manufacturing vessel while mixing at high speed.
8. Load items 4 and 3 into the manufacturing vessel using a transfer pump while mixing at high speed.
9. Mix for 5 minutes.
10. Cool down to 30°C while mixing at slow speed.
11. Add 20 g of item 13 (30°C) in a separate container and dissolve item 1 by using stirrer.
12. Mix for 10 minutes and add to the manufacturing vessel while mixing at high speed.
13. Add 6 g of item 13 in a separate container and dissolve item 9 manually.
14. Add color to the manufacturing vessel while mixing at high speed.
15. Dissolve item 10 in item 5.
16. Add this flavor mixture to the manufacturing vessel while mixing at high speed.
17. Bring the volume up to 1 L with item 13 and finally mix for 15 to 20 minutes at high speed.
18. Check and record the pH (limit: 5.5–6.5 at 25°C).
19. If required, adjust pH with 20% citric acid or 20% sodium citrate solution.
20. Filter the syrup at 1.5 bar.
21. Recirculate approximately 100 to 150 mL syrup.

Pseudoephedrine Hydrochloride, Carbinoxamine Maleate Oral Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
500.00	1	Sucrose	500.00
300.00	2	Glucose liquid	300.00
150.00	3	Glycerin (96%)	150.00
30.00	4	D-Pseudoephedrine hydrochloride	30.00
1.00	5	Carbinoxamine maleate	1.00
4.00	6	Saccharin sodium (powder)	4.00
2.50	7	Sodium benzoate (powder)	2.50
1.25	8	Flavor	1.25
0.03	9	Dye	0.03
0.03	10	Dye	0.03
QS	11	Hydrochloric acid reagent-grade bottles	QS
QS	12	HyFlo filter aid	1.32
QS	13	Purified water	455.00
QS	14	Sodium hydroxide for pH adjustment	QS

Manufacturing Directions

1. Charge 315 mL of deionized water into a suitable tank.
2. Begin heating water to 60°C to 70°C while adding sucrose with stirring.
3. Stir until sugar is dissolved.
4. Remove heat.
5. Add glucose liquid and 125 g of glycerin in this step.
6. Add and dissolve D-pseudoephedrine HCl, carbinoxamine maleate, saccharin sodium, and sodium benzoate with mixing.
7. Cool solution to 30°C to 35°C.
8. Mix flavor with 25 g of glycerin.
9. (*Note*: Temperature of syrup must not be higher than 35°C.) Dissolve dyes, if used, in 5 mL of deionized water and add to syrup with mixing.
10. Adjust to pH 4.25 (range: 4.0–4.5), if necessary, with hydrochloric acid or sodium hydroxide.
11. QS to 1 L with deionized water and mix well.
12. Allow product to stand overnight to let entrapped air escape.
13. Readjust volume to 1 L with deionized water.
14. Add and mix 1.320 g of HyFlo filter aid to the product.
15. Circulate through a press.
16. Filter into tank for filling.

Pseudoephedrine Hydrochloride, Carbinoxamine Maleate Oral Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
500.00	1	Sucrose	500.000
300.00	2	Glucose, liquid	300.000
150.00	3	Glycerin (96%)	150.000
30.00	4	D-Pseudoephedrine hydrochloride	30.000
1.00	5	Carbinoxamine maleate	1.000
4.00	6	Saccharin sodium powder	4.000
2.50	7	Sodium benzoate powder	2.500
1.25	8	Flavor	1.250
0.032	9	Dye	0.032
0.036	10	Dye	0.036
—	11	Acid hydrochloric reagent-grade bottles	QS
1.320	12	Filter aid HyFlo	1.320
455.00	13	Water purified	455
QS	14	Sodium hydroxide for pH adjustment	QS

Manufacturing Directions

1. Charge 315 mL purified water into a suitable tank. Begin heating water to 60°C to 70°C while adding sugar with stirring.
2. Stir until sugar is dissolved. Remove heat. Add glucose liquid and 125 g glycerin in this step.
3. Add and dissolve D-pseudoephedrine HCl, carbinoxamine maleate, saccharin sodium, and sodium benzoate with mixing. Cool solution to 30°C to 35°C.
4. Mix flavor with 25 g of glycerin. Temperature of syrup must not be higher than 35°C.
5. Dissolve dyes, if used, in 5 mL purified water and add to syrup with mixing. Adjust to pH 4.25 (range: 4.0–4.5), if necessary, with hydrochloric acid or sodium hydroxide.
6. QS to 1 L with purified water and mix well. Allow product to stand overnight to let entrapped air escape.
7. Readjust volume to 1 L with purified water.
8. Add and mix 1.320 g of filter aid HyFlo to the product.
9. Circulate through a press. Filter into tank for filling.

Pseudoephedrine and Carbinoxamine Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
500.00	1	Sucrose	500.00
300.00	2	Glucose liquid	300.00
150.00	3	Glycerin	150.00
30.00	4	Pseudoephedrine hydrochloride	30.00
1.00	5	Carbinoxamine maleate	1.00
4.00	6	Saccharine sodium	4.00
2.50	7	Sodium benzoate	2.50
1.25	8	Flavor black currant	1.25
0.032	9	Dye red	0.032
0.036	10	Dye yellow	0.036
QS	11	Hydrochloric acid, to adjust pH	QS
1.32	12	Filter aid HyFlo	1.32
QS	13	Water purified	QS to 1 L
QS	14	Sodium hydroxide, to adjust pH	QS

Manufacturing Directions

1. Charge 315 mL purified water into a suitable tank.
2. Begin heating water to 60°C to 70°C while adding sugar with stirring. Stir until sugar is dissolved.
3. Remove heat. Add glucose liquid and 40 g sorbitol solution with mixing. Hold balance of sorbitol for step 6.
4. Add and dissolve D-pseudoephedrine HCl, carbinoxamine maleate, saccharin sodium, and sodium benzoate with mixing.
5. Cool solution to 30°C to 35°C.
6. Mix flavors with balance of sorbitol and add to syrup.
7. Add glycerin. Temperature of syrup must not be higher than 35°C.
8. Dissolve dyes, if used, in 5 mL purified water and add to syrup with mixing. Adjust to pH 4.25 (range: 4.0–4.5), if necessary, with hydrochloric acid or sodium hydroxide.
9. QS to 1 L with purified water and mix well.
10. Allow product to stand overnight to let entrapped air escape. Readjust volume to 1 L.
11. Add and mix 1.32 g of filter aid HyFlo to the product. Circulate through a press until sparkling clear.
12. Filter into tank for filling. Fill into suitable approved containers.

Pseudoephedrine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
6.00	1	Pseudoephedrine HCl, 3% excess	6.18
600.00	2	Sucrose	600.00
100.00	3	Glycerin (glycerol)	100.00
100.00	4	Sorbitol (70% solution)	100.00
15.00	5	Propylene glycol	15.00
1.00	6	Methyl paraben	1.00
0.30	7	Propyl paraben	0.30
0.50	8	Saccharin sodium	0.50
0.02	9	Dye (if needed)	0.02
0.05	10	Menthol	0.05
0.132	11	Citric acid	0.13
1.150	12	Sodium citrate	1.15
–	13	Water purified	QS to 1 L

Manufacturing Directions

1. Add 390 g of item 13 to the manufacturing vessel and heat to 90°C to 95°C.
2. Add items 6 and 7 while mixing to dissolve at high speed.
3. Add item 2 while mixing at slow speed. Temperature 90°C to 95°C.
4. Mix for 1 hour at high speed. Cool down to 50°C while mixing at slow speed.
5. Dissolve items 8 and 12 in 10 g of item 13 and add to the manufacturing vessel while mixing at high speed.
6. Dissolve item 11 in 10 g of item 13 and add to the manufacturing vessel while mixing at high speed. Load items 4 and 3 into the manufacturing vessel using transfer pump while mixing at high speed.
7. Mix for 5 minutes. Cool down to 30°C while mixing at slow speed.
8. Add 20 g of item 13 (30°C) in a separate container and dissolve item 1 by using stirrer.
9. Mix for 10 minutes and add to the manufacturing vessel while mixing at high speed. Add 6 g of item 13 in a separate container and dissolve item 9 manually.
10. Add color to the manufacturing vessel while mixing at high speed.
11. Dissolve item 10 in item 5. Add this flavor mixture to the manufacturing vessel while mixing at high speed. Make up the volume to 1 L with item 13 and finally mix for 15 to 20 minutes at high speed.
12. Check and record the pH (limit: 5.5–6.5 at 25°C).
13. If required, adjust pH with 20% citric acid or 20% sodium citrate solution.
14. Filter the syrup at 1.5 bar. Recirculate about 100 to 150 mL syrup.

Ribavirin Inhalation Solution

Virazole is a brand name for ribavirin, a synthetic nucleoside with antiviral activity. Virazole for inhalation solution is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100-mL glass vial contains 6 g ribavirin, and when reconstituted to the recommended volume of 300 mL with sterile water for injection or sterile water for inhalation (no preservatives added) contains 20 mg of ribavirin per milliliter, with a pH of approximately 5.5. Aerosolization is to be carried out in a small particle aerosol generator (SPAG-2) nebulizer only.

Risperidone Oral Solution

Risperdal is available as a 1 mg/mL oral solution. The inactive ingredients for this solution are tartaric acid, benzoic acid, sodium hydroxide, and purified water.

Ritonavir Capsules

Norvir soft gelatin capsules are available for oral administration in a strength of 100 mg ritonavir with the following inactive ingredients: butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxyl 35 castor oil, and titanium dioxide.

Ritonavir Oral Solution

Norvir oral solution is available for oral administration as 80 mg/mL ritonavir in a peppermint- and caramel-flavored vehicle. Each 8-oz bottle contains 19.2 g ritonavir. Norvir oral solution also contains ethanol, water, polyoxyl 35 castor oil, propylene glycol, anhydrous citric acid to adjust pH, saccharin sodium, peppermint oil, creamy caramel flavoring, and FD&C yellow No. 6.

Ritonavir and Lopinavir Oral Solution

Kaletra oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: acesulfame potassium, alcohol, artificial cotton candy flavor, citric acid, glycerin, high fructose corn syrup, Magnasweet-110 flavor, menthol, natural and artificial vanilla flavor, peppermint oil, polyoxyl 40 hydrogenated castor oil, polyvinyl pyrrolidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water.

Rivastigmine Tartarate Oral Solution

Exelon oral solution is supplied as a solution containing rivastigmine tartrate, equivalent to 2 mg/mL rivastigmine base for oral administration. Inactive ingredients are citric acid, D&C yellow No. 10, purified water, sodium benzoate, and sodium citrate.

Salbutamol Aerosol

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 units (g)
1.17	1	Salbutamol, 10% excess	26.40
0.11	2	Oleic acid, 10% excess	2.64
277.61	3	Trichloromonofluoromethane	5664.00
721.09	4	Dichlorodifluoromethane	14700.00

Manufacturing Directions

1. Filter approximately 5 kg of the trichloromonofluoromethane and the oleic acid through a suitable 0.2-micron filter into a stainless steel concentrate container.
2. Slowly add the salbutamol to the solution in step 1 and mix for about 15 minutes.
3. Filter most of the remaining trichloromonofluoromethane through a suitable 0.2-micron filter into the suspension holding tank.
4. Add the slurry from step 2 to the holding tank.
5. Rinse the concentrate container with filtered trichloromonofluoromethane and add the rinses to the holding tank.
6. Make up the final mass of 5.693 kg with filtered trichloromonofluoromethane.
7. Mix for 5 minutes. Sample (to determine nonvolatile matter, range: 0.49–0.53 w/w).
8. Fill 5.7 g of suspension into a clean aluminum vial and immediately crimp on the metering valve. Pressure fill, through metering valve, sufficient dichlorodifluoromethane to produce a final fill weight of 20.4 g. Check-weigh each aerosol to ensure that the fill weight is in the range of 20 to 20.8 g. At the start of manufacture, fill the vials and apply nonmetering valves. Pressure-test these vials using a special gauge adaptor to ensure the correct propellant mix is being used. The internal pressure measured at 22°C should be 50 to 60 psi.
9. Store the filled aerosols for a period of 2 weeks and check the weight again.
10. Test each aerosol by actuation to ensure correct operation.

Salbutamol Syrup Sugar Free

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
20.75	1	Citric acid (monohydrate)	4.15
10.00	2	Sodium benzoate	2.00
6.25	3	Sodium citrate	1.25
3.75	4	Saccharin sodium	0.75
2.00	5	Salbutamol sulfate, 20% excess	0.48
5.00	6	Sodium chloride	1.00
5.00	7	Strawberry flavor	1.00
10.00	8	Tangerine flavor	2.00
15.00	9	Hydroxypropyl methylcellulose (Methocel E4M)	3.00
–	10	Water purified	QS to 1 L

Manufacturing Directions

1. Add 700 g of item 10 to the manufacturing vessel and heat to 70°C.
2. Add item 9 slowly while mixing at low speed. Mix for 30 minutes.
3. Cool down to 25°C with continuous mixing at low speed.
4. Add 20 g of item 10 (25°C) in a separate stainless steel container and dissolve items 3, 4, and 6 and add to the manufacturing vessel.
5. Add 20 g of item 10 (25°C) in a separate container and dissolve item 1 by and add to the manufacturing vessel.
6. Add 20 g of item 10 (25°C) in a separate container and dissolve item 2 and add to the manufacturing vessel.
7. Add 20 g of item 10 (25°C) in a separate container and dissolve item 5 by and add to the manufacturing vessel.
8. Add items 7 and 8 to the manufacturing vessel while mixing.
9. Make up the volume up to 1 L with item 10 (25°C) and finally mix for 20 minutes at high speed.
10. Assemble the Seitz filter press and wash the filters using about 250 L purified water (25°C) by passing through filters at 0.2 bar.
11. Filter the syrup at 1.5 bar. Recirculate about 30 to 40 mL syrup.
12. Transfer the filtered syrup to the storage vessel.

Salbutamol Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
2.00	1	Salbutamol sulphate (20%)	0.480
2500.00	2	Sucrose	500.000
5.00	3	Methyl paraben	1.000
1.00	4	Propyl paraben	0.20
5.00	5	Citric acid (monohydrate)	1.00
2.80	6	Sodium citrate	0.57
1000.00	7	Sorbitol (70% solution)	200.00
1.10	8	Flavor	0.22
1.10	9	Flavor	0.22
50.00	10	Propylene glycol	10.00
–	11	Water purified	QS to 1 L

Manufacturing Directions

See above.

Salicylic Acid Collodion

Salicylic acid 17% w/w, alcohol, 26.3% w/w, t-butyl alcohol, denatonium benzoate, flexible collodion, and propylene glycol dipelargonate.

Salmeterol Xinafoate Inhalation Aerosol

Salmeterol xinafoate inhalation aerosol contains salmeterol xinafoate as the racemic form of the 1-hydroxy-2-naphthoic acid salt of salmeterol. It is a pressurized, metered-dose aerosol unit for oral inhalation. It contains a microcrystalline suspension of salmeterol xinafoate in a mixture of two chlorofluorocarbon propellants (trichlorofluoromethane and dichlorodifluoromethane) with lecithin. 36.25 μg of salmeterol xinafoate is equivalent to 25 μg of salmeterol base. Each actuation delivers 25 μg of salmeterol base (as salmeterol xinafoate) from the valve and 21 μg of salmeterol base (as salmeterol xinafoate) from the actuator. Each 6.5-g canister provides 60 inhalations and each 13-g canister provides 120 inhalations.

Salmeterol Xinafoate Inhalation Aerosol

Bill of Materials			
Scale (mg/application)	Item	Material Name	Qty/1000 application (g)
0.25	1	Salmeterol (used as salmeterol xinafoate)	0.250
7.28	2	Miglyol 829 (caprylic/capric diglycerol succinate)	7.280
0.15	3	Peppermint oil	0.150
0.18	4	Menthol	0.180
113.00	5	*N*-Butane	QS to 113.000

Manufacturing Directions

1. Transfer Miglyol 829 by pumping from the released and tared container into mixing vessel.
2. After pumping Miglyol 829, set the propeller with optimum circulation and revolution to ensure no air entrapment.
3. Weigh out required amount of salmeterol xinafoate transfer directly into mixing vessel while mixing slowly.
4. Keep the preparation under stirring without interruption or change in rpm.
5. Dissolve menthol in peppermint oil at 25°C by slow stirring in another mixing vessel. Continue stirring until the solution becomes clear.
6. Transfer the clean menthol solution (step 5) into step 4 while stirring at the set speed. Continue stirring for 1 hour.
7. Store the base solution in aluminum can with polyethylene stopper and screw cap.

Scopolamine Nasal Spray

Charge 2.6 g of scopolamine into a pressure-addition vessel and dissolve with stirring in 405.6 g of ethanol in which 0.26 g of oleic acid has previously been dissolved. After sealing and evacuation thereof, 6.7 kg of HFA 134a that has previously been aerated with carbon dioxide and adjusted to a pressure of 8 bar (20) in another pressure addition vessel is added by stirring. The solution obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Selenium Sulfide Shampoo with Conditioner

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Selenium sulfide	10.00
2.00	2	Methyl paraben	2.00
10.00	3	Magnesium aluminum silicate type IIA	10.00
20.00	4	Titanium	20.00
0.17	5	Dye	0.17
230.00	6	Sodium alkyl ether sulfate/sulfonate	230.00
30.00	7	Cocamide DEA surfactant	30.00
40.00	8	Cocoamphocarboxyglycinate	40.00
10.00	9	Hydrolyzed protein	10.00
4.00	10	Perfume	4.00
QS	11	Citric acid	QS
QS	12	Sodium chloride	QS
QS	13	Deionized purified water	QS to 1 L

Note: Item 11 is used for pH adjustment, if necessary and item 12 is used for viscosity adjustment, if necessary.

Manufacturing Directions

1. Selenium sulfide is toxic; handle carefully and use approved respiratory protection.
2. Add 7 mL of purified water to an appropriate mill containing full-charge alumina grinding cylinder media.
3. Add selenium sulfide.
4. Seal the mill and agitate for approximately 10 minutes to wet down the powdered material.
5. Recycle for approximately 5 minutes with the pump set at 1040 mm Hg.
6. Stop agitation.
7. If necessary, add purified water (25–30°C) to nearly cover the grinding media.
8. Seal the mill and recirculate the slurry for 1 to 2 hours with the pump set to obtain the required particle size specifications for the selenium sulfide.
9. Load 250 mL of purified water into a suitable jacketed mixing tank and heat to 60°C to 70°C.
10. With good stirring, add and dissolve methyl paraben.
11. Slowly add and disperse the magnesium aluminum silicate. Continue mixing until fairly smooth.
12. Stop mixing and allow to hydrate for 1 hour.
13. Add and disperse titanium dioxide.
14. Mix for 30 minutes.
15. With good stirring, add the selenium sulfide slurry and rinse the mill with purified water.
16. Mix for 30 minutes.
17. Stop mixing and add sodium lauryl ether sulfate/sulfonate.
18. Mix slowly for 5 minutes.
19. Add cocamide DEA.
20. Mix slowly for approximately 3 minutes.
21. Add coco-amphocarboxyglycinate.
22. Mix slowly for 30 minutes.
23. Separately dissolve hydrolyzed protein (hydrogel) in 4 mL of purified water and mix until uniform.
24. Add solution from above to the tank and mix until uniform.
25. Add perfume and mix for 1 minute.
26. Dissolve dye in 2 mL of warm purified water (50–60°C) and add to mixing tank.
27. Mix until uniform.
28. Check and record pH; adjust to 4.5 to 5.0, if necessary, using citric acid. Record amount of citric acid used and the adjusted pH.
29. Add purified water QS to 980 mL and mix for 30 minutes.
30. Check and record viscosity.
31. If necessary, adjust by adding sodium chloride.
32. Deaerate by slow stirring under vacuum or use of a suitable deaerator.
33. Mix for 1 hour.

Sertraline Hydrochloride Oral Concentrate

Sertraline hydrochloride is a selective serotonin reuptake inhibitor for oral administration. It is chemically unrelated to other selective serotonin reuptake inhibitors or tricyclic, tetracyclic, or other available antidepressant agents. It is supplied in a multidose 60-mL bottle. Each milliliter of solution contains sertraline hydrochloride equivalent to 20 mg of sertraline. The solution contains the following inactive ingredients: glycerin, alcohol (12%), menthol, butylated hydroxytoluene. The oral concentrate must be diluted before administration.

Sertraline Hydrochloride Solution

Zoloft oral concentrate is available in a multidose 60-mL bottle. Each milliliter of solution contains sertraline hydrochloride equivalent to 20 mg of sertraline. The solution contains the following inactive ingredients: glycerin, alcohol (12%), menthol, butylated hydroxytoluene.

Simethicone Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
144.00	1	Simethicone emulsion 30% (Simethicone Antifoam M30)[a]	144.00
60.00	2	Polyethylene glycol (PEG 6000)	60.00
1.50	3	Xanthan gum (Keltrol F)	1.50
1.50	4	Methylcellulose 4000 (Methocel A4M)	1.50
1.50	5	Potassium sorbate	1.50
1.20	6	Methyl paraben	1.20
0.20	7	Propyl paraben	0.20
1.500	8	Saccharin sodium	1.50
0.80	9	Banana green flavor	0.80
1.02	10	Citric acid (monohydrate)	1.02
0.24	11	Sodium citrate powder	0.24
–	12	Water purified	QS to 1 L

[a]Equivalent to 43.2 mg of simethicone.

Manufacturing Directions

1. Load 240 g of item 12 in mixer. Heat to 90° to 95°C. Dissolve items 6 and 7 by mixing with recirculation for 5 minutes.
2. Load item 2 in mixer. Mix to clear solution at 90°C to 95°C for 5 minutes, under vacuum 0.4 to 0.6 bar.
3. Cool down to 25°C to 30°C. Take the PEG paraben solution out of the mixer and keep in a stainless steel container.
4. Load 512 g of item 12 in mixer. Heat to 90°C to 95°C and then cool to 65°C to 70°C.
5. Take out 208 g of item 12 (65–70°C) from the mixer in a stainless steel container. Disperse item 3 by continuous stirring by mixer.
6. Disperse item 4 in mixer containing item 12 at 65°C to 70°C (step 4) while mixing and homogenizing at high speed for 5 minutes under vacuum 0.4 to 0.6 bar.
7. Cool to 20°C to 25°C with continuous mixing and recirculation.
8. Add PEG paraben solution from step 3 to mixer while mixing at speed 18 rpm.
9. Add item 3 mucilage from step 5 to mixer while mixing at speed 18 rpm.
10. Homogenize at high speed under vacuum 0.4 to 0.6 bar for 5 minutes while mixing.
11. Dissolve items 5 and 8 in 12 g of item 12 in a stainless steel container and add to mixer while mixing.
12. Add item 1 to the mixer while mixing.
13. Rinse the container of item 1 (step 12) with 12 g of item 12 and add the rinsing to the mixer.
14. Add item 9 to the mixer while mixing.
15. Mix and homogenize at low speed under vacuum 0.4 to 0.6 bar for 5 minutes.
16. pH is a critical factor for Simethicone emulsion. Limit is between 4.4 and 4.6. Carefully adjust the pH.
17. Add item 12 (25–30°C) to make up the volume up to 1 L.
18. Mix at slow speed under vacuum 0.4 to 0.6 bar for 5 minutes.
19. Filter the bulk through 630-micron sieve in a clean stainless steel storage tank.

Sirolimus Solution

Sirolimus is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. It is available for administration as an oral solution containing 1 mg/mL sirolimus; the inactive ingredients include phosphatidylcholine, propylene glycol, mono- and diglycerides, ethanol, soy fatty acids, and ascorbyl palmitate, and polysorbate 80. The oral solution contains 1.5% to 2.5% ethanol.

Sodium Chloride Nasal Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
90.00	1	Sodium chloride	90.00
3.00	2	Benzalkonium chloride solution 5%	3.00
QS	3	Water purified	QS to 1 L

Manufacturing Directions

1. Charge 50% item 1 in a suitable stainless steel container and heat to 85°C to 90°C.
2. Add and dissolve item 2 at room temperature.
3. Add item 1 and make up volume.

Stavudine for Oral Suspension

Zerit (stavudine) for oral solution is supplied as a dye-free, fruit-flavored powder in bottles with child-resistant closures providing 200 mL, 1 mg/mL, stavudine solution on constitution with water per label instructions. The powder for oral solution contains the following inactive ingredients: methyl paraben, propyl paraben, sodium carboxymethylcellulose, sucrose, and antifoaming and flavoring agents.

Sucralfate Suspension

Carafate suspension for oral administration contains 1 g sucralfate per 10 mL. Carafate suspension also contains colloidal silicon dioxide, FD&C red No. 40, flavor, glycerin, methylcellulose, methyl paraben, microcrystalline cellulose, purified water, simethicone, and sorbitol solution.

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
1000.00	1	Sucralfate	200.00
5.00	2	Methyl paraben	1.00
1.50	3	Propyl paraben	0.30
1500.00	4	Sorbitol 70%	300.00
2.50	5	Saccharin sodium	0.50
20.00	6	Natrosol 250M	4.00
30.00	7	Avicel HC 591	6.00
20.00	8	Sodium phosphate dibasic	4.00
7.50	9	Sodium phosphate monobasic	1.50
1.00	10	Lemon flavor	0.20
QS	11	Water purified	QS to 1 L

Manufacturing Directions

1. Charge 40% of item 11 in a stainless steel jacketed vessel and heat to 90°C to 95°C.
2. Add items 2 and 3 and mix to dissolve. Cool to 40°C.
3. Charge item 11 and item 6 in a separate vessel at 70°C to 80°C and stir for 30 minutes.
4. Add and disperse item 7 in step 3.
5. Transfer to step 1 and mix to disperse.
6. In a separate vessel, add and mix item 4 with items 1 and 11.
7. Add to step 6.
8. Add flavor and bring to volume.

Sulfacetamide Sodium and Sulfur Cleanser and Suspension

Each gram of Plexion (sodium sulfacetamide 10% and sulfur 5%) cleanser contains 100 mg sodium sulfacetamide and 50 mg sulfur in a cleanser base containing water, sodium methyl oleyltaurate, sodium cocoyl isethionate, disodium oleamido MEA sulfosuccinate, cetyl alcohol, glyceryl stearate and PEG-100 stearate, stearyl alcohol, PEG-55 propylene glycol oleate, magnesium aluminum silicate, methyl paraben, disodium EDTA, butylated hydroxytoluene, sodium thiosulfate, fragrance, xanthan gum, and propyl paraben. Each gram of Plexion (sodium sulfacetamide 10% and sulfur 5%) topical suspension contains 100 mg sodium sulfacetamide and 50 mg sulfur in a topical suspension containing water, propylene glycol, isopropyl myristate, light mineral oil, polysorbate 60, sorbitan monostearate, cetyl alcohol, hydrogenated cocoglycerides, stearyl alcohol, fragrances, benzyl alcohol, glyceryl stearate and PEG-100 stearate, dimethicone, zinc ricinoleate, xanthan gum, disodium EDTA, and sodium thiosulfate.

Sulfadiazine and Trimethoprim Veterinary Oral Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
400.00	1	Sulfadiazine	400.00
80.00	2	Trimethoprim	80.00
50.00	3	Sodium hydroxide	50.00
20.00	4	Kollidon CL-M	20.00
QS	5	Water purified	QS to 1 L

Manufacturing Directions

1. Charge item 3 into a stainless steel vessel along with item 5. Mix and dissolve.
2. Add and suspend item 4. Mix well.
3. Add and suspend items 1 and 2. Homogenize if necessary.
4. Fill.

Sulfamethoxazole and Trimethoprim Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
200.00	1	Sulfamethoxazole	40.00
40.00	2	Trimethoprim	8.00
2.50	3	Carrageenan (Hydrogel 843T)	0.50
18.75	4	Tragacanth	3.75
2.50	5	Saccharin sodium dihydrate	0.50
0.625	6	Anise oil	0.125
3.125	7	Methyl paraben	0.625
2.70	8	Propyl paraben	0.54
2.17	9	Alcohol dehydrated	0.435
2914.00	10	Sorbitol solution	582.80
403.75	11	Glycerin	80.75
QS	12	Water purified	QS to 1 L

Manufacturing Directions

1. Add and disperse Hydrogel 843T in approximately 8 mL purified water.
2. Heat 30 mL purified water to 100°C and add to dispersion from step 1 with mixing.
3. Let stand overnight.
4. Load trimethoprim and 7 g sulfamethoxazole into a suitable mixer. Blend.
5. Moisten blend with approximately 25 mL water.
6. Spread mass as small pancakes onto oven trays and dry at 50°C for approximately 14 hours.
7. Retain balance of sulfamethoxazole for later use.
8. While mixing, add 75 mL water. Mix until homogenous.
9. Charge approximately 350 mL water into a suitable stainless steel mixing tank. Add and dissolve saccharin with mixing.
10. Add tragacanth and continue mixing for 4 hours.
11. Separately add and dissolve the following ingredients in alcohol: methyl paraben, propyl paraben, and anise oil.
12. Add solution from step above and sorbitol to the preparation from step 1. Mix for 3 hours and let stand overnight.
13. Add gel from step above with mixing. Mix for approximately 15 minutes.
14. Pass trimethoprim/sulfamethoxazole mass from step 4 and balance of sulfamethoxazole through a 595-micron aperture screen in Fitz mill knives forward, medium speed, and slowly add to main tank with continuous agitation.
15. Add glycerin to main tank with mixing.
16. Pass the whole batch through a colloid mill until particle size and homogeneity meet specifications. Rinse mill and other equipment with purified water. Add the rinsings to the batch and mix.
17. If necessary, deaerate the product mixing under vacuum (ca. 20–25 in of mercury). Release vacuum and check volume.
18. Bring to volume with water and mix.
19. Stir the suspension until homogeneous. Fill while stirring.

Sulfamethoxazole and Trimethoprim Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
80.00	1	Sulfamethoxazole	80.00
16.00	2	Trimethoprim	16.00
30.00	3	Kollidon CL-M	30.00
100.00	4	Sucrose	100.00
QS	5	Water purified	QS to 1 L
2.00	6	Vanillin	2.00
2.00	7	Flavor chocolate	2.00

Manufacturing Directions

1. Charge in a suitable stainless steel jacketed vessel items 4 and 5. Heat to dissolve.
2. Cool to 40°C.
3. Add, after passing through 200-mesh sieve, items 1 to 3 into step 2. Mix to dissolve.
4. Add flavors. Mix and fill.

Sulfamethoxazole and Trimethoprim Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
80.00	1	Sulfamethoxazole	80.00
16.00	2	Trimethoprim	16.00
50.00	3	Sucrose	5.00
30.00	4	Lutrol F 127 or Lutrol F 68	30.00
QS	5	Water purified	QS to 1 L
QS	6	Vanillin	QS
QS	7	Flavor chocolate	QS

Manufacturing Directions

1. Charge in a suitable stainless steel jacketed vessel items 3 and 4. Heat to dissolve.
2. Cool to 40°C.
3. Add, after passing through 200-mesh sieve, items 1, 2, and 4 into step 2. Mix to dissolve.
4. Add flavors, if used. Mix and fill.

Sulfathiazole Veterinary Oral Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
8.00	1	Sulfathiazole	8.00
225.00	2	Kollidon 25	225.00
QS	3	Preservative	QS
QS	4	Water purified	QS to 1 L

Manufacturing Directions

1. Charge item 4 in a suitable stainless steel jacketed vessel. Heat to 70°C.
2. Add and disperse item 2.
3. Add and dissolve item 1 to a clear solution
4. Filter, if necessary, and fill.
5. Optionally, an antioxidant such as 0.02% sodium bisulfite or 0.5% cysteine may be added if necessary.

Sulfidoxine Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
20.00	1	Sulfidoxine	20.00
680.00	2	Lutrol E 400	680.00
QS	3	Preservatives	QS
QS	4	Water purified	QS to 1 L

Manufacturing Directions

1. Charge items 1 and 2 in a suitable stainless steel jacketed vessel. Heat to 60°C and mix.
2. In a separate vessel, charge item 4 and heat to 90°C to 95°C and then add item 3 (e. g., parabens) and dissolve. Cool to 40°C.
3. Add step 2 into step 1. Mix to clear solution.

Sulfidoxine and Pyrimethamine Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
2.70	1	Tylose	2.70
1.00	2	Methyl paraben	1.00
0.20	3	Propyl paraben	0.20
600.00	4	Sugar	600.00
0.15	5	Sodium hydroxide	0.15
6.00	6	Trisodium citrate dehydrate	6.00
2.00	7	Benzoic acid	2.00
100.00	8	Sorbitol syrup	100.00
4.00	9	Tween 80	4.00
100.00	10	Sulfadoxine micronized	100.00
5.00	11	Pyrimethamine	5.00
0.20	12	Flavor	0.20
0.20	13	Flavor	0.20
0.20	14	Flavor	0.20
QS	15	Water purified	QS to 1 L

Manufacturing Directions

1. Boil a suitable quantity of item 15, cool down to 70°C, and add and dissolve items 2 and 3.
2. Add item 1 and dissolve in item 15 in a separate container and then add to step 1.
3. In a separate container add and dissolve sodium hydroxide, sodium citrate, and benzoic acid in item 15 and add to step 1.
4. Add and mix sorbitol with Tween 60 and item 10, stir for 15 minutes, and add to step above.
5. Add item 11 to step above and mix to dissolve.
6. Add flavors and bring to volume.

Sumatriptan Nasal Spray

Each Imitrex nasal spray contains 5 or 20 mg of sumatriptan in a 100-μL unit-dose aqueous buffered solution containing monobasic potassium phosphate, anhydrous dibasic sodium phosphate, sulfuric acid, sodium hydroxide, and purified water. The pH of the solution is approximately 5.5. The osmolality of the solution is 372 or 742 mOsmol for the 5- and 20-mg Imitrex nasal spray respectively.

Sumatriptan Nasal Spray

Manufacturing Directions

1. Charge 2.6 g of sumatriptan into a pressure-addition vessel and dissolve with stirring in 405.6 g of ethanol in which 0.26 g of oleic acid has previously been dissolved.
2. After closing and evacuation thereof, 6.7 kg of HFA 134a that has previously been aerated with carbon dioxide and adjusted to a pressure of 7 bar (20°C) in another pressure-addition vessel is added with stirring.
3. The preparation obtained is dispensed into aluminum containers sealed with metering valves by means of the pressure-filling technique.

Terfenadine Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
30.00	1	Terfenadine, 8% excess	6.48
2250.00	2	Sucrose	450.00
7.50	3	Sodium methyl paraben	1.50
2.500	4	Sodium propyl paraben	0.50
300.00	5	Propylene glycol	60.00
15.00	6	Polysorbate 80 (Tween 80)	3.00
50.00	7	Benzyl alcohol	10.00
0.24	8	Anise oil	0.048
15.00	9	Magnesium aluminium silicate (Veegum HV)	3.00
125.00	10	Glycerin	25.00
18.74	11	Carboxymethylcellulose sodium	3.74
0.76	12	Citric acid (monohydrate)	0.15
–	13	Water purified	QS to 1 L

Manufacturing Directions

1. Add 240 g of item 13 to the mixer and heat to 90°C. Add and dissolve item 2 while mixing.
2. Add and dissolve items 3 and 4 in the mixer at step 1 while mixing at speed 18 to 20 rpm for 15 minutes.
3. Cool down to about 50°C to 55°C.
4. Filter the syrup.
5. Collect the syrup in clean stainless steel tank.
6. Clean mixer with item 13 and transfer the filtered syrup from step 4. Maintain temperature at 35°C.
7. Add 80 g of item 13 (70°C) in a separate stainless steel container and disperse item 9 by using stirrer. Keep aside for 1 hour for hydration.
8. Add item 10 in a separate stainless steel container and disperse item 11 while mixing with stirrer.
9. Add 80 g of item 13 (70°C) while mixing. Make a gel and keep aside.
10. Add 160 g of item 13 (60°C) in a separate stainless steel container.
11. Dissolve item 6. Avoid foam formation. Add item 1 slowly while mixing at slow speed. Add item 5 while mixing at slow speed. Keep the solution aside.
12. Transfer items 1, 9, and 11 dispersions from steps 3, 4, and 5, respectively to the mixer.
13. Mix at speed 18 rpm for 10 minutes.
14. Mix item 8 in item 7 and add to the mixer. Mix for 2 minutes.
15. Dissolve item 12 in 3.2 g of item 13 and add to the mixer. Mix for 2 minutes.
16. Add cold item 13 (25°C) to make up the volume to 1 L.
17. Homogenize for 10 minutes at high speed under vacuum 0.5 bar, 18 to 20 rpm, temperature 25°C.
18. Check the dispersion for uniformity.
19. Check the pH (limit: 8–9 at 25°C). If required, adjust the pH with 20% solution of citric acid or sodium citrate.
20. Filter the suspension through a 500-micron sieve to storage tank.

Terfenadine Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
12.00	1	Terfenadine	12.00
30.00	2	Lutrol F 127	30.00
36.00	3	Cremophor RH 40	36.00
QS	4	Preservatives	QS
QS	5	Water purified	QS to 1 L

Manufacturing Directions

1. Charge item 5 in a suitable stainless steel jacketed vessel and heat to 40°C.
2. Add and dissolve item 2 and 3 in step 1.
3. While stirring, add item 1 and suspend.
4. Homogenize if necessary and fill.

Theophylline Sodium Glycinate Elixir

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
125.00	1	Theophylline sodium glycinate[a]	25.00
4000.00	2	Sucrose	800.00
7.50	3	Sodium benzoate	1.50
0.75	4	Saccharin sodium	0.15
0.025	5	FD&C red No. 40	0.005
1.00	6	Flavor	0.20
QS	7	Water purified	QS to 1 L

[a] 125 mg theophylline sodium glycinate is equivalent to 60 mg theophylline hydrate.

Manufacturing Directions

1. Add 400 g of item 7 to the manufacturing vessel and heat to 95°C to 98°C. Add items 3 and 4 to dissolve. Mix for 10 minutes at low speed.
2. Add item 2 while mixing at low speed, temperature 95°C to 98°C. When addition is over, mix for 30 minutes at high speed.
3. Cool to 30°C while mixing at low speed.
4. Add 50 g of item 7 (25–30°C) in a separate container and dissolve item 1 by using stirrer. Mix for 10 minutes and transfer to the manufacturing vessel at step 3.
5. Rinse the container (step 3) with 1 g of item 7 (25–30°C) and transfer the rinsings to the manufacturing vessel while mixing at low speed.
6. Dissolve item 5 in 1 g of item 7 in a stainless steel container with slow stirring by stirrer. Transfer to the manufacturing vessel while mixing at low speed.
7. Add item 6 to the manufacturing vessel step 4 while mixing. Mix for 10 minutes at low speed.
8. Make up the volume to 1 L with item 7 and, finally, mix for 5 to 10 minutes at high speed.
9. Check and record the pH (limit: 8.5–9.0 at 25°C).
10. Filtration: Assemble the filter press. Wash the filters using about 1 L of purified water (25°) by passing through filters at 0.2 bar. Filter the syrup at 1.5 bar. Recirculate about 20 to 30 mL syrup.
11. Transfer the filtered syrup to the storage vessel.

Thiabendazole Suspension

Mintezol (Thiabendazole) is an anthelmintic provided as a suspension, containing 500 mg thiabendazole per 5 mL. The suspension also contains sorbic acid 0.1% added as a preservative. Inactive ingredients in the tablets are acacia, calcium phosphate, flavors, lactose, magnesium stearate, mannitol, methylcellulose, and sodium saccharin. Inactive ingredients in the suspension are an antifoam agent, flavors, polysorbate, purified water, sorbitol solution, and tragacanth.

Thiothixene Oral Concentrate

Ingredients are thiothixene (2–30 mg/30 mL), alcohol, cherry flavor, dextrose, passion fruit flavor, sorbitol solution, and water.

Timolol Maleate Opthalmic Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
2.50	1	Timolol maleate	2.50
QS	2	Vehicle (pluraflo 1220 92.37%, ethanol 2.11%, anhydrous glycerin 5.16%)	QS to 1 L

Manufacturing Directions

1. Add timolol. Cover tightly and stir until a clear solution is obtained.
2. Add glycerin, ethanol, and pluraflo to a clean vessel.

Tolnaftate Foot Care Microemulsion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
155.00	1	Ethoxydiglycol	155.00
130.00	2	Polyglyceryl-6 dioleate	130.00
450.00	3	PEG-8 caprylic/capric glycerides	450.00
10.00	4	Tolnaftate	10.00
100.00	5	Water purified	100.00
50.00	6	Apricot kernel oil PEG-6 esters	50.00
100.00	7	Caprylic/Capric triglycerides	100.00
5.00	8	Chlorocresol	5.00

Manufacturing Directions

1. Mix items 1 to 3 and dissolve item 4 in this mixture.
2. Add items 5 to 8 and mix until uniform.

Tolu Balsam Cough Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
11.03	1	Tolu balsam tincture	11.03
2.50	2	Magnesium carbonate	2.50
15.00	3	Sucrose	15.00
QS	4	Water purified	90.000 mL
0.77	5	Methyl paraben	0.77
0.086	6	Propyl paraben	0.086
514.36	7	Sucrose	0.51
129.24	8	Glycerin (96%)	0.13
2.00	9	Dextromethorphan hydrobromide	2.00
1.00	10	Ephedrine HCl[a]	1.00
8.00	11	Ammonium chloride	8.00
0.40	12	Chlorpheniramine maleate	0.40
1.00	13	Phenylephrine hydrochloride	1.00
333.32	14	Glucose liquid	0.33
0.35	15	Flavor	0.35
0.15	16	Flavor	0.15
1.02	17	Ipecac fluid extract	1.01
8.57	18	Alcohol[b]	8.57
0.0375	19	Dye	0.037
QS	20	Acid hydrochloric	QS
QS	21	Water purified	QS to 1 L

[a]May be deleted.
[b]Tolu balsam tincture contains 80% alcohol. Use this item optionally to dissolve flavors.

Manufacturing Directions

1. Charge tolu balsam tincture into mixing tank and add magnesium carbonate.
2. Mix well to suspend.
3. Add sugar (item 3) with mixing. Add 90 mL purified water (item 4) and mix thoroughly.
4. Allow to set for 1 hour.
5. Mix periodically while circulating through filter.
6. Solution must be brilliantly clear. Filter and save for next part.
7. Charge 210.5 mL purified water (item 21) into suitable tank.

8. Add and dissolve aseptoforms M and P with heat 90°C to 95°C and mixing.
9. Add and dissolve sugar (item 7) with mixing.
10. Heat if necessary. Add glycerin, continue agitation, and cool to room temperature. Add filtrate from step above to cooled syrup.
11. Add and dissolve the following ingredients with mixing: dextromethorphan HBr, ephedrine HCl (if used), ammonium chloride, chlorpheniramine maleate, and phenylephrine HCl.
12. Add glucose. Mix well. Add and dissolve in alcohol: flavors and ipecac fluid extract.
13. Add to tank, or in a separate container add flavors and ipecac extract to 10 mL glucose liquid, and mix. Add this to the main mixture.
14. Rinse the container with a further 5 mL glucose liquid and add the rinsing to the mixture.
15. Add the remaining glucose liquid. Mix well.
16. Dissolve in 1.75 mL purified water and add.
17. Check pH (range: 4–5). Adjust to pH 4 to 5 with hydrochloric acid.
18. Make the volume to 1 L with purified water.
19. Filter until sparkling clear. Add 0.5 g Hyflo® to mixing tank, mixing until uniform.
20. Filter into tank for filling.

Tolu Balsam Cough Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
11.03	1	Tolu balsam tincture	11.03
2.50	2	Magnesium carbonate (powder)	2.50
15.00	3	Sucrose (granulated sugar)	15.00
QS	4	Purified water	90.00 mL
0.77	5	Methyl paraben	0.77
0.086	6	Propyl paraben	0.86
514.36	7	Sucrose (granulated sugar)	514.36
129.24	8	Glycerin (96%)	129.24
2.00	9	Dextromethorphan hydrobromide	2.00
1.00	10	Ephedrine HCl (powder)	1.00
8.00	11	Ammonium chloride	8.00
0.40	12	Chlorpheniramine maleate	0.40
1.00	13	Phenylephrine HCl	1.00
333.32	14	Glucose (liquid)	333.32
0.35	15	Flavor	0.35
0.15	16	Flavor	0.15
1.01	17	Ipecac (fluid extract)	1.01
8.57	18	Alcohol (ethanol, 190 proof)	8.57
0.037	19	Dye	0.037
QS	20	Hydrochloric acid (reagent-grade bottles)	QS
QS	21	Purified water	212.00 mL

Manufacturing Directions

1. Charge tolu balsam tincture into mixing tank and add magnesium carbonate.
2. Mix well to suspend.
3. Add sugar (item 3) with mixing.
4. Add 90 mL purified water (item 4) and mix thoroughly.
5. Allow to set for 1 hour.
6. Mix periodically while circulating through Shriver filter (or equivalent).
7. Solution must be brilliantly clear.
8. Filter and save for next part.
9. Charge 210.5 mL purified water (item 21) into suitable tank.
10. Add and dissolve parabens with heat (90–95°C) and mixing.
11. Add and dissolve sugar (item 7) with mixing. Heat if necessary.
12. Add glycerin, continue agitation, and cool to room temperature.
13. To cooled syrup, add filtrate from step above.
14. Add and dissolve the following ingredients with mixing: dextromethorphan hydrobromide, ephedrine HCl, ammonium chloride, chlorpheniramine maleate, and phenylephrine HCl.
15. Add glucose. Mix well.
16. Add and dissolve flavors and Ipecac fluid extract in 190-proof alcohol.
17. To the tank or in a separate container add flavors and Ipecac extract to 10 mL of glucose liquid and mix.
18. Add this mixture to the main mixture.

19. Rinse the container with a further 5 mL of liquid glucose and add the rinsing to the mixture.
20. Add the remaining liquid glucose. Mix well.
21. Dissolve in 1.75 mL purified water and add.
22. Check pH (range: 4–5).
23. Use hydrochloric acid to adjust pH to 4 to 5, with 4.5 being optimum (~0.3 mL HCl per liter of syrup).
24. QS to 1 L with purified water.
25. Filter until sparkling clear.
26. Add a suitable filter aid and mix until uniform.
27. Filter into tank for filling.

Tretinoin Solution (50 mg/100 g)

Formulation

I. Tretinoin (BASF), 0.05 g; Cremophor RH 40 [1], 14.0 g; propylene glycol [1], 15.0 g; butylhydroxytoluene, 0.05 g; alpha-bisabolol nat. (BASF), 0.1 g
II. Water, 70.0 g; parabens/sorbic acid, QS

Manufacturing

Heat mixture I to 40°C to 50°C to obtain a clear solution. Introduce this warm solution slowly in solution II. It forms a clear yellow solution.

Tretinoin Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.50	1	Tretinoin (BASF)	0.50
140.00	2	Cremophor RH 40	140.00
150.00	3	Propylene glycol	150.00
0.50	4	Butylated hydroxytoluene	0.50
1.00	5	Alpha bisabolol natural (BASF)	1.00
QS	6	Water purified	QS to 1 L
QS	7	Parabens	QS
QS	8	Sorbic acid	QS

Manufacturing Directions

1. Charge items 1 to 5 in a suitable stainless steel jacketed vessel. Heat to 40°C to 50°C to obtain a clear solution.
2. In a separate jacketed vessel, charge item 6 and heat to 90°C to 95°C.
3. Add and dissolve items 7 and 8. Cool to 40°C.
4. Add step 3 into step 1.
5. Mix to clear solution.
6. Filter if necessary and fill.

Triamcinolone Acetonide Nasal Spray

Tri-Nasal spray is a metered-dose manual-spray pump in an amber polyethylene terephthalate bottle with 0.05% w/v triamcinolone acetonide in a solution containing citric acid, EDTA, polyethylene glycol 3350, propylene glycol, purified water, sodium citrate, and 0.01% benzalkonium chloride as a preservative. Tri-Nasal Spray pH is 5.3.

Manufacturing Directions

Dissolve 20 g triamcinolone acetonide in 1.5 kg ethanol. The solution is dispensed into open aluminum containers and these are sealed with suitable metering valves. The containers are filled by means of the pressure-filling technique with a total of 4 kg of HFA 227 that has been aerated with carbon dioxide and adjusted to a pressure of 5 bar (20°C).

Triclosan Oral Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
QS	1	Vehicle (pluronic F108 55.80%, ethanol 21.30%, water 22.90%)	QS to 1 L
2.80	2	Triclosan monophosphate	2.80
10.00	3	Menthol	10.00
1.00	4	Sodium saccharin	1.00
0.50	5	Monosodium glycyrhizzinate	0.50
QS	6	Flavors and colors	QS

Manufacturing Directions

1. Mill and screen the menthol and triclosan monophosphate to reduce particle size.
2. Add the menthol, triclosan monophosphate, sodium saccharin, and monoammonium glycyrizzinate into a clean vessel.
3. Add propylene glycol to the vessel.
4. Subsequently add the poloxamer and water to the vessel.
5. Mix until uniform.

Triprolidine and Pseudoephedrine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.25	1	Triprolidine HCl, 4.8% excess	0.26
6.00	2	Pseudoephedrine HCl, 3.0% excess	6.18
600.00	3	Sucrose	600.00
100.00	4	Glycerin (glycerol)	100.00
100.00	5	Sorbitol (70% solution)	100.00
15.00	6	Propylene glycol	15.00
1.00	7	Methyl paraben	1.00
0.30	8	Propyl paraben	0.30
0.50	9	Saccharin sodium	0.50
0.04	10	Quinoline yellow	0.04
0.05	11	Menthol	0.05
0.25	12	Raspberry flavor	0.25
1.15	13	Sodium citrate	1.15
QS	14	Water purified	QS to 1 L

Manufacturing Directions

1. Add 400 g of item 14 to the manufacturing vessel and heat to 90°C to 95°C.
2. Add items 7 and 8 while mixing to dissolve at high speed.
3. Add item 3 while mixing at slow speed. Temperature 90°C to 95°C.
4. Mix for 1 hour at high speed. Cool down to 50°C while mixing at slow speed.
5. Add items 9 and 13 to the manufacturing vessel while mixing at high speed.
6. Load items 5 and 4 into the manufacturing vessel using transfer pump while mixing at high speed.
7. Add 20 g of cold item 14 (30°C) in a separate container and dissolve items 1 and 2 by using stirrer.
8. Mix for 10 minutes and add to the manufacturing vessel while mixing at high speed.
9. Add 1 g of item 14 in a separate container and dissolve item 10 manually.
10. Add color to the manufacturing vessel while mixing at high speed. Dissolve item 11 in item 12. Then add item 6 to it. Add this flavor mixture to the manufacturing vessel while mixing at high speed.
11. Make up the volume 1 L with item 14 and, finally, mix for 15 to 20 minutes at high speed.
12. Check and record the pH (limit: 5.8–6.8 at 25°C).
13. If required, adjust pH with 20% citric acid or 20% sodium citrate solution.
14. Filter the syrup at 1.5 bar. Recirculate about 20 to 30 mL syrup.

Tulobuterol Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
1.00	1	Tulobuterol hydrochloride	0.20
5.00	2	Water purified	100.00 mL
3.75	3	Glycerin	75.00 mL
0.03	4	Methyl paraben	0.60
0.0075	5	Propyl paraben	0.15
QS	6	Red dye	25.00 mg
QS	7	Flavor	5.00
QS	8	Sorbitol (70%)	QS to 1 L

Manufacturing Directions

1. Heat 50 mL water to approximately 80°C and 95°C in a suitable vessel.
2. Add the methyl paraben and propyl paraben. Rinse the containers with some of the remaining water if necessary. Stir until dissolved, maintaining temperature at about 80°C.
3. Warm about 340 mL sorbitol solution to 40°C and 55°C in a suitable vessel.
4. Transfer the warm sorbitol to the final mixing vessel and add the hot paraben solution from step 2, stirring continuously. Rinse paraben solution container with 5 mL hot water and add to the bulk.
5. Dissolve tulobuterol and the dye in about 25 mL remaining water, rinsing the containers with some of the remaining water if necessary.
6. Add the solution from step above to the final vessel, mixing continuously. It is important to ensure all of the colored solution is transferred. Rinse the container with a portion of the remaining water.
7. Add the glycerol and flavor to the bulk solution. Rinse the glycerol container with the remaining water and add to the bulk. Make up to volume with the sorbitol solution.
8. Mix gently until a uniform syrup is obtained, avoiding incorporation of air bubbles.
9. If necessary, circulate through a filter press until sparkling clear.
10. Pass filtered clear syrup into a suitable holding tank.

Tolnaftate Foot Care Microemulsion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
155.00	1	Ethoxydiglycol	155.00
130.00	2	Polyglyceryl-6 dioleate	130.00
450.00	3	PEG-8 caprylic/capric glycerides	450.00
10.00	4	Tolnaftate	10.00
100.00	5	Deionized water	100.00
50.00	6	Apricot kernel oil PEG-6 esters	50.00
100.00	7	Caprylic/Capric triglycerides	100.00
5.00	8	Chlorocresol	5.00

Manufacturing Directions

1. Mix items 1 to 3 and dissolve item 4 in this mixture.
2. Add items 5 to 8 and mix until uniform.

Triprolidine and Pseudoephedrine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.25	1	Triprolidine HCl (4.8% excess)	0.26
6.00	2	Pseudoephedrine HCl (3.0% excess)	6.18
600.00	3	Sucrose	600.00
100.00	4	Glycerin (glycerol)	100.00
100.00	5	Sorbitol (70% solution)	100.00
15.00	6	Propylene glycol	15.00
1.00	7	Methyl paraben	1.00
0.30	8	Propyl paraben	0.30
0.50	9	Saccharin sodium	0.50
0.04	10	Quinoline yellow	0.04
0.05	11	Menthol	0.05
0.25	12	Raspberry flavor	0.25
1.15	13	Sodium citrate	1.15
QS	14	Purified water	QS to 1 L

Manufacturing Directions

1. Add 400 g of purified water to the manufacturing vessel and heat to 90°C to 95°C.
2. Add items 7 and 8 while mixing to dissolve at high speed.
3. Add item 3 while mixing at slow speed (temperature: 90–95°C).
4. Mix for 1 hour at high speed.
5. Cool down to 50°C while mixing at slow speed.
6. Add items 9 and 13 to the manufacturing vessel while mixing at high speed.
7. Load items 5 and 4 into the manufacturing vessel using a transfer pump while mixing at high speed.
8. Add 20 g of cold purified water (30°C) in a separate container and dissolve items 1 and 2 by using stirrer.
9. Mix for 10 minutes and add to the manufacturing vessel while mixing at high speed.
10. Add 1 g of purified water in a separate container and manually dissolve item 10.
11. Add color to the manufacturing vessel while mixing at high speed.
12. Dissolve item 11 in item 12, then add item 6.
13. Add this flavor mixture to the manufacturing vessel while mixing at high speed.
14. Bring the volume up to 1 L with item 14 and finally mix for 15 to 20 minutes at high speed.
15. Check and record the pH (limit: 5.8–6.8 at 25°C).
16. If required, adjust pH with 20% citric acid or 20% sodium citrate solution.
17. Filter the syrup at 1.5 bar.
18. Recirculate about 20 to 30 mL syrup.

Undecylenic Acid and Chloroxylenol Solution

This is an antifungal solution for topical use containing 25% undecylenic acid and 3% chloroxylenol as its active ingredients in a penetrating oil base. Available in 1-oz bottles with special brush applicator.

Urea Peroxide Ear Drops

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
65.00	1	Urea peroxide (40% excess)	91.00
15.00	2	Sodium citrate (dihydrate, powder)	15.00
5.00	3	Polysorbate 20 (Tween 20)	5.00
2.50	4	Tartaric acid (12663)	2.50
QS	5	Anhydrous glycerin	QS
QS	6	Nitrogen	QS

Manufacturing Directions

1. Add 500 mL of glycerin into a suitable tank.
2. Start mixing at slow speed, and heat the contents to 70°C to 75°C.
3. Flood tank with nitrogen, increase mixing speed, and slowly add sodium citrate.
4. Add tartaric acid.
5. Mix for at least 30 minutes or until dissolved.
6. Maintain the temperature at 70°C to 75°C.
7. When sodium citrate is completely dissolved, cool to 25°C to 30°C with constant mixing.
8. Prepare urea peroxide by breaking up lumps and screening to remove large particles.
9. Wear gloves.
10. Add an additional 250 to 300 mL of glycerin into tank.
11. Add urea peroxide slowly to prevent lumping, while mixing constantly.
12. Mix at high speed after addition.
13. Add polysorbate 20 with constant mixing and QS to final volume with glycerin.
14. Mix for at least 30 minutes and until solution is clear.
15. Pass solution through an approximately No. 100 mesh (150-μm or similar) screen and collect in clean, dry carboys. (The filter support screen in a millipore holder may be used for filtering; the solution is too viscous to flow through a membrane or any cellulosic filter.)

Valproic Acid Capsules

Valproic acid is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid. Capsules and syrup are antiepileptics for oral administration. Each soft elastic capsule contains 250 mg valproic acid. Ingredients for the 250-mg capsules are corn oil, FD&C yellow No. 6, gelatin, glycerin, iron oxide, methyl paraben, propyl paraben, and titanium dioxide.

Valproic Acid Syrup

Valproic acid is a carboxylic acid designated as 2-propylpentanoic acid. It is also known as dipropylacetic acid. Capsules and syrup are antiepileptics for oral administration. The syrup contains the equivalent of 250 mg valproic acid per 5 mL as the sodium salt. Inactive ingredients are FD&C red No. 40, glycerin, methyl paraben, propyl paraben, sorbitol, sucrose, water, and natural and artificial flavors.

Vancomycin Hydrochloride Oral Solution

Vancocin HCl for oral solution contains vancomycin hydrochloride equivalent to 10 g (6.7 mmol) or 1 g (0.67 mmol) vancomycin. Calcium disodium edetate, equivalent to 0.2 mg edetate per gram of vancomycin, is added at the time of manufacture. The 10-g bottle may contain up to 40 mg of ethanol per gram of vancomycin.

Vitamin A and Vitamin D Infant Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1500 IU	1	Vitamin A palmitate (1.7 MM IU/g) (50% excess)	1.323
400 IU	2	Vitamin D (40 MM IU/g) (Cholecalciferol) (25% excess)	0.012
10.00	3	Polysorbate 80 (Tween 80)	10.00
0.88	4	Vitamin E (oily; α-tocopheryl acetate)	0.88
0.50	5	Edetate disodium (sodium EDTA)	0.50
1.00	6	Ascorbic acid	1.00
0.10	7	Saccharin sodium	0.10
600.00	8	Glycerin (glycerol)	600.00
100.00	9	Sorbitol (70% solution)	100.00
50.00	10	Propylene glycol	50.00
1.00	11	Flavor	1.00
1.50	12	Flavor	1.50
QS	13	Dye	QS
QS	14	Dye	QS
–	15	Purified water	QS to 1 L

Manufacturing Directions

1. This product is a microemulsion and thermolabile preparation. The temperature of solution must not exceed 25°C at the time of processing. Store bulk at a temperature of 15°C to 20°C under nitrogen protection. Period of storage should not exceed 48 hours prior to filling in the bottle.
2. Collect 200 g of purified water in a melting vessel.
3. Heat to 90°C to 95°C for 10 minutes and then cool to 20°C to 25°C.
4. Bubble nitrogen gas into purified water for 20 minutes.
5. Load 100 g of purified water into the manufacturing vessel.
6. Bubble nitrogen gas during all stages of the processing.
7. Add items 5, 6, and 7 one by one to the manufacturing vessel while mixing.
8. Check that all materials are dissolved completely.
9. Add items 8 and 9 and 20 g of item 10 one by one to the manufacturing vessel while mixing at slow speed.
10. Mix for 5 minutes.
11. Avoid aeration.
12. Add item 3 in a stainless steel container.
13. Mix items 1, 2, and 4 one by one using a stirrer.
14. Mix for 1 hour at slow speed.
15. Avoid aeration.
16. Add the oil phase to the aqueous phase in the manufacturing vessel at a rate of 4 mL/min while mixing; keep on bubbling nitrogen gas throughout the process.
17. Dissolve items 11 and 12 in 30 g of item 10 in a stainless steel container by slow stirring.
18. Add to manufacturing vessel while mixing.
19. Dissolve items 14 and 13 in 40 g of purified water (25–30°C) in a stainless steel container with slow stirring.
20. Add to manufacturing vessel while mixing.
21. Adjust the volume to 1.0 L with cooled purified water.
22. Check and record the volume and pH (limit: 2.5–4.8).
23. Filter the solution through a prefilter and 0.2-μm membrane filter into the receiving tank.
24. Bubble with nitrogen gas for 15 minutes.
25. Store the solution with a nitrogen blanket.

Vitamins A and D Infant Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1500 U	1	Vitamin A palmitate 1.7 million U/g, 50% excess	1.32
400 U	2	Vitamin D 40 MU/g (Cholecalciferol), 25% excess	0.0125
10.00	3	Polysorbate 80 (Tween 80)	10.00
0.88	4	Vitamin E oil (alpha-tocopheryl acetate)	0.88
0.50	5	Edetate disodium (sodium EDTA)	0.50
1.00	6	Ascorbic acid	1.00
0.100	7	Saccharin sodium	0.10
600.00	8	Glycerin (glycerol)	600.00
100.00	9	Sorbitol (70% solution)	10000
50.00	10	Propylene glycol	50.00
1.00	11	Flavor	1.00
1.50	12	Flavor	1.50
0.02	13	Dye	0.02
0.003	14	Dye	0.003
–	15	Water purified	QS to 1 L

Manufacturing Directions.

1. Collect 200 g of item 15 in melting vessel.
2. Heat to 90°C to 95°C for 10 minutes and then cool to 20°C to 25°C.
3. Bubble nitrogen gas into item 15 for 20 minutes.
4. Load 100 g of item 15 to the manufacturing vessel.
5. Bubble nitrogen gas during all stages of the processing.
6. Add items 5, 6, and 7 one by one to the manufacturing vessel while mixing.
7. Check that all materials are dissolved completely.
8. Add items 8 and 9 and 20 g of item 10 one by one to the manufacturing vessel while mixing at slow speed. Mix for 5 minutes. Avoid aeration.
9. Add item 3 in a stainless steel container.
10. Mix items 1, 2, and 4 one by one using stirrer. Mix for 1 hour at slow speed. Avoid aeration.
11. Add oil phase to the aqueous phase in the manufacturing vessel at a rate of 4 mL/min while mixing, continuing to bubble nitrogen gas, throughout the process.
12. Dissolve items 11 and 12 in 30 g of item 10 in a stainless steel container by slow stirring. Add into manufacturing vessel while mixing.
13. Dissolve items 14 and 13 in 40 g of item 15 (25–30°C) in a stainless steel container by slow stirring.
14. Add into manufacturing vessel while mixing.
15. Adjust the volume to 1 L with cooled item 15.
16. Check and record the volume and pH (limit: between 2.5 and 4.8).
17. Filter the solution through a prefilter and a membrane filter of 0.2 micron into the receiving tank.
18. Bubble with nitrogen gas for 15 minutes. Store the solution with nitrogen blanket.

Vitamin A and Vitamin D_3 Drops

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/L (g)
30000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	1.90
3000 IU	2	Vitamin D_3 (40 MM IU/g)	7.50 mg
12.00	3	Cremophor (relative humidity, 40%)	12.00
0.30	4	Butylhydroxytoluene	0.30
10.00	5	Lutrol E 400	10.00
0.80	6	Paraben	0.80
0.20	7	Sorbic acid	0.20
QS	8	Water	QS to 1 L

Manufacturing Directions

1. Heat mixture of items 1 to 5 and solution of items 6 to 8 to about 65°C and add this slowly to the well-stirred mixture of items 1 to 5.
2. Clear or slightly opalescent yellow liquid is obtained.

Vitamin A and Vitamin D_3 Drops

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/L (g)
30000 U	1	Vitamin A palmitate 1.7 million U/g	1.90
3000 U	2	Vitamin D_3 40 million U/g	7.5 mg
12.0	3	Cremophor RH 40	12.00
0.3	4	Butylhydroxytoluene	0.30
10.0	5	Lutrol E 400	10.00
0.8	6	Parabens (propyl and methyl)	0.80
0.2	7	Sorbic acid	0.20
74.8	8	Water purified	74.80

Manufacturing Directions

1. Heat mixture of items 1 to 5 and solution of items 6 to 8 to about 65°C.
2. Add this slowly to the well-stirred mixture of items 1 to 5. Yellow clear or slightly opalescent liquid is obtained.

Vitamin A and Vitamin D_3 Oral Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (mg)
1000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	60.00
100 IU	2	Vitamin D_3 (40 MM IU/g)	0.30
0.002	3	Butylhydroxytoluene	0.20
3.00	4	Cremophor EL or Cremophor (relative humidity, 40%)	3.00 g
QS	5	Preservative	QS
QS	6	Flavor	QS
QS	7	Water	QS to 1 L

Manufacturing Directions

1. Heat mixture of items 1 to 4 to about 65°C, stir well, and slowly add the hot solution of item 5 (65°C).
2. Cool to room temperature and add item 6 to obtain a clear, yellow liquid.

Vitamin A and Vitamin D_3 Oral Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (mg)
1000 U	1	Vitamin A palmitate 1.7 million U/g	60.00
100 U	2	Vitamin D_3 40 million U/g	0.30
0.002	3	Butylhydroxytoluene	0.20
3.00	4	Cremophor EL or Cremophor RH 40	3000.00
QS	5	Preservative	QS
QS	6	Flavor	QS
QS	7	Water purified	QS to 1 L

Manufacturing Directions

1. Heat mixture of items 1 to 4 to about 65°C. Stir well.
2. Add slowly the hot solution of item 5 (65°C).
3. Cool to room temperature and add item 6. A clear, yellow liquid is formed.

Vitamin A and Vitamin D_3 Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
30000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	19.00
10000 IU	2	Vitamin D_3 (40 MM IU/g)	0.25
70.00 mg	3	Cremophor (relative humidity, 40%)	7.00
QS	4	II. Sugar syrup (50%)	QS to 1 L

Manufacturing Directions

1. Heat mixture of items 1 to 3 to approximately 45°C, stir well, and slowly add item 4 to obtain a clear, yellow liquid (pH 6.2).

Vitamin A and Vitamin D_3 Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
30000 U	1	Vitamin A palmitate 1.7 million U/g	19.00
10000 U	2	Vitamin D_3 40 million U/g	0.25
70.00	3	Cremophor RH 40	7.0
QS	4	Sugar syrup 50%	QS to 1 L

Manufacturing Directions

1. Heat mixture of items 1 to 3 to about 45°C. Stir well.
2. Add slowly the item 4. A clear, yellow liquid with pH 6.2 is formed.

Vitamin A and Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
25000 U	1	Vitamin A palmitate 1.7 million U/g	15.00
50.00	2	Vitamin E acetate	50.00
210.00	3	Cremophor RH 40[a]	210.00
QS	4	Preservative	QS
QS	5	Water purified	QS to 1 L

[a]The quantity is reduced by 1.0 g if DL-alpha-tocopherol is also added at 1.0-g level in the formulation.

Manufacturing Directions

1. Mix the vitamins with Cremophor RH 40 (and DL-alpha-tocopherol, if used) at 60°C.
2. Add solution of preservatives (at 37°C) slowly, with stirring. Clear, yellow viscous liquids are formed.

Vitamin A and Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
5000 U	1	Vitamin A palmitate 1.7 million U/g	3.33
50.00	2	Vitamin E acetate	60.00
150.00	3	Cremophor RH 40	150.00
150.00	4	Alcohol	150.00
QS	5	Water purified	QS to 1 L

Manufacturing Directions

1. Heat mixture items 1 to 3 to about 65°C. Stir well.
2. Slowly add the mixture of items 4 and 5. Color is yellow and clarity should be clear (turbity units: 25 FTU). It must be tested to see whether the ethanol concentration has a sufficient preservative efficiency. The addition of butylhydroxytoluene as antioxidant is recommended.

Vitamin A and Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
5000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	3.33
50.00	2	Vitamin E acetate	60.00
150.00	3	Cremophor (relative humidity, 40%)	150.00
150.00	4	Ethanol (96%)	150.00
QS	5	Water	QS to 1 L

Manufacturing Directions

1. Heat mixture of items 1 to 3 to about 65°C, stir well, and slowly add the mixture of items 4 and 5.
2. Color is yellow; clarity is clear (turbity units 25 FTU).
3. It must be determined whether or not the ethanol concentration has a sufficient preservative efficiency.
4. The addition of butylhydroxytoluene as an antioxidant is recommended.

Vitamin A and Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L
25000 IU	1	Vitamin A palmitate (1.7 Mio IU/g)	1.50
50.00	2	Vitamin E acetate	5.00
210.00	3	Cremophor (relative humidity, 40%)[a]	21.00
QS	5	Preservative	QS
QS	6	Water	71.50

[a]The quantity is reduced by 1.0 g if 1.0 g of d,l-α-tocopherol is also added in the formulation.

Manufacturing Directions

1. Mix the vitamins with Cremophor (and d,l-α-tocopherol, if used) at 60°C.
2. Add solution of preservatives (at 37°C) slowly, with stirring to produce clear, yellow viscous liquids.

Vitamin A Concentrate, Water-Miscible

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100000 U	1	Vitamin A palmitate 1.7 million U/g	65.00
2.00	2	Butylhydroxytoluene	2.00
210.00	3	Cremophor RH 40	210.00
QS	4	Preservative	QS
QS	5	Water purified	QS to 1 L

Manufacturing Directions

1. Heat the mixture of items 1 to 3 to about 65°C. Stir well.
2. Add very slowly the warm solution of items 4 and 5 (65°C). Clear, yellow liquid, miscible with water, is formed.

Vitamin A Concentrate, Water-Miscible

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	6.50
2.00	2	Butylhydroxytoluene	0.20
210.00	3	Cremophor (relative humidity, 40%)	21.00
QS	4	Preservative	QS
QS	5	Water	QS to 1 L

Manufacturing Directions

1. Heat the mixture of items 1 to 3 to approximately 65°C. Stir well.
2. Add slowly the warm solution of items 4 and 5 (65°C) to obtain a clear, yellow liquid that is miscible with water.

Vitamin A Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/1000 Tablets (g)
50000 IU	1	Vitamin A palmitate (1.7 Mio IU/g)	3.00
110.00	2	Cremophor (relative humidity, 40%)	11.00
1.00	3	Butylhydroxytoluene	0.10
QS	4	Water	85.90

Manufacturing Directions

1. Heat the mixture of items 1 to 3 to about 65°C. Stir well.
2. Add slowly the hot water (65°C) to obtain a clear or slightly opalescent yellow solution of low viscosity.
3. Lutrol E 400 can be added at a level of 5% (compensated for by item 4).

Vitamin A Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50000 U	1	Vitamin A palmitate 1.7 million U/g	30.00
110.00	2	Cremophor RH 40	110.00
1.00	3	Butylhydroxytoluene	1.00
QS	4	Water purified	QS to 1 L

Manufacturing Directions

1. Heat the mixture of items 1 to 3 to approximately 65°C. Stir well.
2. Add slowly the hot water (65°C). The solution should be yellow and clear or slightly opalescent and of low viscosity. Lutrol E 400 can be added at a level of 5%, compensated by item 4.

Vitamin B Complex Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.600	1	Thiamine hydrochloride	0.600
0.550	2	Riboflavin 5-phosphate sodium	0.550
2.50	3	Nicotinamide	2.50
1.20	4	Dexpanthenol	1.20
0.550	5	Pyridoxine hydrochloride	0.550
2.00	6	Sorbic acid	2.00
0.05	7	EDTA sodium	0.05
2.25	8	Vanillin	2.25
465.00	9	Sucrose	465.00
25.00	10	Kollidon 25	25.00
90.00	11	Glycerol	90.00
100.00	12	Propylene glycol (pharma)	100.00
310.00	13	Water purified	310.00

Manufacturing Directions

1. Dissolve the sucrose in the heat mixture of glycerol, propylene glycol and water. Cool to room temperature.
2. Dissolve the other components to obtain a clear solution.

Vitamin B Complex Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.66	1	Dexpanthenol	0.66
4.40	2	Nicotinamide	4.44
0.22	3	Pyridoxine HCl	0.22
0.60	4	Riboflavin-5-phosphate sodium	0.60
1.50	5	Thiamine HCl	1.50
350.00	6	Sorbitol (70% solution)	350.00
11.20	7	Propylene glycol	11.20
0.84	8	Methyl paraben	0.84
0.16	9	Propyl paraben	0.16
550.00	10	Maltitol solution (Lycasin 80/55)	550.00
0.15	11	Edetate disodium (sodium EDTA)	0.15
3.72	12	Citric acid (monohydrate)	3.72
3.72	13	Sodium citrate	3.72
2.50	14	Sodium benzoate	2.50
0.50	15	Saccharin sodium	0.50
150.00	16	Glycerin (glycerol)	150.00
1.50	17	Flavor	1.50
1.00	18	Flavor	1.00
–	19	Water purified	QS to 1 L

Manufacturing Directions

1. Load items 6, 10, and 16 in a suitable manufacturing vessel and mix for 5 minutes.
2. Dissolve items 8 and 9 in item 7 in a stainless steel container.
3. Put the whole container in hot water (60–70°C) and stir to dissolve.
4. Add the clear solution to mixer.
5. Dissolve items 11 and 12 in 40 g of item 19 in a stainless steel container.
6. Add the clear solution to mixer.
7. Dissolve items 13, 14, and 15 in 50 g of item 19 in a stainless steel container. Add the clear solution to mixer and mix for 5 minutes.
8. Dissolve item 1 in 10 g of item 19 in a stainless steel container.
9. Add the clear solution to mixer. Dissolve items 3 and 5 in 10 g of item 19 in a stainless steel container. Add the clear solution to mixer.
10. Dissolve items 2 and 4 in 30 g of item 19 in a stainless steel container.
11. Add the clear yellow solution to mixer and mix for 5 minutes.
12. Add items 17 and 18 to mixer. Make up the volume up to 1 L with item 19 and finally mix for 15 to 20 minutes.
13. Check and record the pH (limit: 4.4–4.8 at 25°C). If required, adjust pH with 20% citric acid or 20% sodium citrate solution.
14. Filter the syrup at 1.5 bar. Recirculate about 200 to 300 mL syrup.
15. Transfer the filtered syrup to the storage vessel, flushing with nitrogen gas. Store the syrup under nitrogen blanket NMT 2 days before filling.

Vitamin B Complex Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.60	1	Thiamine hydrochloride (BASF)	0.60
0.55	2	Riboflavin 5-phosphate sodium	0.55
2.50	3	Nicotinamide	2.50
12.00	4	Dexpanthenol (BASF)	12.00
0.55	5	Pyridoxine hydrochloride	5.50
2.00	6	Sorbic acid	20.00
0.050	7	EDTA sodium	0.50
2.25	8	Vanillin	22.50
465.00	9	Sucrose	465.00
25.00	10	Kollidon 25	25.00
90.00	11	Glycerin	90.00
100.00	12	Propylene glycol	100.00
QS	13	Water purified	QS to 1 L

Manufacturing Directions

1. Charge glycerin, propylene glycol, and purified water in a suitable stainless steel jacketed vessel. Heat to 65°C.
2. Add and dissolve sucrose in step 1.
3. Cool to room temperature.
4. Add and dissolve all other items.
5. Filter if necessary. Fill.

Vitamin B Complex and Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.150	1	Thiamine hydrochloride	0.15
0.15	2	Riboflavin phosphate sodium	0.15
0.70	3	Nicotinamide	0.70
0.035	4	Dexpanthenol	0.035
0.15	5	Pyridoxine hydrochloride	0.15
2.25	6	Ascorbic acid, crystalline	2.25
0.28	7	Orange aroma	0.28
0.56	8	EDTA sodium	0.56
186.50	9	Propylene glycol (pharma) + water (2:1)	186.50
0.15	10	Parabens	0.155
84.30	11	Sorbitol, crystalline	84.30
562.50	12	Sucrose, crystalline	562.50
QS	13	Water purified	QS to 1 L

Manufacturing Directions

1. Dissolve items 1 to 8 in item 2.
2. Prepare solution of items 10 to 13 by heating, cool, and mix with solution balance of formulation.
3. Adjust to pH 4.2 to 4.5. Adjust volume with item 13; use more if necessary. Use nitrogen as inert gas during packaging.

Vitamin B Complex (without B_{12}) Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
570.00	1	Sucrose	570.00
70.00	2	Glycerin	70.00
3.72	3	Citric acid (monohydrate)	3.72
1.00	4	Edetate disodium (sodium EDTA)	1.00
0.90	5	Calcium pantothenate, 10% excess	1.00
5.70	6	Sodium citrate	5.70
0.84	7	Methyl paraben	0.84
0.18	8	Propyl paraben	0.16
1.90	9	Benzoic acid	1.90
1.14	10	Strawberry flavor manefils	1.14
9.60	11	Alcohol	9.60
1.50	12	Thiamine HCl, 50% excess	1.50
0.20	13	Pyridoxine hydrochloride, 10% excess	0.22
4.00	14	Nicotinamide, 10% excess	4.40
0.30	15	Riboflavin sodium phosphate, 50% excess	0.60
–	16	Water purified	QS to 1 L

Manufacturing Directions

1. Flush with nitrogen gas (purity 99.95%).
2. Add 400 g of item 16 to the manufacturing vessel and heat to 90°C to 95°C.
3. Add item 1 while mixing at low speed. After addition of item 1 mix for 30 to 35 minutes at high speed and temperature 90°C to 95°C.
4. Cool to 40°C while mixing at low speed.
5. Disperse 1 g filter aid in 10 g cooled item 16 (25–30°C) in a stainless steel container to prepare a slurry.
6. Add the slurry to syrup in syrup vessel. Mix for 15 minutes at high speed.
7. Filter the syrup at 1.5 bar.
8. Recirculate about 40 to 60 mL syrup.
9. Transfer the filtered syrup to the storage vessel. Recharge the filtered syrup to the manufacturing vessel. Start mixing.
10. Add item 2 to the syrup vessel while mixing at high speed.
11. Add item 3 to the syrup vessel while mixing to dissolve at high speed.
12. Dissolve item 4 in 6 g of cooled item 16 (25–30°C) and add to the syrup vessel while mixing at high speed.
13. Dissolve item 5 in 6 g of cooled item 16 and add to the syrup vessel while mixing at high speed for 30 minutes.
14. Dissolve item 6 in 10 g of cooled item 16 (25 –30°C) and add to the syrup vessel while mixing at high speed.
15. Dissolve items 7, 8, 9, and 10 in item 11 in a stainless steel container and add to the syrup vessel while mixing at high speed for 15 minutes.
16. Dissolve items 12 and 13 in 6 g of cooled item 16 (25–30°C) in a separate stainless steel container and add to the syrup vessel while mixing at high speed.
17. Rinse the container with 1 g of cooled item 16 (25–30°C) and add the rinsing to the syrup vessel while mixing at high speed.
18. Flush the vessel with nitrogen gas purity 99.95% for 15 minutes.
19. Dissolve item 14 in 9 g of cooled item 16 in a separate stainless steel container and add to the syrup vessel while mixing at high speed.
20. Rinse the container with 1 g of cooled item 16 (25–30°C) and add the rinsing to the syrup vessel while mixing at high speed.
21. Dissolve item 15 in 4 g of cooled item 16 (25–30°C) in a separate stainless steel container and add to the syrup vessel while mixing at high speed.
22. Rinse the container with 1 g of cooled item 16 and add the rinsing to the syrup vessel while mixing at high speed.
23. Make up the volume to 1 L with cooled item 16 (25–30°C) and finally mix for 15 minutes at high speed.
24. Check and record the pH (limit: 4.3–4.7 at 25°C).
25. If required, adjust pH with 10% solution of citric acid or sodium citrate.
26. Flush the syrup with nitrogen gas purity 99.95% for 15 minutes.
27. Close the tank. Hold the syrup for 12 hours. Filter the syrup at 1.5 bar. Recirculate about 40 to 60 mL syrup.
28. Transfer the filtered syrup to the storage vessel.

Vitamin B Complex, A, C, D, and Calcium Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
675.00	1	Glycerin	675.00
16.66	2	Niacinamide powder white	16.66
2.739	3	Riboflavin-5′-phosphate sodium, 3% excess	2.822
0.500	4	Methyl paraben	0.500
1.0	5	Acid benzoic	1.00
105.0	6	Saccharin sodium powder	105.00
73.360	7	Calcium chloride granules (dihydrate)	73.36
28.785	8	Ferrous gluconate	28.78
2.25	9	Thiamine HCl powder regular, 35% excess	3.37
1.000	10	Pyridoxine hydrochloride	1.00
83.33	11	Acid ascorbic white powder, 35% excess	112.50
0.258	12	Oil orange terpeneless	0.25
0.081	13	Alcohol	0.081
80.00	14	Polysorbate 80	80.00
0.167	15	Butylated hydroxyanisole	0.16
0.666	16	Viosterol in corn oil (synthetic oleovitamin D USP 1000 mD/g), 25% excess	0.83
0.056	17	Vitamin A palmitate 1500000 U/g	0.056
10.000	18	Carmel acid proof	10.00
QS	19	Water purified	QS to 1 L

Manufacturing Directions

Product must not stand more than 1 week before filling. Avoid unnecessary exposure of product to light, air, and heat. Manufacture and store product under complete CO_2 protection. Avoid vigorous mixing.

1. Charge glycerin and 210 mL purified water into a stainless steel jacketed tank.
2. Add with mixing in the following order: niacinamide, riboflavin-5′-phosphate sodium, methylparaben, benzoic acid, and saccharin sodium.
3. Continue mixing and heat to 95°C to 100°C and hold to completely dissolve the ingredients.
4. Add, in portions, calcium chloride and stir until complete solution.
5. Continue mixing and cool to 70°C to 75°C. Add with mixing and dissolve ferrous gluconate at 70°C to 75°C. Check for absence of nondissolved material.
6. Check volume if necessary replace the purified water lost by heating with additional purified water, previously boiled, QS to 750 mL.
7. Cool with mixing to room temperature 25°C to 30°C while bubbling CO_2 gas through. Continue the CO_2 gas bubbling for balance of process.
8. Add and dissolve each ingredient in the order named: thiamine HCl, pyridoxine HCl, and ascorbic acid. Dissolve oil orange in ethyl alcohol and add with stirring.
9. Heat polysorbate 80 to 50°C to 60°C and hold for approximately 10 minutes with slow mixing.
10. Add and dissolve butylated hydroxyanisole.
11. Mix slowly and saturate with CO_2 while cooling to 25°C to 30°C.
12. Add and dissolve viosterol in corn oil and vitamin A palmitate, mixing well with CO_2 gas blowing.
13. Add polysorbate solution to main batch and mix thoroughly. Rinse container with a portion of main batch.
14. Heat 50 mL purified water to 35°C to 40°C while bubbling CO_2 gas through.
15. Add caramel color. Mix well until uniform.
16. Add to main batch. Rinse container with a small quantity of purified water that has been previously saturated with CO_2 gas.
17. Add to main batch. Add purified water that has been previously saturated with CO_2 gas.
18. Bring to volume.
19. Filter, without using filter aid. Cycle to achieve clarity. Keep carbon dioxide cover.

Vitamin B Complex and Iron Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
910.00	1	Sorbitol solution	910.00
0.019	2	Propyl paraben	0.019
0.170	3	Methyl paraben	0.170
1.500	4	Niacinamide powder white	1.500
0.300	5	Riboflavin	0.300
103.600	6	Propylene glycol	103.60
126.400	7	Glycerin	126.40
26.132	8	Iron sulfate granular	26.13
0.0375	9	Dye	0.037
0.250	10	Pyridoxine hydrochloride	0.25
1.200	11	Saccharin sodium powder dihydrate	1.20
22.000	12	Sodium cyclamate powder	22.00
30.000	13	Acid ascorbic white powder	30.00
0.800 g	14	Sodium bicarbonate	0.80
0.360	15	Thiamine hydrochloride powder regular	0.36
0.625	16	D-Pantothenyl alcohol (dexpanthenol FCC)	0.62
0.0020	17	Vitamin B_{12} μg (cyanocobalamin)	2.00 mg
0.007	18	Flavor	0.700 mL
QS	19	Water purified	QS to 1 L
QS	20	Filter aid HyFlo	QS
QS	21	Acid hydrochloric	QS
QS	22	Sodium hydroxide	QS

Manufacturing Directions

1. Manufacture under complete CO_2 protection.
2. Load 780 g (portion of item 2) of sorbitol solution into a stainless steel jacketed tank. Remaining sorbitol to be used later.
3. Add parabens (unless added previously), niacinamide, and riboflavin to the sorbitol or glucose solution.
4. Heat solution to 85°C to 90°C and mix until the ingredients are dissolved.
5. Remove heat. While mixing, cool the main solution to 50°C to 60°C.
6. Hold at this temperature while bubbling CO_2 into it. CO_2 protection is continued for the remainder of the manufacturing procedure.
7. Heat 50 mL purified water to boiling and bubble CO_2 into it while cooling to 55°C.
8. Add and dissolve, with mixing, iron sulfate with 30 mL purified water at 55°C. Use CO_2 protection.
9. Warm the solution to 50°C to 55°C while mixing to dissolve. Then add the solution slowly, with good mixing, to the solution.
10. The above addition should be made as soon as possible to prevent oxidation. Add the pyridoxine, saccharin sodium, and sodium cyclamate and mix until dissolved.
11. Cool the solution to 30°C. Add the ascorbic acid with good stirring to 78 g of reserved sorbitol; make a slurry. Use a container that has plenty of headspace.
12. Add the sodium bicarbonate slowly in small portions to the ascorbic acid slurry with stirring until all of the powder has been added and most of the foaming has stopped.
13. Add this slurry slowly to the solution from the step above with vigorous mixing until a uniform solution results.
14. Rinse the mixing container with 22 g of the reserved sorbitol and add to the product with stirring.
15. Add and dissolve thiamine hydrochloride with mixing. If necessary, warm the D-pantothenyl alcohol until liquefied and add it to the 0.5 mL CO_2-saturated purified water.
16. Use an additional 0.5 mL CO_2-saturated purified water to thoroughly rinse the container of D-pantothenyl alcohol and add this to the D-pantothenyl alcohol solution.
17. Mix the D-pantothenyl alcohol solution thoroughly until homogeneously dispersed.
18. Add the D-pantothenyl alcohol solution to the main solution with mixing. Use an additional 0.5 mL CO_2-saturated purified water to rinse out the container in which the D-pantothenyl alcohol solution is made and add to the product with mixing.
19. Dissolve vitamin B_{12} in 0.5 mL purified water to make a clear solution and add this solution to the product with good mixing.
20. Dissolve the flavor in 10 g of propylene glycol, reserved from step above, with good stirring. Add this solution to the product with good mixing. Check pH (range: 3.0–3.3).

Adjust, if necessary, with a solution of 10% sodium hydroxide or 10% hydrochloric acid depending on the test results.

21. Adjust the volume of the product with the remaining 30 g of the sorbitol solution or, if necessary, purified water to 1 L.
22. Mix for 1 hour. Allow to stand overnight to eliminate entrapped CO_2 gas. Readjust volume to 1 L with purified water. Mix for 1 hour. Filter by adding HyFlo filter aid and mixing it, followed by passing through filter press. Do not allow temperature to exceed 30°C. Bubble CO_2 gas into clear filtrate for 5 minutes. Then seal tank and hold product under CO_2 protection.

Vitamin B Complex and Iron Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
910.00	1	Sorbitol solution	910.00
0.019	2	Propyl paraben	0.019
0.17	3	Methyl paraben	0.17
1.50	4	Niacinamide (white powder)	1.50
0.30	5	Riboflavin	0.30
103.60	6	Propylene glycol	103.60
126.40	7	Glycerin	126.40
26.13	8	Iron sulfate (granular)	26.132
0.037	9	Dye	37.50 mg
0.25	10	Pyridoxine hydrochloride	0.25
1.20	11	Saccharin sodium (dihydrate powder)	1.20
22.00	12	Sodium cyclamate (powder)	22.00
30.00	13	Ascorbic acid (white powder)	30.00
0.80	14	Sodium bicarbonate (powder)	0.80
0.36	15	Thiamine hydrochloride (powder, regular)	0.36
0.625	16	D-Pantothenyl alcohol (dexpanthenol)	0.62
0.002	17	Vitamin B_{12} (cyanocobalamin)	2.00 mg
0.007	18	Flavor	0.70 mL
QS	19	Deionized purified water	QS to 1 L
QS	20	HyFlo filter aid	QS
QS	21	Hydrochloric acid	QS
QS	22	Sodium hydroxide	QS

Manufacturing Directions

1. Manufacture under complete carbon dioxide (CO_2) protection.
2. Load 780 g (portion of item 2) of sorbitol solution into a jacketed stainless steel tank; the remaining sorbitol will be used later.
3. Add parabens (unless added previously), niacinamide, and riboflavin to the sorbitol or glucose solution.
4. Heat solution to 85°C to 90°C and mix until the ingredients are dissolved.
5. Remove heat.
6. While mixing, cool the main solution to 50°C to 60°C.
7. Hold at this temperature while bubbling CO_2 into it.
8. CO_2 protection must be continued for the remainder of the manufacturing procedure.
9. Heat 50 mL of purified water to boiling and bubble CO_2 into it while cooling to 55°C.
10. Add and dissolve, with mixing, iron sulfate with 30 mL of purified water at 55°C.
11. Use CO_2 protection.
12. Warm the solution to 50°C to 55°C while mixing to dissolve, then slowly add the solution, with good mixing, to the solution above.
13. The above addition should be made as soon as possible to prevent oxidation.
14. Add the pyridoxine, saccharin sodium, and sodium cyclamate and mix until dissolved.
15. Cool the solution to 30°C.
16. Add the ascorbic acid, with good stirring, to 78 g of reserved sorbitol. Make a slurry.
17. Use a container that has plenty of headspace.
18. Then add the sodium bicarbonate slowly in small portions to the ascorbic acid slurry, with stirring, until all of the powder has been added and most of the foaming has stopped.
19. Add this slurry slowly to the solution from the step above with vigorous mixing until a uniform solution results.

20. Rinse the mixing container with 22 g of the reserved sorbitol and add to the product with stirring.
21. Add and dissolve thiamine hydrochloride with mixing.
22. If necessary, warm the D-pantothenyl alcohol until liquefied and add it to the 0.5-mL CO_2-saturated purified water.
23. Use an additional 0.5 mL of CO_2-saturated purified water to thoroughly rinse the container of D-pantothenyl alcohol and add this to the D-pantothenyl alcohol solution.
24. Mix the D-pantothenyl alcohol solution thoroughly until it is homogeneously dispersed.
25. Add the D-pantothenyl alcohol solution to the main solution with mixing.
26. Use an additional 0.5 mL of CO_2-saturated purified water to rinse out the container in which the D-pantothenyl alcohol solution is made and add to the product with mixing.
27. Dissolve the vitamin B_{12} in 0.5 mL of purified water to make a clear solution and add this to the product with good mixing.
28. Dissolve the guarana flavor in 10 g of propylene glycol, reserved from earlier step, with good stirring.
29. Add this solution to the product with good mixing.
30. Check pH (range: 3.0–3.3).
31. Adjust, if necessary, with a solution of 10% sodium hydroxide or 10% hydrochloric acid depending on the test results.
32. Adjust the volume of the product with the remaining 30 g of the sorbitol solution and, if necessary, purified water to 1 L.
33. Mix for 1 hour.
34. Allow to stand overnight to eliminate entrapped CO_2 gas.
35. Readjust volume to 1 L with purified water.
36. Mix for 1 hour.
37. Filter by adding HyFlo filter aid and mixing it, followed by passing through a filter press.
38. Do not allow temperature to exceed 30°C.
39. Bubble CO_2 gas into clear filtrate for 5 minutes, then seal tank, and hold product under CO_2 protection.

Vitamin B Complex and Vitamin C Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.60	1	Thiamine hydrochloride	0.60
0.55	2	Riboflavin phosphate sodium	0.55
2.50	3	Nicotinamide	2.50
1.20	4	Dexpanthenol	1.20
0.55	5	Pyridoxine hydrochloride	0.55
9.00	6	Ascorbic acid, crystalline	9.00
0.25	7	Orange flavor	0.25
0.05	8	EDTA sodium	0.05
0.50	9	Propyl gallate	0.50
2.00	10	Sorbic acid	2.00
5.00	11	Kollidon 25	5.00
10.00	12	Sorbitol, crystalline	10.00
9.00	13	Glycerol	9.00
10.00	14	1,2-Propylenglycol Pharma	10.00
5.00	15	Water purified	5.00
60.00	16	Sugar syrup (64% sucrose in water)	60.00

Manufacturing Directions

1. Mix solution of items 1 to 5 with sugar syrup.
2. Adjust the clear solution to about pH 4.2.
3. Use nitrogen as an inert gas in the final packaging. 10 g provides 2 to 3 times the recommended daily allowance.

Vitamin B Complex and Vitamin C Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.60	1	Thiamine hydrochloride	0.60
0.55	2	Riboflavin phosphate sodium	0.55
2.50	3	Nicotinamide	2.50
1.20	4	Dexpanthenol	1.20
0.55	5	Pyridoxine hydrochloride	0.55
9.00	6	Ascorbic acid (crystalline)	9.00
0.25	7	Orange flavor	0.25
0.05	8	EDTA sodium	0.05
0.50	9	Propyl gallate	0.50
2.00	10	Sorbic acid	2.00
5.00	11	Kollidon® 25	5.00
10.00	12	Sorbitol (crystalline)	10.00
9.00	13	Glycerol	9.00
10.00	14	1,2-Propylenglycol (Pharma)	10.00
5.00	15	Water	5.00
QS	16	Sugar syrup (64% sucrose in water)	QS to 1 kg

Manufacturing Directions

1. Mix solution of items 1 to 5 with sugar syrup, adjust the clear solution to about pH 4.2, and use nitrogen as an inert gas in the final packaging; 10 g provides two to three RDA.

Vitamin B Complex and Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.15	1	Thiamine hydrochloride	0.15
0.15	2	Riboflavin phosphate sodium	0.15
0.70	3	Nicotinamide	0.70
0.035	4	Dexpanthenol	0.035
0.150	5	Pyridoxine hydrochloride	0.15
2.25	6	Ascorbic acid (crystalline)	2.25
0.28	7	Orange aroma	0.28
0.56	8	EDTA sodium	0.56
186.50	9	Propylene glycol (Pharma) + water (2:1)	186.50
0.15	10	Paraben	0.15
84.30	11	Sorbitol (crystalline)	84.30
562.50	12	Sucrose (crystalline)	562.50
42.00	13	Water	42.00

Manufacturing Directions

1. Dissolve items 1 to 8 in item 2.
2. Prepare a solution of items 10 to 13 by heating.
3. Cool and mix with solution of the balance of the formulation.
4. Adjust to a pH of 4.2 to 4.5.
5. Adjust volume with water; use more, if necessary.
6. Use nitrogen as an inert gas during packaging.

Vitamin B Complex, A, C, and D Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
60.00	1	Sucrose	600.00
51.00	2	Methyl paraben	1.00
0.20	3	Propyl paraben	0.20
1.00	4	Edetate disodium	1.00
10.00	5	Ascorbic acid, 50% excess	15.00
0.80	6	Sodium hydroxide	0.80
4.00	7	Nicotinamide, 5% excess	4.20
0.40	8	Riboflavin sodium phosphate, 8% excess	0.43
1.00	9	Thiamine hydrochloride, 50% excess	1.50
1.20	10	Pyridoxine hydrochloride, 10% excess	1.32
0.50	11	Monosodium glutamate	0.50
1.26 μg	12	Cyanocobalamin, 50% excess	0.0018
150.00	13	Propylene glycol	150.00
1000.0 U	14	Vitamin A palmitate 1.75 million/g, 54% excess	0.88
100.0 U	15	Cholecalciferol 40 million/g, 52% excess	0.0038
13.20	16	Polysorbate 80	13.20
2.50	17	Polyoxyl 20 cetostearyl ether	2.50
0.30	18	Lemon oil terpenless	0.30
0.84	19	Strawberry oil composed	0.84
–	20	Purified water	QS to 1 L

Manufacturing Directions

This product is an aqueous solution of water-soluble vitamins with oily vitamin A palmitate and cholecalciferol solubilized in water using the surfactant system of Tween 80 and cetomacrogol. This syrup is a solubilized oil surfactant system and is liable to heat and rate of mixing. The temperature of solution must not exceed 30°C at the time of final mixing. The final mixing must be in continuous manner without any interruption. For the preparation of oily phase, the container must be dry.

1. Before start of batch, cool approximately 80 mL purified water and flush with nitrogen gas (purity 99.95%). Use this water for making solutions and for adjusting the volume.
2. Add 420 g of item 20 to the manufacturing vessel and heat to 90°C to 95°C.
3. Add items 2 and 3 while mixing to dissolve.
4. Add item 1 while mixing at slow speed. After addition of item 1, mix for 30 to 35 minutes at high speed, temperature 90°C to 95°C. Cool to 25°C to 30°C while mixing at low speed.
5. Bubble nitrogen gas for 10 minutes. Add item 4 to the syrup while mixing at high speed to dissolve.
6. Add item 5 to the syrup while mixing at high speed to dissolve.
7. Add 4 g of item 20 (25°C) in a separate container and dissolve item 6 by using stirrer.
8. Transfer the cooled item 6 solution to the syrup tank while mixing at high speed. Mix for 15 minutes.
9. Check pH of the syrup (limit: 3.75–3.85). Add items 7 to 11 one by one to the syrup in manufacturing vessel while mixing at high speed to dissolve.
10. Mix for 10 minutes. Add 6 g of cold item 20 (25°C) in a separate container and dissolve item 12.
11. Add to the manufacturing vessel while mixing at high speed. Rinse the container with cooled item 20, about 2 mL, and transfer the rinsing to the syrup-manufacturing vessel and mix well at high speed.
12. Add item 13 to the manufacturing vessel while mixing at high speed.
13. Warm item 14 to 70°C in a separate stainless steel container in water bath.
14. Warm item 16 to 70°C and mix well with item 14 under nitrogen atmosphere.
15. Add item 15 while mixing. Melt item 17 in stainless steel container and add with stirring to mix well.
16. Cool to 30°C while mixing under nitrogen atmosphere.
17. Add items 18 and 19 to the oily phase solution and mix for 15 minutes at high speed.
18. Check and record the volume of oily phase. Start mixing and continue mixing. Mixing must be continuous.
19. Start the addition of oily phase solution in a thin stream. Do not stop mixing during addition of oily phase. After the addition is over, mix for a further 15 minutes at high speed.
20. Rinse the oily phase vessel with a sufficient quantity of syrup from the syrup vessel. Transfer the rinsing to the syrup vessel.
21. Makeup the volume to 1 L with cooled item 20 (25°C) and, finally, mix for 20 minutes at high speed.
22. Check and record the pH (limit: 3.75–3.85 at 25°C). Filter the syrup at 1.5 bar. Recirculate about 40 to 60 mL syrup.

Vitamin B Complex Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.60	1	Thiamine hydrochloride	0.60
0.55	2	Riboflavin 5-phosphate sodium	0.55
2.50	3	Nicotinamide	2.50
1.20	4	Dexpanthenol	1.20
0.55	5	Pyridoxine hydrochloride	0.55
2.00	6	Sorbic acid	2.00
0.05	7	EDTA sodium	0.05
2.25	8	Vanillin	2.25
465.00	9	Sucrose	465.00
25.00	10	Kollidon® 25	25.00
90.00	11	Glycerol	90.00
100.00	12	Propylene glycol (pharma)	100.00
310.00	13	Water	310.00

Manufacturing Directions

1. Dissolve the sucrose in the heat mixture of glycerol, propylene glycol, and water.
2. Cool to room temperature and dissolve the other components to obtain a clear solution.

Vitamin B Complex Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.66	1	Dexpanthenol	0.66
4.40	2	Nicotinamide	4.40
0.22	3	Pyridoxine hydrochloride	0.22
0.60	4	Riboflavin-5-phosphate sodium	0.60
1.50	5	Thiamine hydrochloride	1.50
350.00	6	Sorbitol (70% solution)	350.00
11.20	7	Propylene glycol	11.20
0.84	8	Methyl paraben	0.84
0.168	9	Propyl paraben	0.168
550.00	10	Maltitol solution (Lycasin 80/55)	550.00
0.15	11	Edetate disodium (sodium EDTA)	0.15
3.72	12	Citric acid (monohydrate)	3.72
3.72	13	Sodium citrate	3.72
2.50	14	Sodium benzoate	2.50
0.50	15	Saccharin sodium	0.50
150.00	16	Glycerin (glycerol)	150.00
1.50	17	Flavor	1.50
1.00	18	Flavor	1.00
–	19	Purified water	QS to 1 L

Manufacturing Directions

1. Load items 6, 10, and 16 in a manufacturing vessel and mix for 5 minutes.
2. Dissolve items 8 and 9 in item 7 in a stainless steel container.
3. Put the entire container in hot water (60–70°C) and stir to dissolve.
4. Add the clear solution to the mixer.
5. Dissolve items 11 and 12 in 40 g of purified water in a stainless steel container.
6. Add the clear solution to the mixer.
7. Dissolve items 13, 14, and 15 in 50 g of purified water in a stainless steel container.
8. Add the clear solution to mixer and mix for 5 minutes.
9. Dissolve item 1 in 10 g of purified water in a stainless steel container.
10. Add the clear solution to mixer.
11. Dissolve items 5 and 3 in 10 g of purified water in a stainless steel container.
12. Add the clear solution to mixer.
13. Dissolve items 2 and 4 in 30 g of purified water in a stainless steel container.
14. Add the clear yellow solution to mixer and mix for 5 minutes.
15. Add items 17 and 18 to mixer.
16. Bring the volume up to 1 L with purified water and finally mix for 15 to 20 minutes.
17. Check and record the pH (limit: 4.4–4.8 at 25°C).
18. If required, adjust pH with 20% citric acid or 20% sodium citrate solution.
19. Filter the syrup at 1.5 bar.
20. Recirculate about 200 to 300 mL syrup.
21. Transfer the filtered syrup to the storage vessel, flushing with nitrogen gas.
22. Store the syrup under a nitrogen blanket for NMT 2 days prior to filling.

Vitamin B Complex Syrup (without B_{12})

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
570.00	1	Sucrose[a]	570.00
70.00	2	Glycerin (glycerol)	70.00
3.72	3	Citric acid (monohydrate)	3.72
1.00	4	Edetate disodium (sodium EDTA)	1.00
0.90	5	Calcium pantothenate (10% excess)	1.00
5.70	6	Sodium citrate	5.70
0.84	7	Methyl paraben	0.84
0.168	8	Propyl paraben	0.168
1.90	9	Benzoic acid	1.90
1.14	10	Strawberry flavor manefils	1.14
9.60	11	Alcohol (ethanol, 95%)	9.60
1.50	12	Thiamine hydrochloride (50% excess)	1.50
0.20	13	Pyridoxine hydrochloride (10% excess)	0.22
4.00	14	Nicotinamide (10% excess)	4.40
0.30	15	Riboflavin sodium phosphate (50% excess)	0.60
QS	16	Purified water	QS to 1 L

[a]513 mg for thiamine mononitrate and 504 mg for thiamine hydrochloride

Manufacturing Directions

1. Flush with nitrogen gas (purity 99.95%).
2. Add 400 g of purified water to the manufacturing vessel and heat to 90°C to 95°C.
3. Add item 1 while mixing at low speed.
4. After addition of item 1, mix for 30 to 35 minutes at high speed (temperature: 90–95°C).
5. Cool to 40°C while mixing at low speed.
6. Disperse 1 g of filter aid in 10 g of cooled purified water (25–30°C) in a stainless steel container to prepare a slurry.
7. Add the slurry to the syrup in syrup vessel.
8. Mix for 15 minutes at high speed.
9. Filter the syrup at 1.5 bar.
10. Recirculate about 40 to 60 mL syrup.
11. Transfer the filtered syrup to the storage vessel.
12. Recharge the filtered syrup to the manufacturing vessel.
13. Start mixing.
14. Add item 2 to the syrup vessel while mixing at high speed.
15. Add item 3 to the syrup vessel while mixing to dissolve at high speed.
16. Dissolve item 4 in 6 g of cooled purified water (25–30°C) and add to the syrup vessel while mixing at high speed.
17. Dissolve item 5 in 6 g of cooled purified water and add to the syrup vessel while mixing at high speed for 30 minutes.
18. Dissolve item 6 in 10 g of cooled purified water (25–30°C) and add to the syrup vessel while mixing at high speed.
19. Dissolve items 7 to 10 in item 11 in a stainless steel container and add to the syrup vessel while mixing at high speed for 15 minutes.
20. Dissolve items 12 and 13 in 6 g of cooled purified water (25–30°C) in a separate stainless steel container and add to the syrup vessel while mixing at high speed.
21. Rinse the container with 1 g of cooled, purified water (25–30°C) and add the rinsing to the syrup vessel while mixing at high speed.
22. Flush the vessel with nitrogen gas (purity 99.95%) for 15 minutes.
23. Dissolve item 14 in 9 g of cooled purified water in a separate stainless steel container and add to the syrup vessel while mixing at high speed.
24. Rinse the container with 1 g of cooled purified water (25–30°C) and add the rinsing to the syrup vessel while mixing at high speed.
25. Dissolve item 15 in 4 g of cooled, purified water (25–30°C) in a separate stainless steel container and add to the syrup vessel while mixing at high speed.
26. Rinse the container with 1 g of cooled, purified water and add the rinsing to the syrup vessel while mixing at high speed.
27. Bring the volume up to 1 L with cooled, purified water (25–30°C) and finally mix for 15 minutes at high speed.
28. Check and record the pH (limit: 4.3–4.7 at 25°C).
29. If required, adjust pH with 10% solution of citric acid or sodium citrate.
30. Flush the syrup with nitrogen gas (purity 99.95%) for 15 minutes.
31. Close the tank.
32. Hold the syrup for 12 hours.
33. Filter the syrup at 1.5 bar.
34. Recirculate about 40 to 60 mL syrup.
35. Transfer the filtered syrup to the storage vessel.

Vitamin B Complex, Vitamin A, Vitamin C, and Vitamin D Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
60.00	1	Sucrose	600.00
51.00	2	Methyl paraben	1.00
0.20	3	Propyl paraben	0.20
1.00	4	Edetate disodium (sodium EDTA)	1.00
10.00	5	Ascorbic acid (50% excess)	15.00
0.80	6	Sodium hydroxide	0.80
4.00	7	Nicotinamide (5% excess)	4.20
0.40	8	Riboflavin sodium phosphate (8% excess)	0.43
1.00	9	Thiamine hydrochloride (50% excess)	1.50
1.20	10	Pyridoxine hydrochloride (10% excess)	1.32
0.50	11	Monosodium glutamate (sodium glutamate)	0.50
1.26 μg	12	Cyanocobalamin (50% excess)	0.0018
150.00	13	Propylene glycol	150.00
1000.00 IU	14	Vitamin A palmitate (1.75 MM IU/g) (54% excess)	0.88
100.00 IU	15	Cholecalciferol (40 MM IU/g) (52% excess)	0.0038
13.20	16	Polysorbate 80 (Tween 80)	13.20
2.50	17	Polyoxyl 20 cetostearyl ether (Cetomacrogol 1000)	2.50
0.30	18	Lemon oil terpeneless	0.30
0.84	19	Strawberry oil (composed)	0.84
QS	20	Purified water	QS to 1 L

Manufacturing Directions

1. This product is an aqueous solution of water-soluble vitamins with oily vitamin A palmitate and cholecalciferol solubilized in water using the surfactant system of Tween 80 and cetomacrogol.
2. This syrup is a solubilized oil surfactant system and is affected by heat and rate of mixing.
3. The temperature of the solution must not exceed 30°C at the time of final mixing.
4. The final mixing must be continuous, without any interruption.
5. For the preparation of oily phase, the container must be dry.
6. Before start of batch, cool about 80 mL of purified water and flush with nitrogen gas (purity 99.95%).
7. Use this water for making solutions and for adjusting the volume.
8. Add 420 g of purified water to the manufacturing vessel and heat to 90 to 95°C.
9. Add items 2 and 3 while mixing to dissolve.
10. Add item 1 while mixing at slow speed.
11. After addition of item 1, mix for 30 to 35 minutes at high speed and a temperature of 90°C to 95°C.
12. Cool to 25°C to 30°C while mixing at low speed.
13. Bubble nitrogen gas for 10 minutes.
14. Add item 4 to the syrup while mixing at high speed to dissolve.
15. Add item 5 to the syrup while mixing at high speed to dissolve.
16. Add 4 g of purified water (25°C) in a separate container and dissolve item 6 by using a stirrer.
17. Transfer the cooled item 6 solution to the syrup tank while mixing at high speed.
18. Mix for 15 minutes.
19. Check the pH of the syrup (limit: 3.75–3.85).
20. Add items 7 to 11 one by one to the syrup in the manufacturing vessel while mixing at high speed to dissolve.
21. Mix for 10 minutes.
22. Add 6 g of cold purified water (25°C) in a separate container and dissolve item 12.
23. Add to the manufacturing vessel while mixing at high speed.
24. Rinse the container with cooled purified water (approximately 2 mL) and transfer the rinsing to the syrup-manufacturing vessel; mix well at high speed.
25. Add item 13 to the manufacturing vessel while mixing at high speed.
26. Warm item 14 to 70°C in a separate stainless steel container in a water bath.
27. Warm item 16 to 70°C and mix well with item 14 under nitrogen atmosphere.
28. Add item 15 while mixing.
29. Melt item 17 in a stainless steel container and add with stirring to mix well.
30. Cool to 30°C while mixing under nitrogen atmosphere.
31. Add items 18 and 19 to the oily phase solution and mix for 15 minutes at high speed.
32. Check and record the volume of the oily phase.

33. Start mixing and continue mixing (mixing must be continuous).
34. Start the addition of the oily phase solution in a thin stream (do not stop mixing during addition of oily phase).
35. After the addition is complete, mix for an additional 15 minutes at high speed.
36. Rinse the oily phase vessel with a sufficient quantity of syrup from the syrup vessel.
37. Transfer the rinsing to the syrup vessel.
38. Bring the volume up to 1 L with cooled purified water (25°C) and finally mix for 20 minutes at high speed.
39. Check and record the pH (limit: 3.75–3.85 at 25°C).
40. Filter the syrup at 1.5 bar.
41. Recirculate about 40 to 60 mL syrup.

Vitamin B Complex, Vitamin A, Vitamin C, Vitamin D, and Calcium Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
675.00	1	Glycerin (96%)	675.00
16.66	2	Niacinamide (white powder)	16.66
2.73	3	Riboflavin-5′-phosphate sodium (3% excess)	2.82
0.50	4	Methyl paraben	0.50
1.00	5	Acid benzoic	1.00
105.00	6	Saccharin sodium (powder)	105.00
73.36	7	Calcium chloride (granules, dihydrate)	73.36
28.78	8	Ferrous gluconate	28.78
2.25	9	Thiamine hydrochloride (powder, regular) (35% excess)	3.375
1.00	10	Pyridoxine hydrochloride	1.00
83.33	11	Ascorbic acid (white powder) (35% excess)	112.50
0.25	12	Oil orange terpeneless	0.25
0.081	13	Alcohol (ethanol; 190 proof, Nonbeverage)	0.081
80.00	14	Polysorbate 80	80.00
0.16	15	Butylated hydroxyanisole (BHA)	0.16
0.66	16	Viosterol in corn oil (syn., oleovitamin D; 1000 mD/g) (25% excess)	0.83
0.056	17	Vitamin A palmitate (1500000 Units/g)	0.056
10.00	18	Caramel (acid proof)	10.00
QS	19	Deionized purified water	QS to 1 L

Manufacturing Directions

1. Product must not stand more than 1 week before filling.
2. Avoid unnecessary exposure of product to light, air, and heat.
3. Manufacture and store product under complete CO_2 protection.
4. Avoid vigorous mixing.
5. Charge glycerin and 210 mL purified water into a stainless steel jacketed tank.
6. Add, with mixing, in the following order: niacinamide, riboflavin-5′-phosphate sodium, methyl paraben, USP, benzoic acid, and saccharin sodium.
7. Continue mixing, heat to 95°C to 100°C, and hold to completely dissolve the ingredients.
8. Add in calcium chloride portions and stir until complete solution is obtained.
9. Continue mixing and cool to 70°C to 75°C.
10. Add ferrous gluconate with mixing and dissolve at 70°C to 75°C.
11. Check for the absence of undissolved material.
12. Check volume; if necessary, replace lost purified water by heating with additional previously boiled purified water; QS to 750 mL.
13. Cool with mixing to room temperature (25–30°C) while bubbling CO_2 gas through.
14. Continue the CO_2 gas bubbling for balance of the process.
15. Add and dissolve each ingredient in this order: thiamine hydrochloride, pyridoxine hydrochloride, and ascorbic acid.
16. Dissolve oil orange in ethyl alcohol and add to mixture with stirring.
17. Heat polysorbate 80 to 50°C to 60°C and hold for approximately 10 minutes with slow mixing.
18. Add and dissolve butylated hydroxyanisole.
19. Mix slowly and saturate with CO_2 while cooling to 25°C to 30°C.
20. Add and dissolve viosterol in corn oil and vitamin A palmitate, mixing well, and continuing CO_2 gas bubbling.
21. Add polysorbate solution to main batch and mix thoroughly.
22. Rinse container with a portion of the main batch and add.
23. Heat 50 mL purified water to 35°C to 40°C while bubbling CO_2 gas through.
24. Add the caramel color.
25. Mix well until uniform consistency is obtained.

26. Add to main batch.
27. Rinse container with a small quantity of purified water that has been previously saturated with CO_2 gas.
28. Add to the main batch.
29. Add purified water that has been previously saturated with CO_2 gas; QS to 1 L.
30. Filter, without using a filter aid; cycle to achieve clarity.
31. Maintain carbon dioxide cover.

Vitamin B Complex, Vitamin A, Vitamin C, Vitamin D, and Vitamin E Pediatric Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
8333 IU	1	Vitamin A palmitate (1.7 M IU/g) (50% excess)	7.35
666 IU	2	Vitamin D (40 M IU/g) (cholecalciferol)	0.021
75.00	3	Polysorbate 80 (Tween 80)	75.00
0.005	4	Lemon oil terpeneless	0.50
0.88	5	Vitamin E (oily) (α-tocopheryl acetate)	0.88
0.50	6	Edetate disodium (sodium EDTA)	0.50
83.33	7	Ascorbic acid (30% excess)	108.33
1.00	8	Saccharin sodium	1.00
2.50	9	Thiamine hydrochloride (50% excess)	3.75
16.66	10	Nicotinamide (5% excess)	17.50
0.833	11	Pyridoxine hydrochloride (5.6% excess)	0.88
2.00	12	Riboflavin sodium phosphate (7.9% excess as riboflavin)	2.16
700.00	13	Glycerin (glycerol)	700.00
250.00	14	Purified water	250.00

Manufacturing Directions

1. This product is a microemulsion and is a thermolabile preparation.
2. The temperature of the solution must not exceed 25°C at the time of processing.
3. Add 200 g of purified water to the manufacturing vessel.
4. Bubble nitrogen gas during all stages of the process.
5. Charge items 6 to 12 one by one into the manufacturing vessel while mixing.
6. Check that all materials are dissolved completely.
7. Load item 13 into the manufacturing vessel while mixing at slow speed.
8. Mix for 5 minutes.
9. Add item 3 in a separate stainless steel container.
10. Mix items 1, 2, 4, and 5 one by one using stirrer.
11. Mix for 1 hour at slow speed.
12. Add oil phase preparation to the aqueous phase at a rate of 4 mL/min while mixing at slow speed and continue nitrogen gas bubbling throughout the process.
13. Rinse the oil phase container with 50 g of nitrogen-bubbled and cooled purified water and transfer the rinsing to the manufacturing vessel.
14. Adjust the volume to 1 L using nitrogen-bubbled purified water.
15. Mix for 15 minutes at slow speed.
16. Check and record the volume and pH (limit: pH 2.8–4.2).
17. Filter the solution through a Sartorius prefilter and 0.2-μm membrane filter into receiving tank.
18. Bubble with nitrogen gas for 15 minutes.

Vitamin B Complex, Vitamin C, and Iron Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
QS	1	Glucose (liquid), NF	QS to 1 L
225.00	2	Purified water, USP	225.00
0.30	3	Methyl paraben	0.30
1.00	4	Acid benzoic, USP	1.00
5.00	5	Alcohol (ethanol; 190 proof, nonbeverage), USP	5.00
10.00	6	Nicotinamide niacinamide (white powder), USP	10.00
10.00	7	Riboflavin; use riboflavin 5 phosphate sodium	1.64
2.00	8	Pyridoxine hydrochloride, USP	2.00
20.00	9	Ascorbic acid (white powder), USP	28.00
0.03	10	Dye	0.03
0.02	11	Dye	0.02
2.00	12	Thiamine hydrochloride (powder, regular), USP	2.40
2.00	13	D-pantothenyl alcohol	2.50
2.00 μg	14	Vitamin B_{12} (cyanocobalamin, USP)	3.40 mg
200.00	15	Sucrose, NF	200.00
0.028 mL	16	Flavor	2.80 mL
QS	17	Hydrochloric acid	2.00 mL
QS	18	Carbon dioxide gas	QS

Manufacturing Directions

1. This preparation is susceptible to oxidation and must be protected from air and sunlight at all times.
2. Carbon dioxide must be used extensively to prevent oxygen from reacting with the materials.
3. All purified water must be boiled prior to use for 10 minutes and cooled under CO_2 protection.
4. Charge 100 mL of purified water into a suitably sized stainless steel tank.
5. Add the riboflavin, nicotinamide, benzoic acid, and paraben.
6. Rinse the tank down with 10 mL purified water, seal, and heat with mixing to 95°C.
7. Continue mixing and heating for 15 minutes, until solution is complete.
8. Commence cooling with continuous mixing.
9. When the solution has cooled to 50 to 70°C, add and dissolve the sugar.
10. Commence CO_2 protection when the temperature reaches 40°C.
11. Slurry the ascorbic acid in 75 or 110 mL of CO_2-saturated purified water (use the smaller quantity only if using a total of 225 mL water) and add to bulk solution when temperature has reached 25°C to 35°C.
12. Rinse the ascorbic acid vessel with 10 mL purified water and add rinsing to bulk.
13. Mix for at least 30 minutes.
14. Dissolve thiamine and pyridoxine in 20 mL CO_2-saturated purified water and add to bulk solution at 25 to 35°C.
15. Add 10 mL CO_2-saturated purified water to the D-pantothenyl alcohol and warm on a water bath until solution is complete.
16. Add vitamin B_{12} and mix until dissolved.
17. Add and dissolve dyes.
18. Add this solution to the bulk solution and mix thoroughly.
19. Mix flavor with 95% of alcohol and add to the bulk solution.
20. Rinse the container with the remaining alcohol and add to the bulk with vigorous agitation.
21. Check pH (range: 3.0–3.3).
22. Use hydrochloric acid to adjust, if necessary.
23. Adjust the final volume with liquid glucose.
24. Filter through suitable medium until clear and bright.

Vitamin B Complex, Vitamin C, and Iron Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
QS	1	Sorbitol solution, USP	QS to 1 L
QS	2	Purified water, USP	225.00
0.20	3	Methyl paraben	0.20
0.20	4	Propyl paraben, NF	0.02
2.00	5	Nicotinamide niacinamide (white powder), USP	10.00
10.00	6	Riboflavin; use riboflavin 5 phosphate sodium	1.64
10.00	7	Iron sulfate (ferrous sulfate; granular), USP	10.00
3.60	8	Saccharin sodium (powder), USP	3.60
2.00	9	Pyridoxine hydrochloride, USP	2.00
25.00	10	Ascorbic acid (white powder), USP	28.00
0.03	11	Dye	0.030
0.02	12	Dye	0.020
2.00	13	Thiamine hydrochloride (powder, regular), USP	2.40
2.00	14	D-Pantothenyl alcohol	2.50
2.0 μg	15	Vitamin B_{12} cyanocobalamin, USP	3.40 mg
1.00	16	Flavor	1.00
10.00	17	Propylene glycol, USP	10.00
QS	18	Hydrochloric acid	2.00 mL
—	19	HyFlo filter aid	1 g
QS	20	Carbon dioxide gas	QS

Manufacturing Directions

1. This preparation is susceptible to oxidation and must be protected from air and sunlight at all times.
2. Carbon dioxide must be used extensively to prevent oxygen from reacting with the materials.
3. All purified water must be boiled prior to use for 10 minutes and cooled under CO_2 protection.
4. Charge 950 g of sorbitol solution into a jacketed stainless steel tank and heat to 95°C to 100°C.
5. Heat 250 mL of purified water to boiling for 10 minutes and bubble CO_2 into it while cooling to room temperature.
6. Add, with stirring, the parabens, niacinamide, and riboflavin 5-phosphate sodium.
7. Rinse the container with 5 mL of water.
8. Stir well.
9. Mix until solution is obtained and check the clarity.
10. Remove the source of heat from the vessel.
11. Thoroughly deoxygenate the liquid by bubbling CO_2 through the liquid and allow to cool to 50°C to 60°C.
12. Heat 15 mL of water to 70°C, saturate with CO_2, and dissolve saccharin sodium (item 8) and pyridoxine hydrochloride in 5 mL of water; add to the main bulk.
13. Rinse the container with 2.5 mL of water.
14. Cool the solution to 30°C with CO_2 protection.
15. Dissolve ascorbic acid in 120 mL of water.
16. Rinse the container with 5 mL of water.
17. Dissolve dyes in 3 mL of water.
18. Rinse the container with 2 mL of water.
19. Mix dye solution with ascorbic acid solution.
20. Add this to the main bulk with stirring.
21. Dissolve thiamine in 30 mL of water and add to the main bulk.
22. Rinse the container with 2.5 mL of water.
23. Add 10 mL of water to the D-pantothenyl and warm up on a water bath until in solution.
24. Add this mixture to the main bulk.
25. Rinse the container with 2.5 mL of water.
26. Dissolve vitamin B_{12} in 12.5 mL of water and add to the main bulk.
27. Rinse the container with 2.5 mL of water.
28. Mix flavor with 7.5 g of propylene glycol until mixture is homogeneous and add to the main bulk.
29. Rinse the container with 2.5 g of propylene glycol and add to the main bulk with vigorous agitation.
30. Check pH (range: 3.0–3.3).
31. Use hydrochloric acid to adjust, if necessary.
32. Adjust the volume of the product with sorbitol solution and mix for 30 minutes to ensure homogeneity.
33. Add the HyFlo filter aid and mix.
34. Filter the liquid through a filter press previously washed in purified water.
35. Transfer the clear filtrate into a clean closed vessel.
36. Mix for 15 minutes while bubbling CO_2 gas.

Vitamin C Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Ascorbic acid (white powder), USP	100.00
979.00	2	Propylene glycol, USP	979.00

Manufacturing Directions

1. Keep under CO_2 protection at all times. Avoid contact with iron. Use stainless steel or glass-lined equipment only.
2. Load 868 g propylene glycol into a glass-lined or suitable stainless steel jacketed tank.
3. While mixing, heat to 70 to 80°C.
4. Bubble CO_2 gas into the propylene glycol from the bottom of the tank.
5. Add and dissolve the ascorbic acid into the propylene glycol with a minimum of stirring under CO_2 protection.
6. When the ascorbic acid is in solution, immediately cool to approximately 25°C while continuing to mix.
7. Also, while cooling, change adding CO_2 from the bottom of the tank to adding it at the top of the tank.
8. QS to 1 L, using propylene glycol and mix for at least 10 minutes.
9. Use a prefilter pad and a lint-free filter paper; recirculate the product through the filter press until sparkling clear.

Vitamin E and Benzocaine Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Vitamin E acetate	50.00
20.00	2	Benzocaine	20.00
50.00	3	Lutrol F 127	50.00
250.00	4	Cremophor (relative humidity, 40%)	250.00
2.00	5	Sorbic acid	2.00
628.00	6	Water	628.00

Manufacturing Directions

1. Dissolve sorbic acid and benzocaine in water at 60°C. Slowly add the heated mixture of vitamin E acetate and Cremophor at a relative humidity of 40% and temperature of 60°C to 65°C.
2. Cool the clear solution to about 5°C and dissolve Lutrol F 127 to obtain a clear, colorless viscous liquid.

Vitamin E Concentrate, Water-Miscible

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
105.00	1	Vitamin E acetate	105.00
250.00	2	Cremophor (relative humidity, 40%)	250.00
QS	3	Preservative	QS
QS	4	Water	QS to 1 L

Manufacturing Directions

1. Heat the mixture of items 1 and 2 and solution of item 3 in item 4 separately to about 65°C.
2. Slowly add to the well-stirred solution to obtain a clear, colorless liquid that is miscible with water.

Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Vitamin E acetate	50.00
160.00	2	Cremophor (relative humidity, 40%)	160.00
QS	3	Preservative	QS
QS	4	Water	QS to 1 L

Manufacturing Directions

1. Heat mixture of items 1 and 2 and solution of item 3 in 4 to about 65°C.
2. Add them slowly to obtain a clear or lightly opalescent, colorless liquid.

Vitamin E Soft Gel Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
400.00	1	Vitamin E preparation, USP	400.00
25.00	2	Soybean oil, USP	25.00
QS	3	Gelatin mass (clear)	QS

Manufacturing Directions

1. Weigh items 1 and 2 and transfer into a suitable stainless steel container, mix for a minimum of 1 hour, screen transfer to tanks through a No. 80 to No. 100 mesh stainless sieve.
2. Encapsulate 425 mg of mixture into size 7.5 oval capsules using clear gelatin mass.

Vitamin E Solution with Ethanol

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
0.10	1	Vitamin E acetate	0.10
4.00–5.00	2	Cremophor, EL	4.00–5.00
570.00	3	Water	570.00
380.00	4	Ethanol (96%)	380.00

Manufacturing Directions

1. Heat mixture of item 1 and 2 to about 60°C. Stir well.
2. Add slowly add the warm solvent mixture of items 3 and 4 to obtain a clear, colorless liquid of low viscosity.

Vitamin E and Benzocaine Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L. (g)
50.00	1	Vitamin E acetate	50.00
20.00	2	Benzocaine	20.00
50.00	3	Lutrol F 127	50.00
250.00	4	Cremophor RH 40	250.00
2.00	5	Sorbic acid	2.00
628.00	6	Water	628.00

Manufacturing Directions

1. Dissolve sorbic acid and benzocaine in water at 60°C.
2. Add slowly the heated mixture of Vitamin E acetate and Cremophor RH 40 (60–65°C).
3. Cool the clear solution to about 5°C and dissolve Lutrol F 127. A clear, colorless viscous liquid is formed.

Vitamin E and Benzocaine Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Vitamin E acetate	50.00
20.00	2	Benzocaine	20.00
50.00	3	Lutrol F 127	50.00
250.00	4	Cremophor RH 40	250.00
2.00	5	Sorbic acid	2.00
QS	6	Water purified	QS to 1 L

Manufacturing Directions

1. Charge item 6 in suitable stainless steel jacketed vessel. Heat to 60°C.
2. Add and dissolve items 2 and 5.
3. In a separate vessel, charge items 1 and 4 (preheated to 60–65°C) and heat the mixture to 60°C to 65°C.
4. Add step 3 to step 2 and mix until clear solution is obtained.
5. Add and dissolve item 3 and mix.

Vitamin E Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 caps (g)
400.00	1	Vitamin E (D-alpha tocopherol 1000 units E/g)	400.00
25.00	2	Soybean oil	25.00
QS	3	Gelatin mass clear	QS

Manufacturing Directions

1. Weigh and transfer into a suitable stainless steel container soybean oil and preparation of D-alpha tocopherol.
   - Mix for a minimum for 1 hour.
   - Transfer into a suitable tank through an 80- to 100-mesh stainless steel screen.
   - Encapsulate 425 mg of mixture of step 3 into size 7.5 oval capsules using gelatin mass clear.

Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Vitamin E acetate	50.00
160.00	2	Cremophor RH 40	160.00
QS	3	Preservative	QS
QS	4	Water	QS to 1 L

Manufacturing Directions

1. Separately heat mixture of items 1 and 2 and solution of item 3 in 4 to about 65°C.
2. Add the two solutions slowly. A clear or lightly opalescent, colorless liquid should be formed.

Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Vitamin E acetate	50.00
150.00	2	Cremophor RH 40	150.00
QS	3	Preservatives	QS
QS	4	Water purified	QS to 1 L

Manufacturing Directions

1. Charge items 1 and 2 in a stainless steel jacketed vessel and heat to 65°C.
2. In a separate vessel, charge item 4 and heat to 90°C to 95°C and add and dissolve preservatives. Cool to 40°C.
3. Add step 2 into step 1.
4. Fill.

Vitamin E Solution with Ethanol

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
0.10	1	Vitamin E acetate	0.100
4.50	2	Cremophor EL	4.50
570.00	3	Water	570.00
380.00	4	Ethanol	380.00

Manufacturing Directions

1. Heat mixture of item 1 and 2 to about 60°C. Stir well.
2. Slowly add the warm solvent mixture of items 3 and 4. A clear, colorless liquid of low viscosity should be formed.

Vitamin E Solution with Ethanol

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.10	1	Vitamin E acetate (BASF)	0.10
45.00	2	Cremophor EL	45.00
QS	3	Water purified	QS to 1 L
380.00	4	Ethanol	380.00

Manufacturing Directions

1. Charge items 1 and 2 in a suitable stainless steel jacketed vessel. Heat to 60°C.
2. In a separate vessel (jacketed and explosion proof), charge item 3 and 4 and heat to 40°C.
3. Add step 2 to step 1 and stir well.
4. Fill.

Xylometazoline Hydrochloride Nasal Solution

Xylometazoline hydrochloride 0.05%, purified water, sorbitol, and mono and dibasic sodium phosphates.

Xylometazoline Hydrochloride Nasal Solution

Bill of Materials			
Scale (g/100 mL)	Item	Material Name	Qty/L (g)
0.100	1	Xylometazoline HCl	1.00
0.100	2	Disodium edetate (sodium EDTA)	1.00
0.700	3	Sodium chloride	7.00
0.030	4	Benzalkonium chloride (50% solution)	0.30
0.285	5	Monobasic sodium phosphate	2.85
0.306	6	Dibasic sodium phosphate	3.06
–	7	Water purified	QS to 1 L

Manufacturing Directions

This product is a colorless membrane filtered solution; therefore, ensure that the storage tanks for solution are cleaned and free of any contamination. Use freshly boiled and cooled purified water for the manufacturing. Prepare approximately 2 L of freshly boiled and cooled purified water and store in a clean stainless steel storage vessel.

1. Add 800 g of item 7 (20–25°C) to the manufacturing vessel.
2. Dissolve items 2 to 6 one by one in step 1 while mixing for 10 minutes. Check the clarity of the solution.
3. Dissolve item 1 in 100 g of item 7 (25–30°C) in a stainless steel container and add to the manufacturing vessel.
4. Rinse the drug container with 20 g of item 7 and add the rinsing to manufacturing vessel.
5. Make the volume up to 1 L with item 7 (20–25°C) and finally mix for 5 minutes.
6. Check and record the pH at 25°C (limit: 6.3 ± 0.2).
7. Check the cleanliness of the storage tank. Filter the solution through a prefilter and membrane filter, 0.2 micron, into the storage tank. Recirculate first 200 to 300 mL solution.
8. Store the filtered solution in tightly closed stainless steel storage tank. Do not store more than 24 hours in stainless steel storage tank after manufacturing.

Xylometazoline Hydrochloride Children's Nasal Solution

Bill of Materials			
Scale (g/100 mL)	Item	Material Name	Qty/L (g)
0.05	1	Xylometazoline hydrochloride	0.50
0.10	2	Disodium edetate (Sodium EDTA)	1.00
0.70	3	Sodium chloride	7.00
0.30	4	Benzalkonium chloride (50% solution)	0.30
0.28	5	Monobasic sodium phosphate	2.85
0.30	6	Dibasic sodium phosphate	3.06
–	7	Water purified	QS to 1 L

Manufacturing Directions

See above.

Zinc Pyrithione Shampoo

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
547.50	1	Deionized water	547.50
7.50	2	Hydroxyethylcellulose	7.50
347.00	3	TEA-lauryl sulfate	347.00
43.00	4	PEG-20 lanolin alcohol ether	43.00
20.00	5	Glycol stearate	20.00
15.00	6	Cocamide MEA	15.00
10.00	7	Zinc pyrithione (48%)	20.00
QS	8	Fragrance, preservative	QS

Manufacturing Directions

1. Add item 2 to the water and mix.
2. In a separate vessel, combine items 3 to 5, heat to 80°C, and mix.
3. Cool to 50°C.
4. Add items 6 and 7 and mix.
5. Add this mixture to mixture of item 2.
6. Cool to 40°C and add item 8.

COMMERCIAL PHARMACEUTICAL PRODUCTS

- Alupent® (metaproterenol sulfate USP) inhalation aerosol containing 75 mg of metaproterenol sulfate as micronized powder is sufficient medication for 100 inhalations. The Alupent inhalation aerosol containing 150 mg of metaproterenol sulfate as micronized powder is sufficient medication for 200 inhalations. Each metered dose delivers through the mouthpiece 0.65 mg of metaproterenol sulfate (each milliliter contains 15 mg). The inert ingredients are dichlorodifluoromethane, dichlorotetrafluoroethane, and trichloromonofluoromethane as propellants and sorbitan trioleate.
- Custodiol® contains 0.8766 g sodium chloride; 0.6710 g potassium chloride; 0.1842 g potassium hydrogen 2-ketoglutarate; 0.8132 g magnesium chloride • 6 H_2O; 3.7733 g histidine • HCl • H_2O; 27.9289 g histidine; 0.4085 g tryptophan; 5.4651 g mannitol; 0.0022 g calcium chloride – 2 H_2O in sterile water for injection. Anion: Cl – 50 mval. Physical properties: pH 7.02 to 7.20 at 25°C [77° F, pH 7.4–7.45 at 4°C (39.2° F)]. Osmolality: 310 mOsmol/kg.
- Depakene syrup (valproic acid) contains FD&C red No. 40, glycerin, methyl paraben, propyl paraben, sorbitol, sucrose, water, and natural and artificial flavors.
- Dilaudid oral liquid (hydromorphone hydrochloride), each 5 mL (one teaspoon) contains 5 mg of hydromorphone hydrochloride. In addition, other ingredients include purified water, methyl paraben, propyl paraben, sucrose, and glycerin. Dilaudid oral liquid may contain traces of sodium metabisulfite.
- Erythromycin ethylsuccinate (EES) is an ester of erythromycin suitable for oral administration. EES 200 liquid: Each 5-mL teaspoonful of fruit-flavored suspension contains erythromycin ethylsuccinate equivalent to 200 mg of erythromycin. EES 400 liquid: Each 5-mL teaspoonful of orange-flavored suspension contains erythromycin ethylsuccinate equivalent to 400 mg of erythromycin. Inactive: EES 200 liquid: FD&C red No. 40, methyl paraben, polysorbate 60, propyl paraben, sodium citrate, sucrose, water, xanthan gum and natural and artificial flavors. EES 400 liquid: D&C yellow No. 10, FD&C yellow No. 6, methyl paraben, polysorbate 60, propyl paraben, sodium citrate, sucrose, water, xanthan gum, and natural and artificial flavors.
- Gengraf® [cyclosporine capsules, USP (modified)] is a modified oral formulation of cyclosporine that forms an aqueous dispersion in an aqueous environment. Gengraf® capsules [cyclosporine capsules, USP (modified)] are available in 25- and 100-mg strengths. Each 25-mg capsule contains cyclosporine, 25 mg; alcohol, USP, absolute, 12.8% v/v (10.1% wt/vol.). Each 100-mg capsule contains cyclosporine, 100 mg; alcohol, USP, absolute, 12.8% v/v (10.1% wt/vol.). Inactive ingredients: FD&C blue No. 2, gelatin NF, polyethylene glycol NF, polyoxyl 35 castor oil NF, polysorbate 80 NF, propylene glycol USP, sorbitan monooleate NF, titanium dioxide.
- Indocin suspension for oral use contains 25 mg of indomethacin per 5 mL, alcohol 1%, and sorbic acid 0.1% added as a preservative, and the following inactive ingredients: antifoam AF emulsion, flavors, purified water, sodium hydroxide or hydrochloric acid to adjust pH, sorbitol solution, and tragacanth.
- Kaletra (lopinavir/ritonavir) oral solution is available for oral administration as 80 mg lopinavir and 20 mg ritonavir per milliliter with the following inactive ingredients: acesulfame potassium, alcohol, artificial cotton candy flavor, citric acid, glycerin, high fructose corn syrup, magnasweet-110 flavor, menthol, natural & artificial vanilla flavor, peppermint oil, polyoxyl 40 hydrogenated castor oil, povidone, propylene glycol, saccharin sodium, sodium chloride, sodium citrate, and water.
- Miacalcin® (calcitonin-salmon) nasal spray is provided in a 3.7-mL fill glass bottle as a solution for nasal administration. This is sufficient medication for at least 30 doses. Active ingredient: calcitonin-salmon, 2200 IU/mL (corresponding to 200 IU/0.09 mL actuation). Inactive

ingredients: sodium chloride, benzalkonium chloride, hydrochloric acid (added as necessary to adjust pH), and purified water.

- Norvir (ritonavir) oral solution also contains ethanol, water, polyoxyl 35 castor oil, propylene glycol, anhydrous citric acid to adjust pH, saccharin sodium, peppermint oil, creamy caramel flavoring, and FD&C yellow No. 6.
- Omnicef® (cefdinir) for oral suspension after reconstitution contains 125 mg cefdinir per 5 mL or 250 mg cefdinir per 5 mL and the following inactive ingredients: sucrose, NF; citric acid, USP; sodium citrate, USP; sodium benzoate, NF; xanthan gum, NF; guar gum, NF; artificial strawberry and cream flavors; silicon dioxide, NF; and magnesium stearate, NF.
- Rhinocort aqua nasal spray (budesonide) is an unscented, metered-dose manual-pump spray formulation containing a micronized suspension of budesonide in an aqueous medium. Microcrystalline cellulose and carboxymethyl cellulose sodium, dextrose anhydrous, polysorbate 80, disodium edetate, potassium sorbate, and purified water are contained in this medium; hydrochloric acid is added to adjust the pH to a target of 4.5. Rhinocort aqua nasal spray delivers 32 μg of budesonide per spray. Each bottle of Rhinocort aqua nasal spray 32 μg contains 120 metered sprays after initial priming.
- Suprane® (desflurane, USP) is a nonflammable liquid administered via vaporizer and is a general inhalation anesthetic. Desflurane is a colorless, volatile liquid below 22.8°C. Desflurane does not corrode stainless steel, brass, aluminum, anodized aluminum, nickel-plated brass, copper, or beryllium.
- Witch hazel, 50%, inactive ingredients: aloe barbadensis gel, capryl/capramidopropyl betaine, citric acid, diazolidinyl urea, glycerin, methyl paraben, propylene glycol, propyl paraben, sodium citrate, water.
- Abilify (aripiprazole) 1 mg/mL oral solution: Inactive ingredients for this solution include fructose, glycerin, DL-lactic acid, methyl paraben, propylene glycol, propyl paraben, sodium hydroxide, sucrose, and purified water. The oral solution is flavored with natural orange cream and other natural flavors.
- Accuzyme spray contains papain, USP (6.5 × 10.5 USP units of activity based on Lot I0C389 per gram of spray) and urea, USP 10% in a base composed of anhydrous lactose, cetearyl alcohol & ceteth-20 phosphate & dicetyl phosphate, fragrance, glycerin, methyl paraben, mineral oil, potassium phosphate monobasic, propyl paraben, purified water, and sodium hydroxide.
- Aerobid (flunisolide) inhaler is delivered in a metered-dose aerosol system containing a microcrystalline suspension of flunisolide as the hemihydrate in propellants (trichloromonofluoromethane, dichlorodifluoromethane, and dichlorotetrafluoroethane) with sorbitan trioleate as a dispersing agent. Aerobid-M also contains menthol as a flavoring agent. Each activation delivers approximately 250 μg of flunisolide to the patient. One Aerobid inhaler system is designed to deliver at least 100 metered inhalations.
- Astelin® (azelastine hydrochloride) nasal spray, 137 μg, contains 0.1% azelastine hydrochloride in an aqueous solution at pH 6.8 ± 0.3. It also contains benzalkonium chloride (125 μg/mL), EDTA, hypromellose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water.
- Avar™ cleanser (sodium sulfacetamide 10% and sulfur 5%) in each gram contains 100 mg of sodium sulfacetamide and 50 mg of colloidal sulfur in a mild aqueous based cleansing vehicle containing purified water USP, sodium magnesium silicate, sodium thiosulfate, propylene glycol, sodium lauryl sulfate, cetyl alcohol, stearyl alcohol, phenoxyethanol, fragrance.
- Beconase AQ nasal spray, beclomethasone dipropionate, monohydrate, the active component of Beconase AQ nasal spray is a metered-dose manual pump spray unit containing a microcrystalline suspension of beclomethasone dipropionate, monohydrate equivalent to 42 μg of beclomethasone dipropionate, calculated on the dried basis, in an aqueous medium containing microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, benzalkonium chloride, polysorbate 80, and 0.25% v/w phenylethyl alcohol. The pH through expiry is 5.0 to 6.8.
- Celexa® (citalopram HBr) oral solution contains citalopram HBr equivalent to 2 mg/mL citalopram base. It also contains the following inactive ingredients: sorbitol, purified water, propylene glycol, methyl paraben, natural peppermint flavor, and propyl paraben.
- Clarinex syrup is a clear orange-colored liquid containing 0.5 mg/1 mL desloratadine. The syrup contains the following inactive ingredients: propylene glycol USP, sorbitol solution USP, citric acid (anhydrous) USP, sodium citrate dihydrate USP, sodium benzoate NF, disodium edetate USP, purified water USP. It also contains granulated sugar, natural and artificial flavor for bubble gum and FDC yellow No. 6 dye.
- Clindets® (clindamycin phosphate pledgets) contain clindamycin phosphate, USP, at a concentration equivalent to 10 mg clindamycin per milliliter in a vehicle of isopropyl alcohol 52% v/v, propylene glycol, and water. Each Clindets® pledget applicator contains approximately 1 mL of clindamycin phosphate topical solution. Clindamycin phosphate topical solution has a pH range between 4 and 7.
- Clobex® (clobetasol propionate) spray, 0.05%, contains clobetasol propionate, a synthetic fluorinated corticosteroid, for topical use. Each gram of Clobex (clobetasol propionate) spray, 0.05%, contains 0.5 mg of clobetasol propionate, in a vehicle base composed of alcohol, isopropyl myristate, sodium lauryl sulfate, and undecylenic acid.
- Clobex (clobetasol propionate) shampoo, 0.05%, contains clobetasol propionate, a synthetic fluorinated corticosteroid, for topical dermatologic use. Each milliliter of Clobex (clobetasol propionate) shampoo, 0.05%, contains clobetasol propionate, 0.05%, in a shampoo base consisting of alcohol, citric acid, cocobetaine, polyquaternium-10, purified water, sodium citrate, and sodium laureth sulfate. Each gram of Clobex (clobetasol propionate) lotion, 0.05%, contains 0.5 mg of clobetasol propionate, in a vehicle base composed of hypromellose, propylene glycol, mineral oil, polyoxyethylene glycol 300 isostearate, carbomer 1342, sodium hydroxide, and purified water.
- Colace® syrup [docusate sodium, in each tablespoonful (15 mL)] contains docusate sodium 60 mg. Inactive ingredients: citric acid, D&C red No. 33, FD&C red No. 40, flavors, glycerin, propylene glycol, purified water, sodium citrate, sodium saccharin, sorbitol. Colace® liquid 1% solution: each mL contains 10 mg of docusate sodium.
- Depacon solution, valproate sodium, is the sodium salt of valproic acid designated as sodium 2-propylpentanoate. It is available in 5-mL single-dose vials for intravenous injection. Each milliliter contains valproate sodium equivalent to 100 mg valproic acid, EDTA 0.40 mg, and water for injection to volume. The pH is adjusted to 7.6 with sodium

hydroxide and/or hydrochloric acid. The solution is clear and colorless.

- Dextromethorphan–Pseudoephedrine active ingredients: Each 0.8 mL contains 2.5 mg dextromethorphan hydrobromide, USP; 7.5 mg pseudoephedrine hydrochloride, USP. Inactive ingredients: citric acid, flavors, glycerin, high fructose corn syrup, maltol, menthol, polyethylene glycol, propylene glycol, sodium benzoate, sorbitol, sucrose, water.
- Diuril (chlorothiazide) oral suspension contains 250 mg of chlorothiazide per 5 mL, alcohol 0.5%, with methyl paraben 0.12%, propyl paraben 0.02%, and benzoic acid 0.1% added as preservatives. The inactive ingredients are D&C yellow No. 10, flavors, glycerin, purified water, sodium saccharin, sucrose, and tragacanth.
- Dovonex® (calcipotriene solution) scalp solution 0.005% is a colorless topical solution containing 0.005% calcipotriene in a vehicle of isopropanol (51% v/v) propylene glycol, hydroxypropyl cellulose, sodium citrate, menthol, and water.
- Ferrochel® (elemental iron) 70 mg, ferrous fumerate (elemental iron) 81 mg, vitamin C as Ester-C®, ascorbic acid (as calcium ascorbate) 60 mg, threonic acid (as calcium threonate) 0.8 mg, folic acid, USP 1 mg, vitamin B_{12} (cyanocobalamin) 10 μg, Ferrochel® (ferrous bisglycinate chelate) is a registered trademark of Albion International, Inc., Clearfield, Utah, and is protected under U.S. Patent Nos. 4,599,152 and 4,830,716. Ester-C® is a patented pharmaceutical grade material consisting of calcium ascorbate and calcium threonate. Ester-C® is a licensed trademark of Zila Nutraceuticals, Inc. Inactive ingredients: soybean oil, gelatin, glycerin, lecithin (unbleached), yellow beeswax, titanium dioxide, methyl paraben, ethyl vanillin, FD& yellow No. 6, FD& red No. 40, propyl paraben, FD& blue No. 1.
- Efudex solutions and cream are topical preparations containing the fluorinated pyrimidine 5-fluorouracil. Efudex solution consists of 2% or 5% fluorouracil on a weight/weight basis, compounded with propylene glycol, tris (hydroxymethyl) aminomethane, hydroxypropyl cellulose, parabens (methyl and propyl), and disodium edetate.
- Epinephrine inhalation active ingredient (in each inhalation), epinephrine 0.22 mg. Inactive ingredients: ascorbic acid, dehydrated alcohol (34%), dichlorodifluoromethane (CFC 12), dichlorotetrafluoroethane (CFC 114), hydrochloric acid, nitric acid, purified water.
- Epivir (also known as 3TC) is lamivudine, a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C. Epivir oral solution is for oral administration. One milliliter of Epivir oral solution contains 10 mg of lamivudine (10 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methyl paraben, propylene glycol, propyl paraben, sodium citrate (dihydrate), and sucrose (200 mg).
- Epivir-HBV is lamivudine, a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C. Epivir-HBV oral solution is for oral administration. One milliliter of Epivir-HBV oral solution contains 5 mg of lamivudine (5 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methyl paraben, propylene glycol, propyl paraben, sodium citrate (dihydrate), and sucrose (200 mg).
- Exelon® (rivastigmine tartrate) oral solution is supplied as a solution containing rivastigmine tartrate, equivalent to 2 mg/mL of rivastigmine base for oral administration. Inactive ingredients are citric acid, D&C yellow No. 10, purified water, sodium benzoate, and sodium citrate.
- Fleet® Phospho-soda® EZ-Prep™ contains active ingredients (each 15 mL) monobasic sodium phosphate monohydrate 7.2 g and dibasic sodium phosphate heptahydrate 2.7 g.
- Flovent HFA 44 μg inhalation aerosol, Flovent HFA 110 μg inhalation aerosol, and Flovent HFA 220 μg inhalation aerosol contain fluticasone propionate. Flovent HFA 44 μg inhalation aerosol, Flovent HFA 110 μg inhalation aerosol, and Flovent HFA 220 μg inhalation aerosol are pressurized, metered-dose aerosol units intended for oral inhalation only. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) in propellant HFA-134a (1, 1, 1, 2-tetrafluoroethane). It contains no other excipients. Each 10.6-g canister (44 μg) and each 12-g canister (110 and 220 μg) provides 120 inhalations. Flovent HFA should be primed before using for the first time by releasing four test sprays into the air away from the face, shaking well before each spray. In cases where the inhaler has not been used for more than 7 days or when it has been dropped, prime the inhaler again by shaking well and releasing one test spray into the air away from the face. This product does not contain any chlorofluorocarbon (CFC) as the propellant. Under standardized in vitro test conditions, Flovent DISKUS 50 μg delivers 46 μg of fluticasone propionate when tested at a flow rate of 60 L/min for 2 seconds. In adult patients with obstructive lung disease and severely compromised lung function (mean forced expiratory volume in 1 second [FEV 1] 20–30% of predicted), mean peak inspiratory flow (PIF) through a Diskus® is 82.4 L/min (range: 46.1–115.3 L/min). In children with asthma 4 and 8 years old, mean PIF through Flovent Diskus is 70 and 104 L/min, respectively (range: 48–123 L/min).
- Flumadine® (rimantadine hydrochloride, 5 mL) of the syrup contains 50 mg of rimantadine hydrochloride in a dye-free, aqueous solution containing citric acid, parabens (methyl and propyl), saccharin sodium, sorbitol, and flavors.
- Fluticasone propionate, Flonase nasal spray, 50 μg, is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. Flonase nasal spray also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol and has a pH between 5 and 7. It is necessary to prime the pump before first use or after a period of nonuse (1 week or more). After initial priming (6 actuations), each actuation delivers 50 μg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each 16-g bottle of Flonase nasal spray provides 120 metered sprays. After 120 metered sprays, the amount of fluticasone propionate delivered per actuation may not be consistent and the unit should be discarded.
- Fosamax (alendronate sodium) oral solution contains 91.35 mg of alendronate monosodium salt trihydrate, which is the molar equivalent to 70 mg of free acid. Each bottle also contains the following inactive ingredients: sodium citrate dihydrate and citric acid anhydrous as buffering agents, sodium saccharin, artificial raspberry flavor, and purified water. Added as preservatives are sodium propyl paraben 0.0225% and sodium butylparaben 0.0075%.
- Frotical (calcitonin) calcitonin-salmon (rDNA origin) nasal spray is provided in a 3.7-mL fill glass bottle as a

solution for intranasal administration with sufficient medication for at least 30 doses. Each spray delivers 200 IU calcitonin-salmon in a volume of 0.09 mL. Active ingredient: Calcitonin-salmon 2200 IU/mL, corresponding to 200 IU per actuation (0.09 mL). Inactive ingredients: Sodium chloride USP, citric acid USP, phenylethyl alcohol USP, benzyl alcohol NF, polysorbate 80 NF, hydrochloric acid NF or sodium hydroxide NF (added as necessary to adjust pH), and purified water USP.

- Gets The Dry Out® and Visine® pure tears portables preservative free lubricant eye. Glycerin 0.2%, hypromellose 0.2%, polyethylene glycol 400 1%.
- Gordochom containing 25% undecylenic acid and 3% chloroxylenol as its active ingredients in a penetrating oil base.
- Guaifenesin, active ingredient (in each 5 mL tsp): guaifenesin, USP 100 mg, Inactive ingredients: caramel, citric acid, FD&C red No. 40, flavors, glucose, glycerin, high fructose corn syrup, menthol, saccharin sodium, sodium benzoate, water.
- Hydroquinone USP 4% also contains avobenzone, ceteareth-20, cetostearyl alcohol, citric acid, diethylaminoethyl stearate, dimethicone, EDTA, glyceryl dilaurate, glyceryl monostearate, glyceryl stearate, PEG-100 stearate, hydroxyethylcellulose, methyl paraben, octyldodecyl stearoyl stearate, octinoxate, oxybenzone, polysorbate 80, propylene glycol, propyl gallate, propyl paraben, purified water, quaternium-26, sodium metabisulfite, sodium PCA, squalane, ubiquinone, stearyl alcohol, water, glycerin, *Rumex occidentalis* extract.
- Ibuprofen, active ingredient (in each 5 mL), Ibuprofen 100 mg, inactive ingredients (fruit flavor): artifical flavors, carboxymethylcellulose sodium, citric acid, EDTA, FD&C red No. 40, glycerin, microcrystalline cellulose, polysorbate 80, purified water, sodium benzoate, sorbitol solution, sucrose, xanthan gum. Inactive ingredients (grape flavor): acetic acid, artifical flavor, butylated hydroxytoluene, carboxymethylcellulose sodium, citric acid, EDTA, FD&C blue No. 1, FD&C red No. 40, glycerin, microcrystalline cellulose, polysorbate 80, propylene glycol, purified water, sodium benzoate, sorbitol solution, sucrose, xanthan gum. Inactive ingredients (blue raspberry flavor): carboxymethylcellulose sodium, citric acid, edetate disodium, FD&C blue No. 1, glycerin, microcrystalline cellulose, natural and artificial flavors, polysorbate 80, propylene glycol, purified water, sodium benzoate, sodium citrate, sorbitol solution, sucrose, xanthan gum.
- Ibuprofen 200 mg, inactives: FD&C green No. 3, gelatin, light mineral oil, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan, sorbitol.
- Ibuprofen liquid gel, active ingredients (in each LiquiGel): solubilized ibuprofen equal to 200 mg ibuprofen (present as the free acid and potassium salt) pseudoephedrine HCl 30 mg. Inactive ingredients (LiquiGel): D&C yellow No. 10, FD&C red No. 40, fractionated coconut oil, gelatin, pharmaceutical ink, polyethylene glycol, potassium hydroxide, purified water, sorbitan, sorbitol.
- Imitrex (sumatriptan) nasal spray contains sumatriptan. Each Imitrex nasal spray contains 5 or 20 mg of sumatriptan in a 100-μL unit dose aqueous buffered solution containing monobasic potassium phosphate NF, anhydrous dibasic sodium phosphate USP, sulfuric acid NF, sodium hydroxide NF, and purified water USP. The pH of the solution is approximately 5.5. The osmolality of the solution is 372 or 742 mOsmol for the 5- and 20-mg Imitrex nasal spray, respectively.
- Iron protein succinylate is a proprietary stabilized iron compound. The iron is wrapped in a casein protective layer, which allows the iron to pass through the stomach to the intestinal tract for immediate safe and efficacious absorption. Ferretts IPS liquid is for use as a dietary supplement. Each 1 mL contains 2.67 mg iron. Serving size: 15 mL, amount per 15 mL, iron 40 mg (from iron protein succinylate). Other ingredients: purified water, sorbitol solution, propylene glycol, casein (milk protein) strawberry flavor, sodium hydroxide, methyl paraben sodium, propyl paraben sodium, saccharin sodium.
- Kaopectate®: Each 15 mL of Kaopectate antidiarrheal contains bismuth subsalicylate 262 mg, contributing 130 mg total salicylates. Kaopectate antidiarrheal is low sodium, with each 15 mL tablespoonful containing 10 mg sodium. Extra-strength Kaopectate: Each 15 mL of extra-strength Kaopectate antidiarrheal contains bismuth subsalicylate 525 mg, contributing 236 mg total salicylates. Extra-strength Kaopectate is low sodium. Each 15 mL tablespoonful contains sodium 11 mg.
- Keppra® oral solution contains 100 mg of levetiracetam per milliliter. Inactive ingredients: ammonium glycyrrhizinate, citric acid monohydrate, glycerin, maltitol solution, methyl paraben, potassium acesulfame, propyl paraben, purified water, sodium citrate dihydrate, and natural and artificial flavor.
- Lexapro® (escitalopram oxalate) oral solution contains escitalopram oxalate equivalent to 1 mg/mL escitalopram base. It also contains the following inactive ingredients: sorbitol, purified water, citric acid, sodium citrate, malic acid, glycerin, propylene glycol, methyl paraben, propyl paraben, and natural peppermint flavor.
- Loprox® (ciclopirox) shampoo 1% contains the synthetic antifungal agent, ciclopirox. Each gram (equivalent to 0.96 mL) of Loprox shampoo contains 10 mg ciclopirox in a shampoo base consisting of purified water USP, sodium laureth sulfate, disodium laureth sulfosuccinate, sodium chloride USP, and laureth-2. Loprox shampoo is a colorless, translucent solution.
- Loratadine, active ingredient (in each 5-mL teaspoon): loratadine 5 mg. Inactive ingredients: artificial flavor, citric acid, glycerin, propylene glycol, purified water, sodium benzoate, sucrose.
- Lortab elixir, hydrocodone bitartrate and acetaminophen are supplied in liquid form for oral administration. It is affected by light. Lortab elixir contains per 5 mL hydrocodone bitartrate 2.5 mg, acetaminophen 167 mg, alcohol 7%. In addition, the liquid contains the following inactive ingredients: citric acid anhydrous, ethyl maltol, glycerin, methyl paraben, propylene glycol, propyl paraben, purified water, saccharin sodium, sorbitol solution, sucrose, with D&C yellow No. 10 and FD&C yellow No. 6 as coloring and natural and artificial flavoring.
- Lotrimin topical solution contains 10 mg clotrimazole, USP, in a nonaqueous vehicle of PEG-400 NF.
- Marinol® Dronabinol capsules for oral administration: Marinol capsules are supplied as round, soft gelatin capsules containing either 2.5, 5, or 10 mg dronabinol. Each Marinol capsule is formulated with the following inactive ingredients: FD&C blue No. 1 (5 mg), FD&C red No. 40 (5 mg), FD&C yellow No. 6 (5 and 10 mg), gelatin, glycerin, methyl paraben, propyl paraben, sesame oil, and titanium dioxide.
- Megace® ES (megestrol acetate) oral suspension contains megestrol acetate. Megace ES (megestrol acetate) is a concentrated formula supplied as an oral suspension

containing 125 mg of megestrol acetate per mL. Megace ES (megestrol acetate) oral suspension contains the following inactive ingredients: alcohol (max 0.06% v/v from flavor), artificial lime flavor, citric acid monohydrate, docusate sodium, hydroxypropylmethylcellulose (hypromellose), natural and artificial lemon flavor, purified water, sodium benzoate, sodium citrate dihydrate, and sucrose.

- Mepron (atovaquone) suspension is a formulation of microfine particles of atovaquone. The atovaquone particles, reduced in size to facilitate absorption, are significantly smaller than those in the previously marketed tablet formulation. Mepron suspension is for oral administration and is bright yellow with a citrus flavor. Each teaspoonful (5 mL) contains 750 mg of atovaquone and the inactive ingredients benzyl alcohol, flavor, poloxamer 188, purified water, saccharin sodium, and xanthan gum.
- Migranal® is ergotamine hydrogenated in the 9, 10 position as the mesylate salt. Migranal (dihydroergotamine mesylate, USP) nasal spray is provided for intranasal administration as a clear, colorless to faintly yellow solution in an amber glass vial containing dihydroergotamine mesylate, USP 4 mg; caffeine, anhydrous, USP 10 mg; dextrose, anhydrous, USP 50 mg; carbon dioxide, USP QS; purified, USP QS 1 mL.
- Namenda® (memantine hydrochloride) oral solution contains memantine hydrochloride in a strength equivalent to 2 mg of memantine hydrochloride in each milliliter. The oral solution also contains the following inactive ingredients: sorbitol solution (70%), methyl paraben, propyl paraben, propylene glycol, glycerin, natural peppermint flavor No. 104, citric acid, sodium citrate, and purified water.
- Nasacort® HFA nasal aerosol contains triamcinolone acetonide. Nasacort HFA nasal aerosol is a metered-dose aerosol unit containing a microcrystalline suspension of triamcinolone acetonide in tetrafluoroethane (HFA-134a) and dehydrated alcohol USP 0.7% w/w. Each canister contains 15 mg of triamcinolone acetonide.
- Nasonex nasal spray 50 μg mometasone furoate monohydrate is a metered-dose manual pump spray unit containing an aqueous suspension of mometasone furoate monohydrate equivalent to 0.05% w/w mometasone furoate calculated on the anhydrous basis; in an aqueous medium containing glycerin, microcrystalline cellulose and carboxymethylcellulose sodium, sodium citrate, citric acid, benzalkonium chloride, and polysorbate 80. The pH is between 4.3 and 4.9. After initial priming (10 actuations), each actuation of the pump delivers a metered spray containing 100 mg of suspension containing mometasone furoate monohydrate equivalent to 50 μg of mometasone furoate calculated on the anhydrous basis. Each bottle of Nasonex nasal spray 50 μg provides 120 sprays.
- Neoral® is an oral formulation of cyclosporine that immediately forms a microemulsion in an aqueous environment. Neoral soft gelatin capsules (cyclosporine capsules, USP) modified are available in 25- and 100-mg strengths. Each 25-mg capsule contains cyclosporine 25 mg; alcohol, USP dehydrated 11.9% v/v (9.5% wt/vol.). Each 100-mg capsule contains cyclosporine 100 mg alcohol, USP dehydrated 11.9% v/v (9.5% wt/vol.). Inactive ingredients: Corn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil NF, DL-(alpha)-tocopherol USP, gelatin NF, glycerol, iron oxide black, propylene glycol USP, titanium dioxide USP, carmine, and other ingredients.
- Neoral oral solution (cyclosporine oral solution, USP) modified is available in 50 mL bottles. Each milliliter contains cyclosporine 100 mg/mL; alcohol, USP dehydrated 11.9% v/v (9.5% wt/vol.). Inactive ingredients: Corn oil-mono-di-triglycerides, polyoxyl 40 hydrogenated castor oil NF, DL-(alpha)-tocopherol USP, propylene glycol USP.
- Neurontin® (gabapentin) oral solution contains 250 mg/5 mL of gabapentin. The inactive ingredients for the oral solution are glycerin, xylitol, purified water, and artificial cool strawberry anise flavor.
- Nicotrol® inhaler (nicotine inhalation system) consists of a mouthpiece and a plastic cartridge delivering 4 mg of nicotine from a porous plug containing 10 mg nicotine. The cartridge is inserted into the mouthpiece prior to use. Nicotine is the active ingredient; inactive components of the product are menthol and a porous plug which are pharmacologically inactive. Nicotine is released when air is inhaled through the inhaler.
- Nicotrol NS (nicotine nasal spray) is an aqueous solution of nicotine intended for administration as a metered spray to the nasal mucosa. Each 10 mL spray bottle contains 100 mg nicotine (10 mg/mL) in an inactive vehicle containing disodium phosphate, sodium dihydrogen phosphate, citric acid, methyl paraben, propyl paraben, edetate disodium, sodium chloride, polysorbate 80, aroma, and water. The solution is isotonic with a pH of 7. It contains no chlorofluorocarbons. After priming the delivery system for Nicotrol NS, each actuation of the unit delivers a metered dose spray containing approximately 0.5 mg of nicotine. The size of the droplets produced by the unit is in excess of 8 microns. One Nicotrol NS unit delivers approximately 200 applications.
- Nitrolingual® pumpspray (nitroglycerin lingual spray 400 μg) is a metered dose spray containing nitroglycerin. This product delivers nitroglycerin (400 μg per spray, 60 or 200 metered sprays) in the form of spray droplets onto or under the tongue. Inactive ingredients: medium-chain triglycerides, dehydrated alcohol, medium-chain partial glycerides, peppermint oil.
- Oxsoralen ultra lotion: Each milliliter of Oxsoralen lotion contains 10 mg methoxsalen in an inert vehicle containing alcohol (71% v/v), propylene glycol, acetone, and purified water.
- Oxyfast® oral concentrate solution: Each 1 mL of Oxyfast concentrate solution contains oxycodone hydrochloride 20 mg. Inactive ingredients: citric acid, D&C yellow No. 10, sodium benzoate, sodium citrate, sodium saccharine, and water.
- Panafil spray contains papain, USP (not less than 405, 900 units of activity based on Lot IOC389 per gram of spray); urea, USP 10%; and chlorophyllin copper complex sodium, USP 0.5% in a base composed of anhydrous lactose, cetearyl alcohol & ceteth-20 phosphate & dicetyl phosphate, glycerin, methyl paraben, mineral oil, propyl paraben, purified water, and sodium hydroxide.
- Paxil CR (paroxetine hydrochloride) suspension for oral administration: Each 5 mL of orange-colored, orange-flavored liquid contains paroxetine hydrochloride equivalent to paroxetine 10 mg. Inactive ingredients consist of polacrilin potassium, microcrystalline cellulose, propylene glycol, glycerin, sorbitol, methyl paraben, propyl paraben, sodium citrate dihydrate, citric acid anhydrate, sodium saccharin, flavorings, FD&C yellow No. 6, and simethicone emulsion, USP.
- Pediapred (prednisolone sodium phosphate, USP) oral solution is a dye-free, colorless to light straw-colored, raspberry-flavored solution. Each 5 mL (teaspoonful) of Pediapred contains 6.7 mg prednisolone sodium phosphate

(5 mg prednisolone base) in a palatable, aqueous vehicle. Pediapred also contains dibasic sodium phosphate, edetate disodium, methyl paraben, purified water, sodium biphosphate, sorbitol, natural and artificial raspberry flavor.

- Penlac® nail lacquer (ciclopirox) topical solution, 8%, contains a synthetic antifungal agent ciclopirox. It is intended for topical use on fingernails and toenails and immediately adjacent skin. Each gram of Penlac nail lacquer (ciclopirox) topical solution, 8%, contains 80 mg ciclopirox in a solution base consisting of ethyl acetate, NF; isopropyl alcohol, USP; and butyl monoester of poly(methylvinyl ether/maleic acid) in isopropyl alcohol. Ethyl acetate and isopropyl alcohol are solvents that vaporize after application. Penlac nail lacquer (ciclopirox) topical solution, 8%, is a clear, colorless to slightly yellowish solution.
- Plexion®, sodium sulfacetamide, each gram of Plexion (sodium sulfacetamide USP 10% and sulfur USP 5%) cleanser contains 100 mg of sodium sulfacetamide USP and 50 mg of sulfur USP in a cleanser base containing purified water USP, sodium methyl oleyltaurate, sodium cocoyl isethionate, disodium oleamido MEA sulfosuccinate, cetyl alcohol NF, glyceryl stearate (and) PEG-100 stearate, stearyl alcohol NF, PEG-55 propylene glycol oleate, magnesium aluminum silicate, methyl paraben NF, edetate disodium USP, butylated hydroxytoluene, sodium thiosulfate USP, fragrance, xanthan gum NF, and propyl paraben NF. Each cloth of Plexion (sodium sulfacetamide USP 10% and sulfur USP 5%) Cleansing cloths are coated with a cleanser-based formulation. Each gram of this cleanser-based formulation contains 100 mg of sodium sulfacetamide USP and 50 mg of sulfur USP. The cleanser base consists of purified water USP, sodium methyl oleyltaurate, sodium cocoyl isethionate, disodium laureth sulfosuccinate (and) sodium lauryl sulfoacetate, disodium oleamido MEA sulfosuccinate, glycerin USP, sorbitan monooleate NF, glyceryl stearate (and) PEG-100 stearate, stearyl alcohol NF, propylene glycol (and) PEG-55 propylene glycol oleate, cetyl alcohol NF, edetate disodium USP, methyl paraben NF, PEG-150 pentaerythrityl tetrastearate, butylated hydroxytoluene NF, sodium thiosulfate USP, aloe vera gel decolorized, allantoin, alpha bisabolol natural, fragrance, propyl paraben NF. Each gram of Plexion SCT® (sodium sulfacetamide USP 10% and sulfur USP 5%) contains 100 mg of sodium sulfacetamide USP and 50 mg of sulfur USP in a cream containing purified water USP, kaolin USP, glyceryl stearate (and) PEG-100 stearate, witch hazel USP, silicon dioxide, magnesium aluminum silicate, benzyl alcohol NF, water (and) propylene glycol (and) quillaia saponaria extract, xanthan gum NF, sodium thiosulfate USP, fragrance.
- Prevacid for delayed-release oral suspension is composed of the active ingredient lansoprazole, in the form of enteric-coated granules and also contains inactive granules. The packets contain lansoprazole granules which are identical to those contained in Prevacid delayed-release capsules and are available in 15- and 30-mg strengths. Inactive granules are composed of the following ingredients: confectioner's sugar, mannitol, docusate sodium, ferric oxide, colloidal silicon dioxide, xanthan gum, crospovidone, citric acid, sodium citrate, magnesium stearate, and artificial strawberry flavor. The lansoprazole granules and inactive granules, present in unit dose packets, are constituted with water to form a suspension and consumed orally.
- Proventil HFA (albuterol sulfate) inhalation aerosol contains a microcrystalline suspension of albuterol sulfate in propellant HFA-134a (1, 1, 1, 2-tetrafluoroethane), ethanol, and oleic acid. Each actuation delivers 120 μg albuterol sulfate, USP, from the valve and 108 μg albuterol sulfate, USP, from the mouthpiece (equivalent to 90 μg of albuterol base from the mouthpiece). Each canister provides 200 inhalations.
- Proventil inhalation solution contains albuterol sulfate. Proventil inhalation solution is a clear, colorless to light yellow solution and requires no dilution before administration by nebulization. Each milliliter of Proventil inhalation solution 0.083% contains 0.83 mg of albuterol (as 1 mg of albuterol sulfate) in an isotonic aqueous solution containing sodium chloride. Sulfuric acid may be added to adjust pH (3–5). Proventil inhalation solution contains no sulfiting agents or preservatives.
- Prozac® (fluoxetine hydrochloride) oral solution contains fluoxetine hydrochloride equivalent to 20 mg/5 mL (64.7 μmol) of fluoxetine. It also contains alcohol 0.23%, benzoic acid, flavoring agent, glycerin, purified water, and sucrose.
- Rapamune® (sirolimus) is available for administration as an oral solution containing 1 mg/mL sirolimus. The inactive ingredients in Rapamune oral solution are Phosal 50 PG ® (phosphatidylcholine, propylene glycol, mono- and diglycerides, ethanol, soy fatty acids. Oral solution contains 1.5%–2.5% ethanol.
- Retrovir (zidovudine) syrup is for oral administration. Each teaspoonful (5 mL) of Retrovir syrup contains 50 mg of zidovudine and the inactive ingredients sodium benzoate 0.2% (added as a preservative), citric acid, flavors, glycerin, and liquid sucrose. Sodium hydroxide may be added to adjust pH.
- Robitussin CF, active ingredients (in each 5 mL tsp Robitussin CF): dextromethorphan HBr, USP 10 mg, guaifenesin, USP 100 mg, pseudoephedrine HCl, USP 30 mg (in each 2.5 mL Robitussin cough & cold infant drops), dextromethorphan HBr, USP 5 mg, guaifenesin, USP 100 mg, pseudoephedrine HCl, USP 15 mg. Active ingredients (in each 5 mL tsp: Robitussin DM, Robitussin sugar free cough): dextromethorphan HBr, USP 10 mg guaifenesin, USP 100 mg. Active ingredients (in each 2.5 mL Robitussin DM infant drops): dextromethorphan HBr, USP 5 mg, guaifenesin, USP 100 mg, pseudoephedrine HCl, USP 30 mg. Inactive ingredients (Robitussin DM): citric acid, FD&C red No. 40, flavors, glucose, glycerin, high fructose corn syrup, menthol, saccharin sodium, sodium benzoate, water. Inactive ingredients (Robitussin sugar free cough): acesulfame potassium, citric acid, flavors, glycerin, methyl paraben, polyethylene glycol, povidone, propylene glycol, saccharin sodium, sodium benzoate, water. Inactive ingredients (Robitussin DM infant drops): citric acid, FD&C red No. 40, flavors, glycerin, high fructose corn syrup, maltitol, maltol, polyethylene glycol, povidone, propylene glycol, saccharin sodium, sodium benzoate, sodium chloride, sodium citrate, water. Robitussin DM infant drops in 1fl oz bottle: Active ingredients (in each 5 mL tsp): guaifenesin, USP 100 mg, Inactive ingredients: citric acid, FD&C red No. 40, flavors, glucose, glycerin, high fructose corn syrup, maltol, menthol, propylene glycol, saccharin sodium, sodium benzoate, water. Active ingredients (in each 5 mL tsp): chlorpheniramine maleate, USP 1 mg, dextromethorphan HBr, USP 7.5 mg, pseudoephedrine HCl, USP 15 mg. Inactive ingredients: citric acid, FD&C red No. 40, glycerin, high fructose corn syrup, natural and artificial flavors, propylene glycol, purified water, saccharin sodium, sodium benzoate, sodium chloride, sodium citrate. Active ingredient (in each drop): natural honey center

and honey lemon tea: menthol, USP 5 mg, honey citrus and almond with natural honey center: menthol, USP 2.5 mg, inactive ingredients: natural honey center: caramel, corn syrup, glycerin, high fructose corn syrup, honey, natural herbal flavor, sorbitol, sucrose. Honey lemon tea: caramel, citric acid, corn syrup, honey, natural flavor, sucrose, tea extract. Honey citrus: citric acid, corn syrup, flavors, honey, sucrose. almond with natural honey center: caramel, corn syrup, glycerin, honey, natural almond flavor, natural anise flavor, natural coriander flavor, natural fennel flavor, natural honey flavor and other natural flavors, sorbitol, sucrose. Inactive ingredients: citric acid, D&C red No. 33, FD&C yellow No. 6, flavor, glycerin, high fructose corn syrup, polyethylene glycol, purified water, sodium benzoate, sodium citrate, sorbitol solution, sucralose. Active ingredient (in each drop) menthol eucalyptus: menthol, USP 10 mg, cherry and honey-lemon: menthol, USP 5 mg. Active ingredients (in each 5 mL tsp), acetaminophen, USP 160 mg, chlorpheniramine maleate, USP 1 mg, dextromethorphan HBr, USP 5 mg, pseudoephedrine HCl, USP 15 mg. Inactive ingredients: menthol eucalyptus: corn syrup, eucalyptus oil, flavor, sucrose. Cherry: corn syrup, FD&C red No. 40, flavor, methyl paraben, propyl paraben, sodium benzoate, sucrose. Honey-Lemon: citric acid, corn syrup, D&C yellow No. 10, FD&C yellow No. 6, honey, lemon oil, methyl paraben, povidone, propyl paraben, sodium benzoate, sucrose.

- Sandimmune® oral solution (cyclosporine oral solution, USP) is available in 50-mL bottles. Each milliliter contains cyclosporine, USP 100 mg, alcohol, Ph. Helv. 12.5% by volume dissolved in an olive oil, Ph. Helv./Labrafil M 1944 CS (polyoxyethylated oleic glycerides) vehicle which must be further diluted with milk, chocolate milk, or orange juice before oral administration.
- Sandimmune soft gelatin capsules (cyclosporine capsules, USP) are available in 25- and 100-mg strengths. Each 25-mg capsule contains cyclosporine, USP 25 mg, alcohol, USP dehydrated max 12.7% by volume. Each 100-mg capsule contains cyclosporine, USP 100 mg, alcohol, USP dehydrated max 12.7% by volume. Inactive ingredients: corn oil, gelatin, glycerol, Labrafil M 2125 CS (polyoxyethylated glycolysed glycerides), red iron oxide (25- and 100-mg capsule only), sorbitol, titanium dioxide, and other ingredients.
- Sulfamylon® for 5% topical solution is provided in packets containing 50 g of sterile mafenide acetate to be reconstituted in 1000 mL of sterile water for irrigation, USP or 0.9% sodium chloride irrigation, USP. After mixing, the solution contains 5% w/v of mafenide acetate. The solution is an antimicrobial preparation suitable for topical administration. The solution is not for injection. The reconstituted solution may be held up to 28 days after preparation if stored in unopened containers.
- Tahitian Noni® juice is reconstituted *Morinda citrifolia* fruit juice from pure juice puree from French Polynesia, natural grape juice concentrate, natural blueberry juice concentrate, and natural flavors. Not made from dried or powdered *M. citrifolia*.
- Triaz® (benzoyl peroxide) 3%, 6%, and 9% gels, cleansers, and pads are topical, gel-based benzoyl peroxide–containing preparations for use in the treatment of acne vulgaris. Triaz 3% gel contains benzoyl peroxide USP 3% as the active ingredient in a gel-based formulation consisting of purified water USP, C12–15 alkyl benzoate, glycerin USP, cetearyl alcohol, polyacrylamide (and) C13–14 isoparaffin (and) laureth-7, glyceryl stearate (and) PEG-100 stearate, steareth-2, steareth-20, dimethicone, glycolic acid, zinc lactate, lactic acid USP, edetate disodium USP, sodium hydroxide NF.
- Trileptal® (oxcarbazepine) is available as a 300 mg/5 mL (60 mg/mL) oral suspension contains the following inactive ingredients: ascorbic acid, dispersible cellulose, ethanol, macrogol stearate, methyl parahydroxybenzoate, propylene glycol, propyl parahydroxybenzoate, purified water, sodium saccharin, sorbic acid, sorbitol, yellow-plum-lemon aroma.
- Tussionex, each teaspoonful (5 mL) of Tussionex Pennkinetic extended-release suspension contains hydrocodone polistirex equivalent to 10 mg of hydrocodone bitartrate and chlorpheniramine polistirex equivalent to 8 mg of chlorpheniramine maleate. Hydrocodone polistirex: sulfonated styrene-divinylbenzene copolymer complex with 4, 5(alpha)-epoxy-3-methoxy-17-methylmorphinan-6-one. Chlorpheniramine polistirex: sulfonated styrene-divinylbenzene copolymer complex with 2-[p-chloro-(alpha)-[2-(dimethylamino)ethyl]-benzyl]pyridine. Inactive ingredients: ascorbic acid, D&C yellow No. 10, ethylcellulose, FD&C yellow No. 6, flavor, high fructose corn syrup, methyl paraben, polyethylene glycol 3350, polysorbate 80, pregelatinized starch, propylene glycol, propyl paraben, purified water, sucrose, vegetable oil, xanthan gum.
- Zmax (azithromycin extended release) for oral suspension contains the active ingredient azithromycin (as azithromycin dihydrate). Zmax is a single-dose, extended release formulation of microspheres for oral suspension containing azithromycin (as azithromycin dihydrate) and the following excipients: glyceryl behenate, poloxamer 407, sucrose, sodium phosphate tribasic anhydrous, magnesium hydroxide, hydroxypropyl cellulose, xanthan gum, colloidal silicon dioxide, titanium dioxide, artificial cherry flavor, and artificial banana flavor. Each bottle contains azithromycin dihydrate equivalent to 2 g of azithromycin. It is constituted with 60 mL of water and the entire contents are administered orally as a single dose.
- Zoloft oral concentrate is available in a multidose 60 mL bottle. Each milliliter of solution contains sertraline hydrochloride equivalent to 20 mg of sertraline. The solution contains the following inactive ingredients: glycerin, alcohol (12%), menthol, butylated hydroxytoluene (BHT).
- Zomig® (zolmitriptan) nasal spray contains zolmitriptan is supplied as a clear to pale yellow solution of zolmitriptan, buffered to a pH 5. Each Zomig nasal spray contains 5 mg of zolmitriptan in a 100-μL unit dose aqueous buffered solution containing citric acid, anhydrous USP, disodium phosphate dodecahydrate USP, and purified water USP. Zomig nasal spray is hypertonic. The osmolarity of Zomig nasal spray 5 mg is 420 to 470 mOsmol.
- Zyrtec syrup is a colorless to slightly yellow syrup containing cetirizine hydrochloride at a concentration of 1 mg/mL (5 mg/5 mL) for oral administration. The pH is between 4 and 5. The inactive ingredients of the syrup are banana flavor, glacial acetic acid, glycerin, grape flavor, methyl paraben, propylene glycol, propyl paraben, sodium acetate, sugar syrup, and water.

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Pharmaceutical Science

about the book...

While liquid drugs do not share the compression problems of solid dosage forms, the filling problems of powder dosage forms, or the consistency problems of semisolid dosage forms, they do have their own set of considerations in the formulation and manufacturing stages.

Highlights from ***Liquid Products, Volume Three*** include:

- practical details involved in complying with the current good manufacturing practice requirements in liquid manufacturing
- access to what an FDA auditor would be looking for during a liquid manufacturing audit
- issues that may arise during a US FDA inspection
- the protocols used for stability testing for new drugs and new dosage forms, drawn from the most current ICH guidelines

about the author...

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to the memory of John G. Wagner

Preface to the Series—Second Edition

The science and the art of pharmaceutical formulation keeps evolving as new materials, methods, and machines become readily available to produce more reliable, stable, and release-controlled formulations. At the same time, globalization of sourcing of raw and finished pharmaceuticals brings challenges to regulatory authorities and results in more frequent revisions to the current good manufacturing practices, regulatory approval dossier requirements, and the growing need for cost optimization. Since the publication of the first edition of this book, a lot has changed in all of these areas of importance to pharmaceutical manufacturers. The second edition builds on the dynamic nature of the science and art of formulations and provides an evermore useful handbook that should be highly welcomed by the industry, the regulatory authorities, as well as the teaching institutions.

The first edition of this book was a great success as it brought under one umbrella the myriad of choices available to formulators. The readers were very responsive and communicated with me frequently pointing out to the weaknesses as well as the strengths of the book. The second edition totally revised attempts to achieve these by making major changes to the text, some of which include:

1. Complete, revised errors corrected and subject matter reorganized for easy reference. Whereas this series has six volumes differentiated on the basis of the type of dosage form and a separate inclusion of the U.S. OTC products, ideally the entire collection is needed to benefit from the myriad of topics relating to formulations, regulatory compliance, and dossier preparation.
2. Total number of pages is increased from 1684 to 2726.
3. Total number of formulations is expanded by about 30% with many newly approved formulations.
4. Novel formulations are now provided for a variety of drugs; these data are collected from the massive intellectual property data and suggest toward the future trend of formulations. While some of these formulations may not have been approved in the United States or Europe, these do provide additional choices, particularly for the NDA preparation. As always, it is the responsibility of the manufacturer to assure that the intellectual property rights are not violated.
5. A significant change in this edition is the inclusion of commercial products; while most of this information is culled out from the open source such as the FOIA (http://www.fda.gov/foi/default.htm), I have made attempts to reconstruct the critical portions of it based on what I call the generally acceptable standards. The drug companies are advised to assure that any intellectual property rights are not violated and this applies to all information contained in this book. The freedom of information act (FOIA) is an extremely useful conduit for reliable information and manufacturers are strongly urged to make use of this information. Whereas this information is provided free of charge, the process of obtaining the information may be cumbersome, in which case, commercial sources of these databases can prove useful, particularly for the non-U.S. companies.
6. Also included are the new Good Manufacturing Guidelines (2007) with amendments (2008) for the United States and similar updates for European Union and WHO; it is strongly urged that the companies discontinue using all old documents as there are significant changes in the revised form, and many of them are likely to reduce the cost of GMP compliance.
7. Details on design of clean rooms is a new entry that will be of great use to sterile product manufacturers; whereas the design and flow of personnel and material flow is of critical nature, regulatory agencies view these differently and the manufacturer is advised always to comply with most stringent requirements.
8. Addition of a self-auditing template in each volume of the series. While the cGMP compliance is a complex issue and the requirements diversified across the globe, the basic compliance remains universal. I have chosen the European Union guidelines (as these are more in tune with the ICH) to prepare a self-audit module that I recommend that every manufacturer adopt as a routine to assure GMP compliance. In most instances reading the template by those responsible for compliance with keep them sensitive to the needs of GMP.
9. OTC products cross-referenced in other volumes where appropriate. This was necessary since the regulatory authorities worldwide define this class of drug differently. It is important to iterate that regardless of the prescription or the OTC status of a product, the requirements for compliance with the cGMP apply equally.
10. OTC monograph status is a new section added to the OTC volume and this should allow manufacturers to chose appropriate formulations that may not require a filing with the regulatory agencies; it is important to iterate that an approved OTC monograph includes details of formulation including the types and quantities of active drug and excipients, labeling, and presentation. To qualify the exemption, the manufacturer must comply with the monograph in its entirety. However, subtle modifications that are merely cosmetic in nature and where there is an evidence that the modification will not affect the safety and efficacy of the products can be made but require prior approval of the regulatory agencies and generally these approvals are granted.
11. Expanded discussion on critical factors in the manufacturing of formulations provided; from basic shortcuts to smart modifications now extend to all dosage forms. Pharmaceutical compounding is one of the oldest professions and whereas the art of formulations has been

relegated to more objective parameters, the art nevertheless remains. An experienced formulator, like an artist, would know what goes with what and why; he avoids the pitfalls and stays with conservative choices. These sections of the book present advice that is time tested, although it may appear random at times; this is intended for experienced formulators.

12. Expanded details on critical steps in the manufacturing processes provided but to keep the size of the book manageable, and these are included for prototype formulations. The reader is advised to browse through similar formulations to gain more insight. Where multiple formulations are provided for the same drug, it intended to show the variety of possibilities in formulating a drug and whereas it pertains to a single drug, the basic formulation practices can be extended to many drugs of same class or even of diversified classes. Readers have often requested that more details be provided in the Manufacturing Direction sections. Whereas sufficient details are provided, this is restricted to prototype formulations to keep the size of the book manageable and to reduce redundancy.
13. Addition of a listing of approved excipients and the level allowed by regulatory authorities. This new section allows formulators a clear choice on which excipients to choose; the excipients are reported in each volume pertaining to the formulation type covered. The listing is drawn from the FDA-approved entities. For the developers of an ANDA, it is critical that the level of excipients be kept within the range generally approved to avoid large expense in justifying any unapproved level. The only category for which the listing is not provided separately is the OTC volume since it contains many dosage forms and the reader is referred to dosage form–specific title of the series. The choice of excipients forms keeps increasing with many new choices that can provide many special release characteristics to the dosage forms. Choosing correct excipients is thus a tedious exercise and requires sophisticated multivariate statistical analysis. Whereas the formulator may choose any number of novel or classical components, it is important to know the levels of excipients that are generally allowed in various formulations to reduce the cost of redundant exercises; I have therefore included, as an appendix to each volume, a list of all excipients that are currently approved by the U.S. FDA along their appropriate levels. I suggest that a formulator consult this table before deciding on which level of excipient to use; it does not mean that the excipient cannot be used outside this range but it obviates the need for a validation and lengthy justification studies in the submission of NDAs.
14. Expanded section on bioequivalence submission was required to highlight the recent changes in these requirements. New entries include a comprehensive listing of bioequivalence protocols in abbreviated form as approved by the U.S. FDA; these descriptions are provided in each volume where pertinent. To receive approval for an ANDA, an applicant must generally demonstrate, among other things, equivalence of the active ingredient, dosage form, strength, route of administration and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. Bioequivalent drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 U.S.C. 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320. The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-specific BE studies, the U.S. FDA will be issuing product-specific BE recommendations (www.fda.gov/cder/ogd/index.htm). To make this vital information available, an appendix to each volume includes a summary of all currently approved products by the U.S. FDA where a recommendation on conducting bioequivalence studies is made available by the U.S. FDA. When filing an NDA or an ANDA, the filer is faced with the choice of defending the methods used to justify the bioavailability or bioequivalence data. The U.S. FDA now allows application for waiver of bioequivalence requirement; a new chapter on this topic has been added along with details of the dissolution tests, where applicable, approved for various dosage forms.
15. Dissolution testing requirements are included for all dosage forms where this testing is required by the FDA. Surrogate testing to prove efficacy and compliance is getting more acceptance at regulatory agencies; in my experience, a well-designed dissolution test is the best measure of continuous compliance. Coupled with chapters on waivers of bioequivalence testing, this information on dissolution testing should be great value to all manufacturers; it is recommended that manufacturers develop their own in-house specifications, more stringent than those allowed in these listings and the USP.
16. Best-selling products (top 200 prescription products) are identified with an asterisk and a brand name where applicable; in all instances, composition of these products is provided and formulation of generic equivalents. Despite the vast expansion of pharmaceutical sales and shifting of categories of blockbuster drugs, basic drugs affecting gastrointestinal tract, vascular system, and brain remain most widely prescribed.
17. Updated list of approved coloring agents in the United States, Canada, European Union, and Japan is included to allow manufactures to design products for worldwide distribution.
18. Tablet-coating formulations that meet worldwide requirements of color selection are included in the Volume 1 (compressed solids) and Volume 5 (OTC) because these represent the products often coated.
19. Guidelines on preparing regulatory filings are now dispersed throughout the series depending on where these guidelines are more crucial. However, the reader would, as before, need access to all volumes to benefit from the advice and guidelines provided.

As always, comments and criticism from the readers are welcomed and these can be sent to me at Niazi@pharmsci.com or Niazi@niazi.com. I would try to respond to any inquiries requiring clarification of the information enclosed in these volumes.

I would like to express deep gratitude to Sherri R. Niziolek and Michelle Schmitt-DeBonis at Informa, the publisher of

this work, for seeing an immediate value to the readers in publishing the second edition of this book and allowing me enough time to prepare this work. The diligent editing and composing staff at Informa, particularly Joseph Stubenrauch, Baljinder Kaur and others are highly appreciated. Regardless, all errors and omissions remain altogether mine.

In the first edition, I had dedicated each volume to one of my mentors; the second edition continues the dedication to these great teachers.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois, U.S.A.

Preface to the Series—First Edition

No industry in the world is more highly regulated than the pharmaceutical industry because of potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity (amortized over the cost of all molecules racing) to final regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. In the year 2004, it is anticipated that the industry will spend about $20 billion on research and development. The generic market of drugs as the new entities come off patent is one of the fastest growing segments of the pharmaceutical industry, with every major multinational company having a significant presence in this field.

Whereas many stages of new drug development are inherently constrained with time, the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced with appropriate knowledge by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the first major attempt to consolidate the available knowledge about formulations in a comprehensive, and by nature a rather voluminous, presentation.

The book is divided into six volumes, based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and OTC products. The separation of OTC products, even though they may easily fall into one of the other five categories, is made to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of product, and of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of products into these six categories.

Each volume includes a description of regulatory filing techniques for the formulations described. Also included are the current regulatory guidelines on cGMP compliance specific to the dosage form. Advice is offered on how to scale up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and cut the race to file short by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a close paradigm when it comes to selecting formulations—"not invented here" perhaps reigns in the mind of many seasoned formulations scientists subconsciously when they prefer to choose only a certain platform for development. It is expected that with the quick review of possibilities available to formulate made available in this book, scientists will benefit from the experience of others.

For the teachers of formulation sciences, this series offers a wealth of information. Whether it is a selection of a preservative system or the choice of a disintegrant, the series offers a wide choice to study and rationalize.

Many have assisted me in the development of this work that has taken years to compile, and I thank scores of my graduate students and colleagues for their help. A work of this size cannot be produced without errors, although I hope that these errors do not distract the reader from the utility of the book. I would sincerely appreciate if readers point out these mistakes for corrections in future editions.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois, U.S.A.

Preface to the Volume—First Edition

The semisolid drugs category is composed of ointments, creams, gels, suppositories, and special topical dosage forms. They share many common attributes of consistency, presentation, preservation requirement, and the route of administration, mainly topical. As a result, grouping them together for the purpose of defining common formulation practices and problems is justified. The topical dosage forms present unique opportunities to design novel drug delivery systems such as patches and other transdermal systems. Some of these are described in the volume, but the reader is referred to specific patents issued, wherein greater details are readily obtainable. In selecting the formulations, I have tried to provide representative techniques and technologies involved in the preparation of semisolid products; for example, I have included a significant number of what is called "base" formulation, a formulation that can easily carry a drug, depending on the proportion involved. Obviously, considerations such as incompatability of the drug with the ingredients is of pivotal importance; these base formulations of stable emulsions provide a good starting point in the development of new products or even when a different topical consistency is desired. I have also made an effort to highlight those formulations that are currently approved in the United States and provide them as they appear in the Physicans Desk Reference, where possible. Obviously, where the formulations are straightforward, I have chosen to only give the composition or mere identification of ingredients to conserve space for those formulations that need more elaborate description.

The regulatory agencies impose certain specific requirements on the formulation and efficacy determination of drugs contained in these formulations. For example, the cGMP factors, scale-up and postapproval changes, and dermatological testing for irritation or photosensitivity are some of the specified elements.

In this volume, we present over 350 formulations and, in keeping with the tradition in other volumes, a chapter on formulation-related matters. In the regulatory section, we offer a difficult area of compliance, changes to approved new drug applications (NDAs), and abbreviated new drug applications (ANDAs), particularly with reference to semisolid drugs. The stability considerations, particularly the evolving guidelines of the International Conference on Harmonization (ICH), are detailed in this volume, with particular reference to stability-testing requirements in postapproval stages. Unique to this category is the dermal testing of products, including photosensitivity-testing requirements that are still evolving. It is noteworthy that much of the regulatory discussion presented here is drawn from the requirements of the U.S. Food and Drug Administration (FDA) and the harmonized guidelines with the ICH listings. Although it is likely that some of the requirements and recommendations made here might change, it is unlikely that the basic thrust in establishing these guidelines will change. As always, the applicants are highly encouraged to communicate with the FDA on the changes made to these guidelines and especially for any significant changes made to compliance requirements. The Web site of the FDA, http://www.fda.gov, is very comprehensive and continuously evolving; pay special attention to the withdrawal and finalization of guidelines provided. Of particular importance is the listing of new and withdrawn guidelines (http://www.fda.gov/cder/guidance/New-Revised-Withdrawn.PDF), which should be reviewed periodically.

Chapter 1 provides details on how to handle changes made to approved NDAs or ANDAs; this is a significant topic for continued compliance with the cGMP requirements but, unfortunately, the one that is most easily misunderstood or misconstrued. For example, at what level of change should the FDA be informed, either before making a change or after? What happens if a change is made inadvertently and later discovered; how to report this change? Years of experience teaches me that a manufacturer can never be too careful in avoiding a 483 issuance when it comes to changes made to NDAs or ANDAs. The situation gets extremely complex when there are multiple dosage forms, for which the requirements may be different.

Chapter 2 gets into details of changes made pursuant to discussion in chapter 1 when it comes to semisolid drugs. A more detailed description of level of changes is described here, and advice is provided on when to conduct a regulatory review.

Chapter 3 continues the themes developed in the first two chapters and applies to changes made to equipment. This is a topic of special interest to the FDA because in the processing of semisolid products, the equipment plays a pivotal role. The mixing of drugs within the base media is highly affected by the process and mechanism of mixing used. Also, because of the nature of product manufactured, often the cleaning and validation of equipment become serious issues.

Chapter 4 is a comprehensive review of the present thinking of the regulatory authorities on how the stability studies should be designed and conducted and how the data should be interpreted; the induction of ICH guidelines and an attempt to streamline the requirements of testing new drug products have resulted in much dispute when it comes to global marketing of products. Should the stability testing be done at all environmental regional standards, or is it possible to extrapolate these data based on accelerated stability testing? These are some of the questions answered in this chapter, wherein the FDA and ICH guidelines are merged.

Chapter 5 extends the discussion on stability-testing protocols to retest periods and elaborates on the procedures used for continued testing of products.

Chapter 6 introduces a topic of great importance in the development of semisolid, and particularly dermal, products: skin irritation and sensitization studies. Whereas the standard test protocols have almost become universal in their nature, it is always advised that these should be agreed on, most appropriately in a pre-investigational new drug application (IND) filing. Established in 1988, the Office of Drug Evaluation IV (ODE IV) Pre-IND Consultation Program is

designed to facilitate and foster informal early communications between the divisions of ODE IV and potential sponsors of new therapeutics for the treatment of bacterial infections, HIV, opportunistic infections, transplant rejection, and other diseases. The program is intended to serve sponsors of all drug products that may be submitted to any division within ODE IV, including but not limited to drugs for the treatment of life-threatening illnesses [21 CFR 312.82(a)]. Pre-IND advice may be requested for issues related to drug development plans; data needed to support the rationale for testing a drug in humans; the design of nonclinical pharmacology, toxicology, and drug activity studies; data requirements for an IND application; and regulatory requirements for demonstrating safety and efficacy. Included among the ODE IV Pre-IND Program activities are coordination of all Pre-IND interactions with the FDA Topical Microbicide Working Group.

Chapter 7 deals with the topic of photosensitivity caused by drugs; photosafety is a serious issue in the development of topical products. It is worth noting here that certain classes of drugs such as quinolone antibiotics are generally regarded unsafe without thorough testing for photosensitivity. Does photosensitivity correlate with carcinogenicity? These are questions of importance to the regulatory authorities. Chapter 8 includes a variety of topics related to formulation of semisolid drugs, from cGMP considerations to packaging and validation issues; these topics are collated for their particular importance, but the discussions provided are not comprehensive, and the reader is referred to standard texts on formulation theories, particularly where establishing a preservative system is required.

I am grateful to CRC Press for taking this lead in publishing what is possibly the largest such work in the field of pharmaceutical manufacturing. It has been a distinct privilege to have known Mr. Stephen Zollo, the Senior Editor at CRC Press, for years. Stephen has done more than any editor can to encourage me into completing this work on a timely basis. The editorial assistance provided by CRC Press staff was indeed exemplary, particularly the help given by Erika Dery, Naomi Lynch, and others. Although much care has gone into correcting errors, any errors remaining are altogether mine. I shall appreciate the readers bringing these to my attention for correction in future editions of this volume (niazi@pharmsci.com).

This volume is dedicated to John G. Wagner, the John G. Searle Professor Emeritus of Pharmaceutics in the College of Pharmacy and Professor Emeritus of Pharmacology in the Medical School, who passed away recently. Born in Weston, Ontario, Canada, in 1921, Wagner served in the Canada Air Force during World War II and then worked as a research scientist for the Upjohn Co. from 1953 to 1968, joining the University of Medicine in 1968. Wagner was the author of two books and coauthor of more than 340 articles. Throughout his life he received numerous awards, including the American Pharmaceutical Association (APhA) Ebert Prize, 1961; Academy Fellow of the AphA Academy of Pharmaceutical Sciences, 1969; the Centennial Achievement Award, Ohio State University, 1970; the Host-Madsen Medal, Federation Internationale Pharmaceutique, 1972; Outstanding Leadership and Research Award, Delta Chapter of Phi Lambda Epsilon, 1983; AAPS Fellow, American Association of Pharmaceutical Scientists, 1986; and Distinguished Professor, Michigan Association of Governing Boards, 1988. Following retirement, Wagner worked as a consultant to Upjohn, Schering Corp., Warner-Lambert/Parke-Davis, the Food and Drug Administration, and others. John Wagner became famous with the publication of his book, *Biopharmaceutics and Relevant Pharmacokinetics*; he then followed with other books on the subject of pharmacokinetics. This was the time, in the early 1970s, when the discipline of mathematical pharmacokinetics was in its infancy; its creation spearheaded by such giants as Sid Riegelman, Milo Gibaldi, and Gerhard Levy. John took the lead in infusing complex mathematics to the resolution of pharmacokinetic modeling approach; his savvy of introducing Laplace transforms to all kinetics problems bears well in my mind. I never found it difficult to get lost somewhere in the long chain of mathematical transformations; John could easily make any model mathematically awesome. I met John several times when I had invited him to speak at the institutions where I was working to frequent meetings at the Academy of Pharmaceutical Science. John was a slim, trim man who spoke with a comparably lean choice of words. He was indeed a leader, a remarkable educator, and someone who left many indelible impressions on the students in his era—including me.

Sarfaraz K. Niazi, Ph.D.
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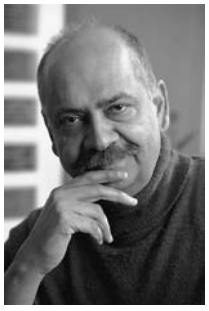
About the Author



Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 35 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents in the field of drug and dosage form delivery systems; he is also licensed to practice law before the U.S. Patent and Trademark Office. Having formulated hundreds of products from the most popular consumer entries to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science and art of formulating and regulatory filings of investigational new drugs (INDs) and new drug applications (NDAs). Dr. Niazi advises the pharmaceutical industry internationally on issues related to formulations, cGMP compliance, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (http://www.pharmsci.com). He can be contacted at Niazi@pharmsci.com

Contents

Part I

Regulatory and Manufacturing Guidance

1

Waiver of In Vivo Bioequivalence Study

I. INTRODUCTION

Bioavailability and bioequivalence studies are expensive to conduct and given the need for multitude of these studies in the development of an NDA or ANDA, there had always existed a need to justify these needs on scientific grounds. This is particularly important for the generic drug industry since the generic competitors must keep their cost of regulatory approval to as low a level as possible. Recently, guidelines have emerged that would allow waiver of both BA and BE studies in some situations. There are also provisions available for the sponsor to challenge the requirement and if the basic criteria set are met, there is a very good possibility of receiving waivers. These waivers are intended to apply to the following:

- Subsequent in vivo BA or BE studies of formulations after the initial establishment of the in vivo BA of immediate-release (IR) dosage forms during the IND period.
- In vivo BE studies of IR dosage forms in ANDAs. Regulations at 21 CFR part 320 address the requirements for bioavailability (BA) and BE data for approval of drug applications and supplemental applications.

Provision for waivers of in vivo BA/BE studies (biowaivers) under certain conditions is provided at 21 CFR 320.22.

Waiver for bioequivalence testing therefore becomes a topic of great interest worldwide. Several consortiums have debated this topic for years and a consensus has begun to develop on this topic. A large number of policy documents address this topic and include the published FDA and ICH guidelines, Health Canada's Guideline on Preparation of DIN Submissions, WHO document (1999) entitled "Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products: a Manual for Drug Regulatory Authorities, Multisource (Generic) Pharmaceutical Products: Guidelines on Registration Requirements to Establish Interchangeability," Note for Guidance on the Investigation of Bioavailability and Bioequivalence, Committee for Proprietary Medicinal Products (CPMP), 26 July 2001 (CPMP/EWP/QWP/98), and Pan-American Network on Regulatory harmonization: Bioavailability and Bioequivalence working group 2004.

The requirement for the in vivo bioequivalence study may be waived for certain generic products [21 USC 360 b (n) (1) (E)]. Categories of products which may be eligible for waivers include, but are not limited to, the following:

- Parenteral solutions intended for injection by the intravenous, subcutaneous, or intramuscular routes of administration.
- Oral solutions or other solubilized forms.
- Topically applied solutions intended for local therapeutic effects. Other topically applied dosage forms intended for local therapeutic effects for nonfood animals only.
- Inhalant volatile anesthetic solutions.

This guidance provides recommendations for sponsors of investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplements to these applications that wish to request a waiver of in vivo bioavailability (BA) or bioequivalence (BE) studies for immediate-release (IR) solid oral dosage forms. These waivers apply to

1. subsequent in vivo BA or BE studies of formulations after the initial establishment of the in vivo BA of IR dosage forms during the IND period and
2. in vivo BE studies of IR dosage forms in ANDAs

Regulations at 21 CFR Part 320 address the requirements for bioavailability (BA) and BE data for approval of drug applications and supplemental applications. Provision for waivers of in vivo BA/BE studies (biowaivers) under certain conditions is provided at 21 CFR 320.22. This guidance explains when biowaivers can be requested for IR solid oral dosage forms based on an approach termed the biopharmaceutics classification system (BCS).

II. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms: dissolution, solubility, and intestinal permeability. According to the BCS, drug substances are classified as follows:

Class 1: High solubility—high permeability
Class 2: Low solubility—high permeability
Class 3: High solubility—low permeability
Class 4: Low solubility—low permeability

In addition, IR solid oral dosage forms are categorized as having rapid or slow dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool to help sponsors justify requests for biowaivers. There are several factors that affect classification of drugs in different classes. Table 1.1 expands this classification to include a more detailed description including the effect of transporter efflux factors.

Observed in vivo differences in the rate and extent of absorption of a drug from two pharmaceutically equivalent solid oral products may be due to differences in drug dissolution in vivo. However, when the in vivo dissolution of an IR solid oral dosage form is rapid in relation to gastric emptying and the drug has high permeability, the rate and extent of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal transit time. Under such circumstances, demonstration of in vivo BA or BE may not be necessary for drug products containing Class 1 drug

Table 1.1 The Biopharmaceutics Classification System (BCS) as Defined by the FDA and Modified by Recent Findings

	High solubility (e.g., when the highest dose strength is soluble in 250 mL or less of aqueous media over a pH range of 1–7.5 at 37°C)	Low solubility
High permeability (e.g., absorption >90% compared to intravenous dose) (drug + metabolite).	Class 1: (generally about 8% of new leads) • High solubility • High permeability • Rapid dissolution for biowaiver • Route of elimination: metabolism, extensive. • Transporter effects: minimal Examples: Abacavir; Acetaminophen; *Acyclovir*[b]; *Amiloride*[S, I]; Amitryptyline[S, I]; Antipyrine; *Atropine*; **Buspirone**[c]; Caffeine; *Captopril*; **Chloroquine**[S, I]; Chlorpheniramine; Cyclophosphamide; Desipramine; **Diazepam**; **Diltiazem**[S, I]; **diphenhydramine**; Disopyramide; **Doxepin**; oxycycline; Enalapril; Ephedrine; Ergonovine; Ethambutol; Ethinyl estradiol; Fluoxetine[I]; Glucose; Imipramine[I]; Ketoprofen; **Ketorolac**; Labetalol; Levodopa[S]; Levofloxacin[S]; **Lidocaine**[I]; Lomefloxacin; **Meperidine**; Metoprolol; Metronidazole; Midazolam[S, I]; Minocycline; Misoprostol; Nifedipine[S]; Phenobarbital; Phenylalanine; Prednisolone; **Primaquine**[S]; Promazine; Propranolol[I]; **Quinidine**[S, I]; **Rosiglitazone**; Salicylic acid; Theophylline; Valproic acid; **Verapamil**[I]; Zidovudine	Class 2: • Low solubility • High permeability • Route of elimination: metabolism, extensive. • Transporter: efflux transporter effects predominant Examples: **Amiodarone**[I]; **Atorvastatin**[S, I]; **Azithromycin**[S, I]; **Carbamazepine**[S, I]; **Carvedilol**; Chlorpromazine[I]; *Ciprofloxacin*[S]; **Cisapride**[S]; **Cyclosporine**[S, I]; **Danazol**; **Dapsone**; Diclofenac; Diflunisal; Digoxin[S]; *Erythromycin*[S, I]; Flurbiprofen; **Glipizide**; Glyburide[S, I]; Griseofulvin; Ibuprofen; **Indinavir**[S]; **Indomethacin**; **Itraconazole**[S, I]; **Ketoconazole**[I]; **Lansoprazole**[I]; **Lovastatin**[S, I]; *Mebendazole*; Naproxen; Nelfinavir[S, I]; Ofloxacin; Oxaprozin; Phenazopyridine; Phenytoin[S]; Piroxicam; Raloxifene[S]; **Ritonavir**[S, I]; **Saquinavir**[S, I]; Saquinavir[S, I]; **Sirolimus**[S]; Spironolactone[I]; **Tacrolimus**[S, I]; Talinolol[S]; **Tamoxifen**[I]; **Terfenadine**[I]; Warfarin
Low permeability	Class 3: • High solubility • Low permeability • Route of elimination: renal and/or biliary elimination of unchanged drug; metabolism poor • Transporter: absorptive effects predominant Examples: *Acyclovir*; *Amiloride*[S, I]; Amoxicillin[S, I]; Atenolol; *Atropine*; Bidisomide; Bisphosphonates; *Captopril*; Cefazolin; Cetirizine; Cimetidine[S]; *Ciprofloxacin*[S]; Cloxacillin; Dicloxacillin[S]; *Erythromycin*[S, I]; Famotidine; Fexofenadine[S]; Folinic acid; *Furosemide*; Ganciclovir; *Hydrochlorothiazide*; Lisinopril; Metformin; *Methotrexate*; Nadolol; Penicillins; Pravastatin[S]; Ranitidine[S]; Tetracycline; Trimethoprim[S]; Valsartan; Zalcitabine	Class 4: • Low solubility • Low permeability • Route of elimination: renal and/or biliary elimination of unchanged drug; metabolism poor • Transporter: absorptive and efflux transporters can be predominant Examples: Amphotericin B; Chlorothiazide; Chlorthalidone; *Ciprofloxacin*[S]; Colistin; *Furosemide*; *Hydrochlorothiazide*; *Mebendazole*; *Methotrexate*; Neomycin

Notes: The compounds listed in *italic* are those falling in more than one category by different authors, which could be a result of the definition of the experimental conditions. The compounds listed in bold are primarily CYP3A substrates where metabolism accounts for more than 70% of the elimination; superscript I and/or S indicate P-gp inhibitors and/or substrate, respectively. The Class 1 and Class 2 compounds are eliminated primarily via metabolism, whereas Class 3 and Class 4 compounds are primarily eliminated unchanged into the urine and bile.

substances, as long as the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients. The BCS approach outlined in this guidance can be used to justify biowaivers for *highly soluble* and *highly permeable* drug substances (i.e., Class 1) in IR solid oral dosage forms that exhibit *rapid in vitro dissolution* using the recommended test methods [21 CFR 320.22(e)].

Several generalizations can be made about the interplay of transporters and the BCS classification.

a. ***Transporter effects are minimal for Class 1 compounds.*** The high permeability/high solubility of such compounds allows high concentrations in the gut to saturate any transporter, both efflux and absorptive. Class 1 compounds may be substrates for both uptake and efflux transporters in vitro in cellular systems under the right conditions [e.g., midazolam and nifedipine are substrates for P-glycoprotein (P-gp)], but transporter effects will not be important clinically. It is therefore possible that some compounds that should be considered Class 1 in terms of drug absorption and disposition are not Class 1 in BCS due to the requirement of good solubility and rapid dissolution at low pH values. Such pH effects would not be limiting in vivo where absorption takes place from the intestine. Examples of this include the NSAIDs diclofenac, diflunisal, flurbiprofen, indomethacin, naproxen, and piroxicam; warfarin is almost completely bioavailable. In contrast, ofloxacin is listed as Class 2 because of its low solubility at pH 7.5.
b. ***Efflux transporter effects will predominate for Class 2 compounds.*** The high permeability of these compounds will allow ready access into the gut membranes and uptake transporters will have no effect on absorption, but the low solubility will limit the concentrations coming into the enterocytes, thereby preventing saturation of the efflux transporters. Consequently, efflux transporters will affect the extent of oral bioavailability and the rate of absorption of Class 2 compounds.
c. ***Transporter-enzyme interplay in the intestines will be important primarily for Class 2 compounds that are substrates for CYP3A and Phase 2 conjugation enzymes.*** For such compounds, intestinal uptake transporters will generally be unimportant due to the rapid permeation of the drug molecule into the enterocytes as a function of their high lipid solubility. That is, absorption of Class 2 compounds is primarily passive and a function of lipophilicity. However, because of the low solubility of these compounds, there will be little opportunity to saturate apical efflux transporters and intestinal enzymes such as cytochrome P450 3A4 (CYP3A4) and UDP-glucuronosyltransferases (UGTs). Thus, changes in transporter expression and inhibition or induction of efflux transporters will cause changes in intestinal metabolism of drugs that are substrates for the intestinal metabolic enzymes. Note the large number of Class 2 compounds in Table 1.1 that are primarily substrates for CYP3A (compounds listed in bold) as well as substrates or inhibitors of the efflux transporter P-gp (indicated by superscripts S and I, respectively). Work in our laboratory has characterized this interplay in the absorptive process for the investigational cysteine protease inhibitor K77 (28, 32) and sirolimus (29), substrates for CYP3A and P-gp, and more recently for raloxifene (33), a substrate for UGTs and P-gp.
d. ***Absorptive transporter effects will predominate for Class 3 compounds.*** For Class 3 compounds, sufficient drug will be available in the gut lumen due to good solubility, but an absorptive transporter will be necessary to overcome the poor permeability characteristics of these compounds. However, intestinal apical efflux transporters may also be important for the absorption of such compounds when sufficient enterocyte penetration is achieved via an uptake transporter.

Table 1.2 Model Drugs to Establish Permeability of Drugs

Drug	Permeability Class
Antipyrine	High (potential IS candidate)
Caffeine	High
Carbamazepine	High
Fluvastatin	High
Ketoprofen	High
Metoprolol	High (potential IS candidate)
Naproxen	High
Propranolol	High
Theophylline	High
Verapamil	High (potential ES candidate)
Amoxicillin	Low
Atenolol	Low
Furosemide	Low
Hydrochlorthiazide	Low
Mannitol	Low (potential IS candidate)
Methyldopa	Low
Polyethylene glycol (400)	Low
Polyethylene glycol (1000)	Low
Polyethylene glycol (4000)	Low (zero permeability marker)
Ranitidine	Low

Table 1.2 lists model drugs suggested for use in establishing suitability of a permeability method. The permeability of these compounds was determined based on data available to the FDA. Potential *internal standards* (IS) and *efflux pump substrates* (ES) are also identified.

For application of the BCS, an apparent passive transport mechanism can be assumed when one of the following conditions is satisfied:

- A linear (pharmacokinetic) relationship between the dose (e.g., relevant clinical dose range) and measures of BA (area under the concentration-time curve) of a drug is demonstrated in humans.
- Lack of dependence of the measured in vivo or in situ permeability is demonstrated in an animal model on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 mL) in the perfusion fluid.
- Lack of dependence of the measured in vitro permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 times the highest dose strength dissolved in 250 mL) is demonstrated in donor fluid and transport direction (e.g., no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected) using a suitable in vitro cell culture method that has been shown to express known efflux transporters (e.g., P-gp).

To demonstrate suitability of a permeability method intended for application of the BCS, a rank-order relationship between test permeability values and the extent of drug absorption data in human subjects should be established using a sufficient number of model drugs. For in vivo intestinal perfusion studies in humans, six model drugs are recommended. For in vivo or in situ intestinal perfusion studies in animals and for in vitro cell culture methods, 20 model drugs are recommended. Depending on study variability, a sufficient

number of subjects, animals, excised tissue samples, or cell monolayers should be used in a study to provide a reliable estimate of drug permeability. This relationship should allow precise differentiation between drug substances of low- and high-intestinal permeability attributes.

For demonstration of suitability of a method, model drugs should represent a range of low (e.g., <50%), moderate (e.g., 50–89%), and high (≥90%) absorption. Sponsors may select compounds from the list of drugs and/or chemicals provided in Attachment A or they may choose to select other drugs for which there is information available on mechanism of absorption and reliable estimates of the extent of drug absorption in humans.

After demonstrating suitability of a method and maintaining the same study protocol, it is not necessary to retest all selected model drugs for subsequent studies intended to classify a drug substance. Instead, a low- and a high-permeability model drug should be used as IS (i.e., included in the perfusion fluid or donor fluid along with the test drug substance). These two IS are in addition to the fluid volume marker (or a zero permeability compound such as Polyethylene glycol 4000) that is included in certain types of perfusion techniques (e.g., closed loop techniques). The choice of IS should be based on compatibility with the test drug substance (i.e., they should not exhibit any significant physical, chemical, or permeation interactions). When it is not feasible to follow this protocol, the permeability of IS should be determined in the same subjects, animals, tissues, or monolayers, following evaluation of the test drug substance. The permeability values of the two IS should not differ significantly between different tests, including those conducted to demonstrate suitability of the method. At the end of an in situ or in vitro test, the amount of drug in the membrane should be determined.

For a given test method with set conditions, selection of a high-permeability internal standard with permeability in close proximity to the low-/high-permeability class boundary may facilitate classification of a test drug substance. For instance, a test drug substance may be determined to be highly permeable when its permeability value is equal to or greater than that of the selected internal standard with high permeability.

The recommended methods for determining solubility, permeability, and in vitro dissolution are discussed below.

A. Solubility

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a biowaiver request. A drug substance is considered *highly soluble* when the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250 mL is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water.

B. Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., in vitro epithelial cell culture methods). In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered *highly permeable* when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.

C. Dissolution

In this guidance, an IR drug product is considered *rapidly dissolving* when no less than 85% of the labeled amount of the drug substance dissolves within 30 min, using U.S. Pharmacopoeia (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm) in a volume of 900 mL or less in each of the following media:

1. 0.1 N HCl or Simulated Gastric Fluid USP without enzymes
2. A pH 4.5 buffer
3. A pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes

III. METHODOLOGY FOR CLASSIFYING A DRUG SUBSTANCE AND FOR DETERMINING THE DISSOLUTION CHARACTERISTICS OF A DRUG PRODUCT

The following approaches are recommended for classifying a drug substance and determining the dissolution characteristics of an IR drug product according to the BCS.

A. Determining Drug Substance Solubility Class

An objective of the BCS approach is to determine the equilibrium solubility of a drug substance under physiological pH conditions. The pH-solubility profile of the test drug substance should be determined at $37 \pm 1^{\circ}C$ in aqueous media with a pH in the range of 1 to 7.5. A sufficient number of pH conditions should be evaluated to accurately define the pH-solubility profile. The number of pH conditions for a solubility determination can be based on the ionization characteristics of the test drug substance. For example, when the pKa of a drug is in the range of 3 to 5, solubility should be determined at pH = pKa, pH = pKa + 1, pH = pKa −1, and at pH = 1 and 7.5. A minimum of three replicate determinations of solubility in each pH condition is recommended. Depending on study variability, additional replication may be necessary to provide a reliable estimate of solubility. Standard buffer solutions described in the USP are considered appropriate for use in solubility studies. If these buffers are not suitable for physical or chemical reasons, other buffer solutions can be used. Solution pH should be verified after addition of the drug substance to a buffer. Methods other than the traditional shake-flask method, such as acid or base titration methods, can also be used with justification to support the ability of such methods to predict equilibrium solubility of the test drug substance. Concentration of the drug substance in selected buffers (or pH conditions) should be determined using a validated stability-indicating assay that can distinguish the drug substance from its degradation products (http://www.fda.gov/cder/guidance/P147_9604 #P147_9604). If degradation of the drug substance is observed as a function of buffer composition or pH, it should be reported along with other stability data recommended in section III.B.3.

The solubility class should be determined by calculating the volume of an aqueous medium sufficient to dissolve the highest dose strength in the pH range of 1 to 7.5. A drug substance should be classified as highly soluble when the highest dose strength is soluble in £250 mL of aqueous media over the pH range of 1 to 7.5.

B. Determining Drug Substance Permeability Class

The permeability class of a drug substance can be determined in human subjects using mass balance, absolute BA, or intestinal perfusion approaches. Recommended methods not involving human subjects include in vivo or in situ intestinal perfusion in a suitable animal model (e.g., rats), in vitro permeability methods using excised intestinal tissues, or monolayers of suitable epithelial cells. In many cases, a single method may be sufficient (e.g., when the absolute BA is 90% or more, or when 90% or more of the administered drug is recovered in urine). When a single method fails to conclusively demonstrate a permeability classification, two different methods may be advisable. Chemical structure or certain physicochemical attributes of a drug substance (e.g., partition coefficient in suitable systems) can provide useful information about its permeability characteristics. Sponsors may wish to consider use of such information to further support a classification.

1. Pharmacokinetic Studies in Humans

a. Mass Balance Studies

Pharmacokinetic mass balance studies using unlabeled, stable isotopes, or a radiolabeled drug substance can be used to document the extent of absorption of a drug. Depending on the variability of the studies, a sufficient number of subjects should be enrolled to provide a reliable estimate of extent of absorption. Because this method can provide highly variable estimates of drug absorption for many drugs, other methods described below may be preferable.

b. Absolute Bioavailability Studies

Oral BA determination using intravenous administration as a reference can be used. Depending on the variability of the studies, a sufficient number of subjects should be enrolled in a study to provide a reliable estimate of the extent of absorption. When the absolute BA of a drug is shown to be 90% or more, additional data to document drug stability in the gastrointestinal fluid is not necessary.

The following methods can be used to determine the permeability of a drug substance from the gastrointestinal tract: (1) in vivo intestinal perfusion studies in humans, (2) in vivo or in situ intestinal perfusion studies using suitable animal models, (3) in vitro permeation studies using excised human or animal intestinal tissues, or (4) in vitro permeation studies across a monolayer of cultured epithelial cells.

In vivo or in situ animal models and in vitro methods, such as those using cultured monolayers of animal or human epithelial cells, are considered appropriate for passively transported drugs. The observed low permeability of some drug substances in humans could be caused by efflux of drugs via membrane transporters such as P-gp. When the efflux transporters are absent in these models, or their degree of expression is low compared to that in humans, there may be a greater likelihood of misclassification of permeability class for a drug subject to efflux compared to a drug transported passively. Expression of known transporters in selected study systems should be characterized. Functional expression of efflux systems (e.g., P-gp) can be demonstrated with techniques such as bidirectional transport studies, demonstrating a higher rate of transport in the basolateral-to-apical direction as compared to apical-to-basolateral direction using selected model drugs or chemicals at concentrations that do not saturate the efflux system (e.g., cyclosporin A, vinblastine, rhodamine 123). An acceptance criterion for intestinal efflux that should be present in a test system cannot be set at this time. Instead, this guidance recommends limiting the use of nonhuman permeability test methods for drug substances that are transported by passive mechanisms. Pharmacokinetic studies on dose linearity or proportionality may provide useful information for evaluating the relevance of observed in vitro efflux of a drug. For example, there may be fewer concerns associated with the use of in vitro methods for a drug that has a higher rate of transport in the basolateral-to-apical direction at low drug concentrations but exhibits linear pharmacokinetics in humans.

Poor absorption or permeation is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight is greater than 500, and the calculated Log P is greater than 5. This is also often referred to as Rule 5 of Lipinsky. However, Lipinski specifically states that the Rule of 5 only holds for compounds that are *not* substrates for active transporters. Since almost all drugs are substrates for some transporter, much remains to be studied about the Lipinsky's rule. In addition, unless a drug molecule can passively gain intracellular access, it is not possible to simply investigate whether the molecule is a substrate for efflux transporters.

2. Intestinal Permeability Methods

The following methods can be used to determine the permeability of a drug substance from the gastrointestinal tract:

1. In vivo intestinal perfusion studies in humans
2. In vivo or in situ intestinal perfusion studies using suitable animal models
3. In vitro permeation studies using excised human or animal intestinal tissues
4. In vitro permeation studies across a monolayer of cultured epithelial cells

In vivo or in situ animal models and in vitro methods, such as those using cultured monolayers of animal or human epithelial cells, are considered appropriate for passively transported drugs. The observed low permeability of some drug substances in humans could be caused by efflux of drugs via membrane transporters such as P-gly-coprotein (P-gp). When the efflux transporters are absent in these models, or their degree of expression is low compared with that in humans, there may be a greater likelihood of misclassification of permeability class for a drug subject to efflux compared with a drug transported passively. Expression of known transporters in selected study systems should be characterized. Functional expression of efflux systems (e.g., P-gp) can be demonstrated with techniques such as bidirectional transport studies, demonstrating a higher rate of transport in the basolateral-to-apical direction as compared with apical-to-basolateral direction using selected model drugs or chemicals at concentrations that do not saturate the efflux system (e.g., cyclosporin A, vinblastine, rhodamine 123). An acceptance criterion for intestinal efflux that should be present in a test system cannot be set at this time. Instead, this guidance recommends limiting the use of nonhuman permeability test methods for drug substances that are transported by passive mechanisms. Pharmacokinetic studies on dose linearity or proportionality may provide useful information for evaluating the relevance of observed in vitro efflux of a drug. For example, there may be fewer concerns associated with the use of in vitro methods for a drug that has a higher rate of transport in the basolateral-to-apical direction at low drug concentrations but exhibits linear pharmacokinetics in humans.

For application of the BCS, an apparent passive transport mechanism can be assumed when one of the following conditions is satisfied:

- A linear (pharmacokinetic) relationship between the dose (e.g., relevant clinical dose range) and measures of BA (area under the concentration—time curve, AUC) of a drug is demonstrated in humans.
- Lack of dependence of the measured in vivo or in situ permeability is demonstrated in an animal model on initial drug concentration (e.g., 0.01, 0.1, and 1 H the highest dose strength dissolved in 250 mL) in the perfusion fluid.
- Lack of dependence of the measured in vitro permeability on initial drug concentration (e.g., 0.01, 0.1, and 1 H the highest dose strength dissolved in 250 mL) is demonstrated in donor fluid and transport direction (e.g., no statistically significant difference in the rate of transport between the apical-to-basolateral and basolateral-to-apical direction for the drug concentrations selected), using a suitable in vitro cell culture method that has been shown to express known efflux transporters (e.g., P-gp).

To demonstrate suitability of a permeability method intended for application of the BCS, a rank-order relationship between test permeability values and the extent of drug absorption data in human subjects should be established using a sufficient number of model drugs. For in vivo intestinal perfusion studies in humans, six model drugs are recommended. For in vivo or in situ intestinal perfusion studies in animals and for in vitro cell culture methods, 20 model drugs are recommended. Depending on study variability, a sufficient number of subjects, animals, excised tissue samples, or cell monolayers should be used in a study to provide a reliable estimate of drug permeability. This relationship should allow precise differentiation between drug substances of low- and high-intestinal permeability attributes.

Given below is a description of various approaches available to study permeability characteristics.

a. Surrogate Methods

As the U.S. FDA has begun accepting recommendations for waiver of bioequivalence requirement, protocols that prove extremely expensive in the drug development cycle, there is a greater need to develop surrogate models that 1 day may prove useful in securing waivers for all classes of drugs. Generally, the methods available currently show that the complexity of assay is directly proportional to its correlation with absorption of drugs in humans. Studies that correlated Log P with human absorption profile and the suitability or lead candidates were elaborated in chapter 4. In this chapter, we will examine more complex assay systems. Data from both complex biological and artificial permeation assays can provide valuable information regarding the absorption of a drug. (Courtesy Millipore Corporation)

Drug transport across epithelial cell barriers, especially the human small intestine, is difficult to predict. The intestinal epithelial cell barrier is a sophisticated organ that has evolved over hundreds of millions of years to become a “smart," effective, and selective xenobiotic screen. Nevertheless, there is large interindividual variability in the intestinal transport of drugs. Genetic variability in key proteins is believed to be causal. There is a pressing need to better understand the key processes and how the system components interact at the molecular, cellular, and tissue level to control drug transport and determine drug absorption in small intestine.

Is it feasible to construct an in silico framework to represent the drug absorption in small intestine at the cellular level with internal dynamic property and concert with the update molecular biochemical mechanism? This new generation of models and computational tools might integrate the available and emerging information at different levels to better account for and predict observed experimental results. Predicting aqueous solubility with in silico tools solubility is a key drug property. It is, however, difficult to measure accurately, especially for poorly soluble compounds, and thus numerous in silico models have been developed for its prediction. Some in silico models can predict aqueous solubility of simple, uncharged organic chemicals reasonably well; however, solubility prediction for charged species and drug-like chemicals is not very accurate. However, extrapolating solubility data to intestinal absorption from pharmacokinetic and physicochemical data and elucidating crucial parameters for absorption and the potential for improvement of bioavailability are important at the preformulation stages.

The poor oral bioavailability of drugs is generally assumed to be due to physiochemical problems, which result in poor solubility in gastrointestinal tract (GI tract) or difficulty in diffusion through small intestine epithelia membrane. Furthermore, the biochemical process also contributes to oral bioavailability. The in vitro cell culture models of the intestinal epithelial cell barrier have evolved to become widely used experimental devices.

The permeability assay uses an artificial membrane composed of hexadecane. The automated systems comprise multiwell system.

b. Parallel Artificial Membrane Permeability Analysis

Early drug discovery ADME assays, such as fast Caco-2 screens (see below), can help in rejecting test compounds that lack good pharmaceutical profiles. A cost-effective, high-throughput method—parallel artificial membrane permeability analysis (PAMPA)—that uses a phospholipid artificial membrane that models passive transport of epithelial cells is becoming increasingly popular. The PAMPA assay uses a range of lipid components that model a variety of different plasma membranes. The support membrane is 0.45 μm Hydrophobic Polyvinylidene Fluoride, 130-μm thick, and artificial memberane is lecithin in dodecane; recommended incubation time is 16 to 24 hours. The permeability and PAMPA assays as described above are robust and reproducible assays for determining passive, transcellular compound permeability. Permeability and PAMPA are automation compatible, relatively fast (4–16 hours), inexpensive, and straightforward and their results correlate with human drug absorption values from published methods. The PAMPA assay provides the benefits of a more biologically relevant system. It is also possible to tailor the lipophilic constituents so that they mimic specific membranes such as the blood–brain barrier. Optimization of incubation time, lipid mixture, and lipid concentration will also enhance the assay’s ability to predict compound permeability.

Modifications of permeability and PAMPA systems have been reported, for example, using the pION PAMPA Evolution 96 System with double-sink and gut-box (http://www.pion-inc.com/products.htm) as a new surrogate assay that predicts the gastrointestinal tract absorption of candidate drug molecules at different pH conditions. Using Beckman Coulter’s Biomek® FX Single Bridge Laboratory Automation Workstation PAMPA Assay System that features a 30-minute incubation time and an on-deck integrated Gut-Box™ and a SpectraMax® microplate spectrophotometer, the permeability coefficients of drug standards with diverse physiochemical properties can be compared from both

PAMPA and Caco-2 assays automated using the Biomek FX Workstation.

These automated assays can be used for high-throughput ADME screening in early drug discovery. The Double-Sink PAMPA permeability assay mimics in vivo conditions by the use of a chemical sink in the acceptor wells and pH gradient in the donor wells. The use of the pION Gut-Box integrated on the deck has shortened the PAMPA assay incubation time to 30 min. The permeability coefficient and rank order correlates well with data obtained using the in vitro Caco-2 assay and in vivo permeability properties measured in rat intestinal perfusions.

c. Caco-2 Drug Transport Assays

Drug absorption generally occurs either through passive transcellular or paracellular diffusion, active carrier transport, or active efflux mechanisms. Several methods have been developed to aid in the understanding of the absorption of new lead compounds. The most common ones use an immortalized cell line (e.g., Caco-2, MDCK, etc.) to mimic the intestinal epithelium. These in vitro models provide more predictive permeability information than artificial membrane systems (i.e., PAMPA and Permeability assays, described above) based on the cells' ability to promote (active transport) or resist (efflux) transport. Various in vitro methods are listed in U.S. FDA guidelines, acceptable to evaluate the permeability of a drug substance, includes monolayer of suitable epithelial cells and one such epithelial cell line that has been widely used as a model system of intestinal permeability is the Caco-2 cell line.

The kinetics of intestinal drug absorption, permeation enhancement, chemical moiety structure–permeability relationships, dissolution testing, in vitro/in vivo correlation, bioequivalence, and the development of novel polymeric materials are closely associated with the concept of Caco-2. Since most drugs are known to absorb via intestines without using cellular pumps, passive permeability models came in the limelight. In a typical Caco-2 experiment, a monolayer of cells is grown on a filter separating two stacked micro well plates. The permeability of drugs through the cells is determined after the introduction of a drug on one side of the filter. The entire process is automated, and when used in conjunction with chromatography and/or mass spectroscopy detection, it enables any drug's permeability to be determined. The method requires careful sample analysis to calculate permeability correctly. Limitations of Caco-2 experiments are 21 days for preparing a stable monolayer, stringent storage conditions; however, tight-junction formation prior to use is the better choice. The villus in the small intestine contains more than one cell type, the Caco-2 cell line does not produce the mucus as observed in the small intestine, and no P-450 metabolizing enzyme activity has been found in the Caco-2 cell line. Test compound solubility may pose a problem in Caco-2 assays because of the assay conditions. Finally, Caco-2 cells also contain endogenous transporter and efflux systems; the later of which works against the permeability process and can complicate data interpretation for some drugs.

The Caco-2 cell line is heterogeneous and is derived from a human colorectal adenocarcinoma. Caco-2 cells are used as in vitro permeability models to predict human intestinal absorption because they exhibit many features of absorptive intestinal cells. This includes their ability to spontaneously differentiate into polarized enterocytes that express high levels of brush border hydrolases and form well-developed junctional complexes. Consequently, it becomes possible to determine whether passage is transcellular or paracellular based on a compound's transport rate. Caco-2 cells also express a variety of transport systems including dipeptide transporters and P-gp. Because of these features, drug permeability in Caco-2 cells correlates well with human oral absorption, making Caco-2 an ideal in vitro permeability model. Additional information can be gained on metabolism and potential drug–drug interactions as the drug undergoes transcellular diffusion through the Caco-2 transport model.

Although accurate and well researched, the Caco-2 cell model requires a high investment of time and resources. Depending on a number of factors, including initial seeding density, culturing conditions, and passage number, Caco-2 cells can take as much as 20 days to reach confluence and achieve full differentiation. During this 20-day period, they require manual or automated exchange of media as frequently as every other day. The transport assays consume valuable drug compounds and normally require expensive, posttransport sample analyses (e.g., LC/MS). Therefore, the use of the Caco-2 transport model in a high-throughput laboratory setting is only possible if the platform is robust, automation compatible, reproducible, and provides high-quality data that correlate well with established methodologies.

The Millipore MultiScreen® Caco-2 assay system is a reliable 96-well platform for predicting human oral absorption of drug compounds (using Caco-2 cells or other cell lines whose drug transport properties have been well characterized). The MultiScreen system format is automation compatible and is designed to offer more cost effective, higher-throughput screening of drugs than a 24-well system. The MultiScreen Caco-2 assay system exhibits good uniformity of cell growth and drug permeability across all 96 wells and low variability between production lots. The plate design supports the use of lower volumes of expensive media and reduced amounts of test compounds. Using the MultiScreen Caco-2 assay system, standard drug compounds are successfully categorized as either "high" or "low" permeable, as defined by the Food and Drug Administration, and the permeability data correlate well with established human absorption values.

Historically, it has been shown that a sigmoidal relationship exists between drug absorption rates as measured with the in vitro Caco-2 model and human absorption. Caco-2 cells are heterogeneous and their properties in final culture may differ based on the selection pressures of a particular laboratory. Direct comparison of compound permeability rates between laboratories is not possible unless the same Caco-2 cells and conditions are used. Therefore, transport rates and permeability classification ranges of specific drugs are expected to vary between reported studies. Most important is the ability to successfully classify compounds as low-, medium-, or high-permeable drugs and produce transport results that correlate to established human absorption values.

Several modifications of Caco-2 cell model have been tested; for example, CYP3A4-Transfected Caco-2 Cells are also used to define the biochemical absorption barriers. Oral bioavailability and intestinal drug absorption can be significantly limited by metabolizing enzymes and efflux transporters in the gut. The most prevalent oxidative drug-metabolizing enzyme present in the intestine is CYP3A4. Currently, more than 50% of the drugs on the market metabolized by P450 enzymes are metabolized by CYP3A4. Oral absorption of CYP3A4 substrates can also be limited by the multidrug resistance transporter P-gp, because there is extensive substrate overlap between these two proteins. P-gp

is an ATP-dependent transporter on the apical plasma membrane of enterocytes that functions to limit the entry of drugs into the cell. There is significant interaction between CYP3A4 and P-gp in the intestine. Although Caco-2 cells express a variety of uptake and efflux transporters found in the human intestine, a major drawback to the use of Caco-2 cells is that they lack CYP3A4. As such, no data regarding the importance of intestinal metabolism on limiting drug absorption can be obtained from normal Caco-2 cells. Caco-2 cells pretreated with 1, 25-dihydroxyvitamin-D_3 (vitamin D_3) express higher levels of CYP3A4 compared with Caco-2 but still underestimate the amount of CYP3A4 in the human intestine. CYP3A4-transfected Caco-2 cells that P-gp can enhance drug metabolism and significantly decrease intestinal drug absorption.

d. Animal Model Testing

Whereas the quantity of substance available at the preformulation stages is generally small, in some instances, early animal testing for absorption potential are needed, particularly if the solid form of the new drug offers many options such as amorphous forms, solvates, and so forth. The absorption models used in animals are well described and would not be discussed here. Establishing good in vitro–in vivo correlation at this stage proves useful because of limited access to sufficient compound to run the entire absorption profiles. The "in vitro–in vivo correlation" (IVIVC) analysis can be made extensive or general conclusions drawn from limited studies; the choice depends on the amount of compound available and the nature or robustness of correlation observed.

e. In Vitro–In Vivo Correlation

The selection of a drug candidate marks the most crucial stage in the life cycle of drug development. Such selection is primarily based on the drug "developability" criteria, which include physicochemical properties of the drug and the results obtained from preliminary studies involving several in vitro systems and in vivo animal models, which address efficacy and toxicity issues. During this stage, exploring the relationship between in vitro and in vivo properties of the drug in animal models provide an idea about the feasibility of the drug delivery system for a given drug. In such correlations, study designs including study of more than one formulation of the modified-release dosage forms and a rank order of release (fast/slow) of the formulations should be incorporated. Even though the formulations and methods used at this stage are not optimal, they prompt better design and development efforts in the future.

There are four levels of IVIVC that have been described in the FDA guidance, which include levels A, B, C, and multiple C.

- *Level A Correlation:* This correlation represents a point-to-point relationship between in vitro dissolution and in vivo dissolution (input/absorption rate). Level A IVIVC is also viewed as a predictive model for the relationship between the entire in vitro release time course and entire in vivo response time course. In general, correlations are linear at this level. Although a concern of acceptable nonlinear correlation has been addressed, no formal guidance on the nonlinear IVIVC has been established. Level A correlation is the most informative and very useful from a regulatory perspective.
- *Level B Correlation:* In level B correlation, the mean in vivo dissolution or mean residence time is compared to the mean in vitro dissolution time by using statistical moment analytical methods. This type of correlation uses all of the in vitro and in vivo data; thus, it is not considered as a point-to-point correlation. This is of limited interest and use because more than one kind of plasma curve produces similar mean residence time.
- *Level C Correlation:* This correlation describes a relationship between the amount of drug dissolved (e.g., % dissolved at 1 hour) at one time point and one pharmacokinetic parameter (e.g., either AUC or C_{max}). Level C correlation is considered the lowest correlation level as it does not reflect the complete shape of the plasma concentration time curve. Similarly, a multiple level C correlation relates one or more pharmacokinetic parameters to the percent drug dissolved at several time points of the dissolution profile and thus may be more useful. Level B and C correlations can be useful in early formulation development, including selecting the appropriate excipients, to optimize manufacturing processes, for quality control purposes, and to characterize the release patterns of newly formulated immediate-release and modified-release products relative to the reference.

The most basic IVIVC models are expressed as a simple linear equation between the in vivo drug absorption and in vitro drug dissolved (released).

Several commercial software programs are available to study IVIVC, for example, PDx-IVIVC (http://www.globomaxservice.com/pdxivivc.htm), which is a comprehensive IVIVC software program that performs deconvolution, calculating the fraction or percentage of drug absorbed, and correlating it with in vitro fraction or percentage dissolved data. It also allows level C correlations (single or multiple) wherein a single-point relationship between a dissolution parameter, for example, percent dissolved in 4 hours and a pharmacokinetic parameter (e.g., AUC, C_{max}, T_{max}) is determined. A successful IVIVC model can be developed if in vitro dissolution is the rate-limiting step in the sequence of events leading to appearance of the drug in the systemic circulation following oral or other routes of administration. Thus, the dissolution test can be used as a surrogate for bioequivalence studies (involving human subjects) if the developed IVIVC is predictive of in vivo performance of the product.

3. Instability in the Gastrointestinal Tract

Determining the extent of absorption in humans based on mass balance studies using total radioactivity in urine does not take into consideration the extent of degradation of a drug in the gastrointestinal fluid before intestinal membrane permeation. In addition, some methods for determining permeability could be based on loss or clearance of a drug from fluids perfused into the human or animal gastrointestinal tract either in vivo or in situ. Documenting the fact that drug loss from the gastrointestinal tract arises from intestinal membrane permeation, instead of a degradation process, will help establish permeability. Stability in the gastrointestinal tract may be documented using gastric and intestinal fluids obtained from human subjects. Drug solutions in these fluids should be incubated at 37°C for a period that is representative of in vivo drug contact with these fluids (e.g., 1 hour in gastric fluid and 3 hours in intestinal fluid). Drug concentrations should then be determined using a validated stability-indicating assay method. Significant degradation (>5%) of a drug in this protocol could suggest potential instability. Obtaining gastrointestinal fluids from human subjects requires intubation and may be difficult in some cases. Use of

gastrointestinal fluids from suitable animal models or simulated fluids such as Gastric and Intestinal Fluids USP can be substituted when properly justified.

C. Determining Drug Product Dissolution Characteristics and Dissolution Profile Similarity

Dissolution testing should be carried out in USP Apparatus I at 100 rpm or Apparatus II at 50 rpm using 900 mL of the following dissolution media (http://www.fda.gov/cder/guidance/P192_20127#P192_20127):

1. NHCl or Simulated Gastric Fluid USP without enzymes
2. A pH 4.5 buffer
3. A pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes

For capsules and tablets with gelatin coating, Simulated Gastric and Intestinal Fluids USP (with enzymes) can be used.

Dissolution testing apparatus used in this evaluation should conform to the requirements in USP (<711> Dissolution). Selection of the dissolution testing apparatus (USP Apparatus I or II) during drug development should be based on a comparison of in vitro dissolution and in vivo pharmacokinetic data available for the product. The USP Apparatus I (*basket method*) is generally preferred for capsules and products that tend to float, and USP Apparatus II (*paddle method*) is generally preferred for tablets. For some tablet dosage forms, in vitro (but not in vivo) dissolution may be slow due to the manner in which the disintegrated product settles at the bottom of a dissolution vessel. In such situations, USP Apparatus I may be preferred over Apparatus II. If the testing conditions need to be modified to better reflect rapid in vivo dissolution (e.g., use of a different rotating speed), such modifications can be justified by comparing in vitro dissolution with in vivo absorption data (e.g., a relative BA study using a simple aqueous solution as the reference product).

A minimum of 12 dosage units of a drug product should be evaluated to support a biowaiver request. Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product (e.g., 10, 15, 20, and 30 min).

When comparing the test and reference products, dissolution profiles should be compared using a similarity factor (f_2). The similarity factor is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent (%) of dissolution between the two curves.

$$f_2 = 50 \times \log \{[1 + (1/n)_{t=1^n} (R_t - T_t)^2] - 05 \times 100\}$$

Two dissolution profiles are considered similar when the f_2 value is >50. To allow the use of mean data, the coefficient of variation should not be more than 20% at the earlier time points (e.g., 10 min), and should not be more than 10% at other time points. Note that when both test and reference products dissolve 85% or more of the label amount of the drug in >15 min using all three dissolution media recommended previously, the profile comparison with an f_2 test is unnecessary.

IV. ADDITIONAL CONSIDERATIONS FOR REQUESTING A BIOWAIVER

When requesting a BCS-based waiver for in vivo BA/BE studies for IR solid oral dosage forms, applicants should note that the following factors could affect their request or the documentation of their request.

A. Excipients

Excipients can sometimes affect the rate and extent of drug absorption. In general, using excipients that are currently in Food and Drug Administration (FDA-) approved IR solid oral dosage forms will not affect the rate or extent of absorption of a highly soluble and highly permeable drug substance that is formulated in a rapidly dissolving IR product. To support a biowaiver request, the quantity of excipients in the IR drug product should be consistent with the intended function (e.g., lubricant). When new excipients or atypically large amounts of commonly used excipients are included in an IR solid dosage form, additional information documenting the absence of an impact on BA of the drug may be requested by the FDA. Such information can be provided with a relative BA study using a simple aqueous solution as the reference product. Large quantities of certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol) may be problematic, and sponsors are encouraged to contact the review division when this is a factor.

B. Prodrugs

Permeability of prodrugs will depend on the mechanism and (anatomical) site of conversion to the drug substance. When it is demonstrated that the prodrug-to-drug conversion occurs predominantly after intestinal membrane permeation, the permeability of the prodrug should be measured. When this conversion occurs prior to intestinal permeation, the permeability of the drug should be determined. Dissolution and pH-solubility data on both prodrugs and drugs can be relevant. Sponsors may wish to consult with appropriate review staff before applying the BCS approach to IR products containing prodrugs.

C. Exceptions

BCS-based biowaivers are not applicable for the following.

1. Narrow Therapeutic Range Drugs

This guidance defines narrow therapeutic range drug products (http://www.fda.gov/cder/guidance/P223_24901#P223_24901) as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, or where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs, sponsors should contact the appropriate Review Division to determine whether a drug should be considered as having a narrow therapeutic range.

2. Products Designed to Be Absorbed in the Oral Cavity

A request for a waiver of in vivo BA/BE studies based on the BCS is not appropriate for dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets).

V. REGULATORY APPLICATIONS OF THE BCS

A. INDs/NDAs

Evidence demonstrating in vivo BA or information to permit the FDA to waive this evidence must be included in NDAs [21 CFR 320.21(a)]. A specific objective is to establish in vivo performance of the dosage form used in the clinical studies

that provided primary evidence of efficacy and safety. The sponsor may wish to determine the relative BA of an IR solid oral dosage form by comparison with an oral solution, suspension, or intravenous injection [21 CFR 320.25 (d)(2) and 320.25 (d)(3)]. The BA of the clinical trial dosage form should be optimized during the IND period.

Once the in vivo BA of a formulation is established during the IND period, waivers of subsequent in vivo BE studies, following major changes in components, composition, or method of manufacture [e.g., similar to SUPAC-IR level 3 changes (http://www.fda.gov/cder/guidance/P239_26745#P239_26745)], may be possible using the BCS. BCS-based biowaivers are applicable to the to-be-marketed formulation when changes in components, composition, or method of manufacture occur to the clinical trial formulation, as long as the dosage forms have rapid and similar in vitro dissolution profiles (see sections II and III). This approach is useful only when the drug substance is highly soluble and highly permeable (BCS Class 1), and the formulations pre- and postchange are *pharmaceutical equivalents* [under the definition at 21 CFR 320.1 (c)]. BCS-based biowaivers are intended only for BE studies. They do not apply to food effect BA studies or other pharmacokinetic studies.

B. ANDAs

BCS-based biowaivers can be requested for rapidly dissolving IR test products containing highly soluble and highly permeable drug substances, provided that the reference-listed drug product is also rapidly dissolving and the test product exhibits similar dissolution profiles to the reference-listed drug product (see sections II and III). This approach is useful when the test and reference dosage forms are pharmaceutical equivalents. The choice of dissolution apparatus (USP Apparatus I or II) should be the same as that established for the reference-listed drug product.

C. Postapproval Changes

BCS-based biowaivers can be requested for significant postapproval changes (e.g., level 3 changes in components and composition) to a rapidly dissolving IR product containing a highly soluble, highly permeable drug substance, provided that dissolution remains rapid for the postchange product and both pre- and postchange products exhibit similar dissolution profiles (see sections II and III). This approach is useful only when the drug products pre- and postchange are pharmaceutical equivalents.

VI. DATA TO SUPPORT A REQUEST FOR BIOWAIVERS

The drug substance for which a waiver is being requested should be highly soluble and highly permeable. Sponsors requesting biowaivers based on the BCS should submit the following information to the FDA for review by the Office of Clinical Pharmacology and Biopharmaceutics (for NDAs) or Office of Generic Drugs, Division of Bioequivalence (for ANDAs).

A. Data Supporting High Solubility

Data supporting high solubility of the test drug substance should be developed (see section III. A.). The following information should be included in the application:

- A description of test methods, including information on analytical method and composition of the buffer solutions
- Information on chemical structure, molecular weight, nature of the drug substance (acid, base, amphoteric, or neutral), and dissociation constants [pKa(s)]
- Test results (mean, standard deviation, and coefficient of variation) summarized in a table under solution pH, drug solubility (e.g., mg/mL), and volume of media required to dissolve the highest dose strength
- A graphic representation of mean pH-solubility profile

B. Data Supporting High Permeability

Data supporting high permeability of the test drug substance should be developed (see section III.B.). The following information should be included in the application:

- For human pharmacokinetic studies, information on study design and methods used along with the pharmacokinetic data
- For direct permeability methods, information supporting the suitability of a selected method that encompasses a description of the study method, criteria for selection of human subjects, animals, or epithelial cell line, drug concentrations in the donor fluid, description of the analytical method, method used to calculate extent of absorption or permeability, and, where appropriate, information on efflux potential (e.g., bidirectional transport data)
- A list of selected model drugs along with data on extent of absorption in humans (mean, standard deviation, and coefficient of variation) used to establish suitability of a method, permeability values for each model drug (mean, standard deviation, and coefficient of variation), permeability class of each model drug, and a plot of the extent of absorption as a function of permeability (mean, standard deviation, or 95% confidence interval) with identification of the low- and high-permeability class boundary and selected internal standard. Information to support high permeability of a test drug substance should include permeability data on the test drug substance, the IS (mean, standard deviation, and coefficient of variation), stability information, data supporting passive transport mechanism where appropriate, and methods used to establish high permeability of the test drug substance.

C. Data Supporting Rapid and Similar Dissolution

For submission of a biowaiver request, an IR product should be rapidly dissolving. Data supporting rapid dissolution attributes of the test and reference products should be developed (see section III.C.). The following information should be included in the application:

- A brief description of the IR products used for dissolution testing, including information on batch or lot number, expiration date, dimensions, strength, and weight.
- Dissolution data obtained with 12 individual units of the test and reference products using recommended test methods in section III.C. The percentage of labeled claims dissolved at each specified testing interval should be reported for each individual dosage unit. The mean percent (%) dissolved, range (highest and lowest) of dissolution, and coefficient of variation (relative standard deviation) should be tabulated. A graphic representation of the mean dissolution profiles for the test and reference products in the three media should also be included.
- Data supporting similarity in dissolution profiles between the test and reference products in each of the three media, using the f_2 metric.

D. Additional Information

The manufacturing process used to make the test product should be described briefly to provide information on the method of manufacture (e.g., wet granulation vs. direct compression). A list of excipients used, the amount used, and their intended functions should be provided. Excipients used in the test product should have been used previously in FDA-approved IR solid oral dosage forms. When requesting a BCS-based waiver for in vivo BA/BE studies for IR solid oral dosage forms, applicants should note that the following factors can affect their request or the documentation of their request:

1. Excipients

Excipients can sometimes affect the rate and extent of drug absorption. In general, using excipients that are currently in FDA-approved IR solid oral dosage forms will not affect the rate or extent of absorption of a highly soluble and highly permeable drug substance that is formulated in a rapidly dissolving IR product. To support a biowaiver request, the quantity of excipients in the IR drug product should be consistent with the intended function (e.g., lubricant). When new excipients or atypically large amounts of commonly used excipients are included in an IR solid dosage form, additional information documenting the absence of an impact on BA of the drug may be requested by the Agency. Such information can be provided with a relative BA study using a simple aqueous solution as the reference product. Large quantities of certain excipients, such as surfactants (e.g., polysorbate 80) and sweeteners (e.g., mannitol or sorbitol), may be problematic, and sponsors are encouraged to contact the review division when this is a factor.

2. Prodrugs

Permeability of prodrugs will depend on the mechanism and (anatomical) site of conversion to the drug substance. When the prodrug-to-drug conversion is shown to occur predominantly after intestinal membrane permeation, the permeability of the prodrug should be measured. When this conversion occurs prior to intestinal permeation, the permeability of the drug should be determined. Dissolution and pH-solubility data on both prodrug and drug can be relevant. Sponsors may wish to consult with appropriate review staff before applying the BCS approach to IR products containing prodrugs.

3. Exceptions

BCS-based biowaivers are not applicable for the following.

a. ***Narrow Therapeutic Range Drugs***

The narrow therapeutic range drug products are defined as those containing certain drug substances that are subject to therapeutic drug concentration or pharmacodynamic monitoring, and/or where product labeling indicates a narrow therapeutic range designation. Examples include digoxin, lithium, phenytoin, theophylline, and warfarin. Because not all drugs subject to therapeutic drug concentration or pharmacodynamic monitoring are narrow therapeutic range drugs, sponsors should contact the appropriate review division to determine whether a drug should be considered to have a narrow therapeutic range.

b. ***Products Designed to Be Absorbed in the Oral Cavity***

A request for a waiver of in vivo BA/BE studies based on the BCS is not appropriate for dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets).

Fast-dissolving/-disintegrating tablets (FDDTs) disintegrate and/or dissolve rapidly in the saliva without the need for water and are thus of importance for patients who cannot or will not swallow. Some tablets are designed to dissolve in saliva remarkably fast, within a few seconds, and are true fast-dissolving tablets. Others contain agents to enhance the rate of tablet disintegration in the oral cavity and are more appropriately termed fast-disintegrating tablets, as they may take up to a minute to completely disintegrate. These tablets, if absorbed through buccal cavity, avoid the first pass liver metabolism and claims have been made for improve bioavailability using these platforms. Some of the key formulation considerations for FDDTs include the need to mask the taste and the most obvious method to is to include sweeteners and flavors; however, these are not a sufficient means for taste-masking many bitter drugs. Thus, most of the FDDT technologies incorporate unique forms of taste masking including adsorption onto or complexation with carriers and spray coating of drug particles. Frequently, the active drug powder is coated, and the coating does not completely dissolve until the drug has been swallowed. Drugs that are particle coated are more appropriately termed fast disintegrating due to the delayed release of the active molecule until they are swallowed. Additionally, effervescence is a physical method of taste masking used in some of the FDDTs. Details about the technology are sketchy as they pertain mostly to proprietary methods.

Currently, four fast-dissolving/-disintegrating technologies have reached the U.S. market: Zydis,® (R.P. Scherer, Inc., Basking Ridge, NJ), WOWTAB™ (Yamanouchi Pharma Technologies, Inc., Palo Alto, CA), and OraSolv® and DuraSolv® (Cima Labs, Inc., Brooklyn Park, MN). Three others are available outside the United States: FlashDose® (Fuisz Technologies, Ltd., Chantilly, VA), Flashtab® (Prographarm Group, Saint Cloud, France), and OraQuick™ (KV Pharmaceutical Co., Inc., St. Louis, MO). Examples of products available in the United States include

Zydis Products

Claritin Reditab: micronized loratadine (10 mg), citric acid, gelatin, mannitol, mint flavor

Feldene Melt: piroxicam (10 or 20 mg), gelatin, mannitol, aspartame, citric anhydrous

Maxalt-MLT: rizatriptan (5 or 10 mg), gelatin, mannitol, aspartame, peppermint flavor

Pepcid RPD: famotidine (20 or 40 mg), gelatin, mannitol, aspartame

Zyprexa Zydis: olanzapine (5, 10, 15, or 20 mg), gelatin, mannitol, aspartame, methylparaben sodium, propylparaben sodium

Zofran ODT: ondansetron (4 or 8 mg), aspartame, gelatin, mannitol, methlparaben sodium, propylparaben sodium, strawberry flavor

Dimetapp Quick Dissolve Children's Cold and Allergy Tablets (OTC)

OraSolv Products

Remeron Soltab: mirtazepine (15, 30, or 45 mg), aspartame, citric acid, crospovidone, hydroxypropyl methylcellulose, magnesium stearate, mannitol, microcrystalline cellulose, polymethacrylate, povidone, sodium bicarbonate, starch, sucrose, orange flavor

Tempra FirstTabs: acetaminophen (80 or 160 mg), inactive ingredients including mannitol (currently available in Canada)

Triaminic Softchew (OTC)

DuraSolv Products

NuLev: hyoscyamine sulfate (0.125 mg), aspartame, colloidal silicon dioxide, crospovidone, mint flavoring, magnesium stearate, mannitol, microcrystalline cellulose

Zomig ZMT: zolmitriptan (2.5 mg), mannitol, microcrystalline cellulose, crospovidone, aspartame, sodium bicarbonate, citric acid, anhydrous, colloidal silicon dioxide, magnesium stearate, orange flavor

WOWTAB Products

Benadryl Allergy & Sinus Fastmelt (OTC)

Children's Benadryl Allergy & Cold Fastmelt (OTC)

Most FDDTs lack the mechanical strength common to traditional tablets. Many products are very lightweight and fragile requiring them to be individually packaged. Because of the formulation of FDDTs, they are also more susceptible to degradation via temperature and humidity.

Animal Products

In general, the generic product being considered for a waiver contains the same active and inactive ingredients in the same dosage form and concentration and has the same pH and physicochemical characteristics as an approved pioneer product. However, the CVM will consider bioequivalence waivers for nonfood animal topical products with certain differences in the inactive ingredients of the pioneer and generic products.

If a waiver of the in vivo bioequivalence and/or the tissue residue study/studies is granted for a food animal drug product, then the withdrawal period established for the pioneer product will be assigned to the generic product. Sponsors may apply for waivers of in vivo bioequivalence studies prior to submission of the ANADAs.

Species Selection

A bioequivalence study generally should be conducted for each species for which the pioneer product is approved on the label, with the exception of "minor" species (as defined in section 514.1 (d) (1) of Title 21 of the Code of Federal Regulations) on the label.

Subject Characteristics

Ordinarily, studies should be conducted with healthy animals representative of the species, class, gender, and physiological maturity for which the drug is approved. The bioequivalence study may be conducted with a single gender for which the pioneer product is approved, unless there is a known interaction of formulation with gender. An attempt should be made to restrict the weight of the test animals to a narrow range in order to maintain the same total dose across study subjects. The animals should not receive any medication prior to testing for a period of 2 weeks or more, depending upon the biological half-life of the ancillary drug.

Human Food Safety Considerations

The toxicology and tolerance developed for the pioneer animal drug are applied to generic copies of the drug. The CVM has concluded that in addition to a bioequivalence study, a tissue residue depletion study should be conducted for approval of a generic animal drug product in a food-producing species. Two drug products may have the same plasma disposition profile at the concentrations used to assess product bioequivalence, but may have very different tissue disposition kinetics when followed out to the withdrawal time for the pioneer product. Therefore, to show the withdrawal period at which residues of the generic product will be consistent with the tolerance for the pioneer product, a tissue residue depletion study is necessary.

The results of a bioequivalence study or tissue residue depletion study in one animal species cannot generally be extrapolated to another species. Possible species differences in drug partitioning or binding in tissues could magnify a small difference in the rate or extent of drug absorbed into a large difference in marker residue concentrations in the target tissue. Therefore, for a pioneer product labeled for more than one food-producing species, a bioequivalence study and a tissue residue depletion study will generally be requested for each major food-producing species on the label.

A traditional withdrawal study, as described in CVM's guidance number 3, "General Principles for Evaluating the Safety of Compounds Used in Food-Producing Animals," is considered the best design for collecting data useful for the calculation of a preslaughter withdrawal period for drugs used in food-producing animals. In the traditional withdrawal study, 20 animals are divided into four or five groups of 4 to 5 animals each. Groups of animals are slaughtered at carefully preselected time points following the last administration of the test product and the edible tissues are collected for residue analysis. A statistical tolerance limit approach is used to determine when, with 95% confidence, 99% of treated animals would have tissue residues below the codified limits.

For purposes of calculating a withdrawal period for a generic animal drug, only the generic product would be tested (i.e., not the pioneer product), and only the marker residue in the target tissue would be analyzed. Other study designs will be considered on a case-by-case basis. Sponsors are encouraged to submit the proposed tissue residue depletion protocol for CVM concurrence before proceeding with the withdrawal study.

The generic animal drug will be assigned the withdrawal time supported by the residue depletion data, or the withdrawal time currently assigned to the pioneer product, whichever is the longer.

The generic animal drug sponsor may request a shorter withdrawal period for the generic product by supplementing the ANADA and providing tissue residue data necessary to support the shorter withdrawal period request. Such a supplement will be reviewed under the agency's policy for Category II supplements. For a Category II supplement, a reevaluation of the safety (or effectiveness) data in the parent application (i.e., the pioneer NADA) may be required [21 CFR 514.106 (b) (2)]. The CVM will ordinarily approve a request for a shorter withdrawal period when the residue data are adequate and when no other human food safety concerns for the drug are evident.

Under 21 CFR 514.1(b)(7), applications are required to include a description of practicable methods for determining the quantity, if any, of the new animal drug in or on food, and any substance formed in or on food because of its use, and the proposed tolerance or withdrawal period or other use restrictions to ensure that the proposed use of the drug will be safe. For certain drug products, a tissue residue depletion study is not needed to ensure that residues of the test product will be consistent with the codified drug tolerance at the withdrawal time assigned to the reference product. These include but may not be limited to products for which a waiver of in vivo bioequivalence testing is granted, and products for which the assay method used in the blood level bioequivalence study is sensitive enough to measure blood levels of the drug for the entire withdrawal period assigned to the reference product. Other requests for waiver of the tissue residue study will be considered on a case-by-case basis.

CVM will not request that the assay methodology used to determine the withdrawal period for the generic product be more rigorous than the approved methodology used to determine the existing withdrawal period for the pioneer product. If an analytical method other than the approved method of analysis is used, the generic sponsor should provide data comparing the alternate method to the approved method.

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2

Quality Risk Management

I. INTRODUCTION

Risk management principles are effectively used in many areas of business and government including finance, insurance, occupational safety, public health, pharmacovigilance, and by agencies regulating these industries. Although there are some examples of the use of *quality risk management* in the pharmaceutical industry today, they are limited and do not represent the full contributions that risk management has to offer. In addition, the importance of *quality systems* has been recognized in the pharmaceutical industry and it is becoming evident that quality risk management is a valuable component of an effective quality system.

It is commonly understood that *risk* is defined as the combination of the probability of occurrence of *harm* and the *severity* of that harm. However, achieving a shared understanding of the application of risk management among diverse *stakeholders* is difficult because each stakeholder might perceive different potential harms, place a different probability on each harm occurring and attribute different severities to each harm. In relation to pharmaceuticals, although there are a variety of stakeholders, including patients and medical practitioners as well as government and industry, the protection of the patient by managing the risk to quality should be considered of prime importance.

The manufacturing and use of a drug (medicinal) product, including its components, necessarily entail some degree of risk. The risk to its quality is just one component of the overall risk. It is important to understand that product *quality* should be maintained throughout the *product lifecycle* such that the attributes that are important to the quality of the drug (medicinal) product remain consistent with those used in the clinical studies. An effective quality risk management approach can further ensure the high quality of the drug (medicinal) product to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Additionally, use of quality risk management can improve the decision making if a quality problem arises. Effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and can beneficially affect the extent and level of direct regulatory oversight.

The purpose of this document is to offer a systematic approach to quality risk management. It serves as a foundation or resource document that is independent of, yet supports, other ICH Quality documents and complements existing quality practices, requirements, standards, and guidelines within the pharmaceutical industry and regulatory environment. It specifically provides guidance on the principles and some of the tools of quality risk management that can enable more effective and consistent risk-based decisions, both by regulators and by industry, regarding the quality of drug substances and drug (medicinal) products across the product lifecycle. It is not intended to create any new expectations beyond the current regulatory requirements.

It is neither always appropriate nor always necessary to use a formal risk management process (using recognized tools and/or internal procedures, e.g., standard operating procedures). The use of informal risk management processes (using empirical tools and/or internal procedures) can also be considered acceptable. Appropriate use of quality risk management can facilitate but does not obviate industry's obligation to comply with regulatory requirements and does not replace appropriate communications between industry and regulators.

II. SCOPE

This guideline provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality. These aspects include development, manufacturing, distribution, and the inspection and submission/review processes throughout the lifecycle of drug substances, drug (medicinal) products, biological and biotechnological products (including the use of raw materials, solvents, excipients, packaging and labeling materials in drug (medicinal) products, biological and biotechnological products).

III. PRINCIPLES OF QUALITY RISK MANAGEMENT

Two primary principles of quality risk management are as follows:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.
- The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

IV. GENERAL QUALITY RISK MANAGEMENT PROCESS

Quality risk management is a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle. A model for quality risk management is outlined in the diagram (Fig. 2.1). Other models could be used. The emphasis on each component of the framework might differ from case to case but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Decision nodes are not shown in the diagram above, because decisions can occur at any point in the process. These decisions might be to return to the previous step and seek further information, to adjust the risk models or even to terminate the risk management process based upon

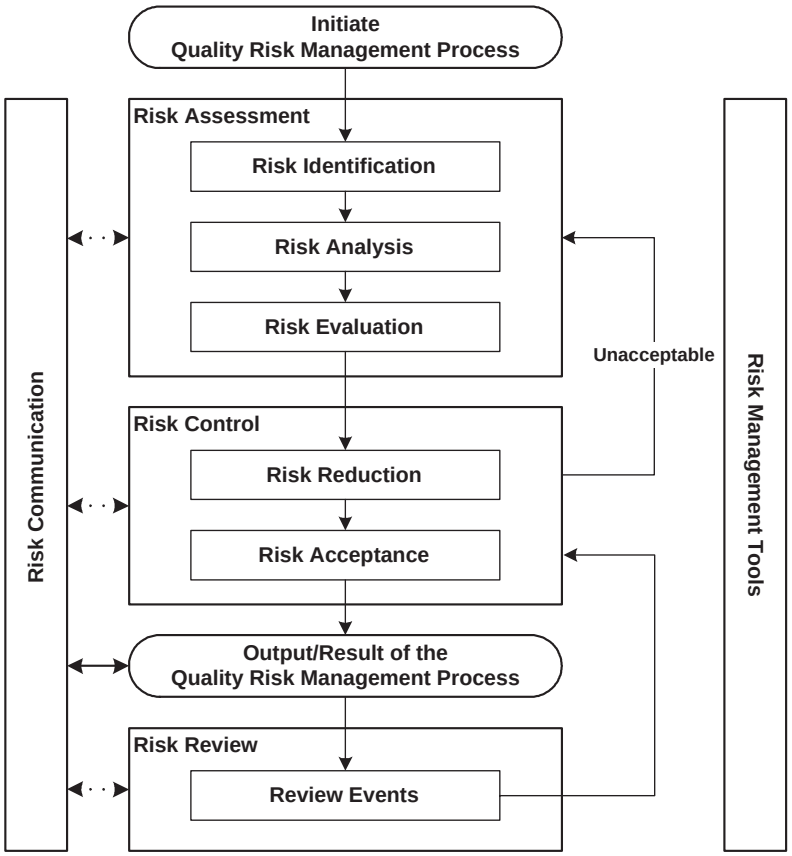

Figure 2.1 Overview of a typical quality risk management process

information that supports such a decision. *Note*: "unacceptable" in the flowchart does not only refer to statutory, legislative, or regulatory requirements, but also to the need to revisit the risk assessment process.

A. Responsibilities

Quality risk management activities are usually, but not always, undertaken by interdisciplinary teams. When teams are formed, they should include experts from the appropriate areas (e.g., quality unit, business development, engineering, regulatory affairs, production operations, sales and marketing, legal, statistics, and clinical) in addition to individuals who are knowledgeable about the quality risk management process.

Decision makers should

- take responsibility for coordinating quality risk management across various functions and departments of their organization and
- assure that a quality risk management process is defined, deployed, and reviewed and that adequate resources are available.

B. Initiating a Quality Risk Management Process

Quality risk management should include systematic processes designed to coordinate, facilitate, and improve science-based decision making with respect to risk. Possible steps used to initiate and plan a quality risk management process might include the following:

- Define the problem and/or risk question, including pertinent assumptions identifying the potential for risk.
- Assemble background information and/or data on the potential hazard, harm, or human health impact relevant to the risk assessment.
- Identify a leader and necessary resources.
- Specify a timeline, deliverables, and appropriate level of decision making for the risk management process.

C. Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (as defined below). Quality risk assessments begin with a well-defined problem description or risk question. When the risk in question is well defined, an appropriate risk management tool (see examples in section V) and the types of information needed to address the risk question will be more readily identifiable. As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?
2. What is the likelihood (probability) it will go wrong?
3. What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses the "What might go wrong?" question, including identifying the possible

consequences. This provides the basis for further steps in the quality risk management process.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. In some risk management tools, the ability to detect the harm (detectability) also factors in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

In doing an effective risk assessment, the robustness of the data set is important because it determines the quality of the output. Revealing assumptions and reasonable sources of uncertainty will enhance confidence in this output and/or help identify its limitations. Uncertainty is due to combination of incomplete knowledge about a process and its expected or unexpected variability. Typical sources of uncertainty include gaps in knowledge gaps in pharmaceutical science and process understanding, sources of harm (e.g., failure modes of a process, sources of variability), and probability of detection of problems.

The output of a risk assessment is either a quantitative estimate of risk or a qualitative description of a range of risk. When risk is expressed quantitatively, a numerical probability is used. Alternatively, risk can be expressed using qualitative descriptors, such as "high," "medium," or "low," which should be defined in as much detail as possible. Sometimes a "risk score" is used to further define descriptors in risk ranking. In quantitative risk assessments, a risk estimate provides the likelihood of a specific consequence, given a set of risk-generating circumstances. Thus, quantitative risk estimation is useful for one particular consequence at a time. Alternatively, some risk management tools use a relative risk measure to combine multiple levels of severity and probability into an overall estimate of relative risk. The intermediate steps within a scoring process can sometimes employ quantitative risk estimation.

D. Risk Control

Risk control includes decision making to reduce and/or accept risks. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort used for risk control should be proportional to the significance of the risk. Decision makers might use different processes, including benefit–cost analysis, for understanding the optimal level of risk control.

Risk control might focus on the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks, and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level (see Fig. 2.1). Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks might also be used as part of a risk control strategy. The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. Hence, it might be appropriate to revisit the risk assessment to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk, or it can be a passive decision in which residual risks are not specified. For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

E. Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process (see Fig. 2.1: dashed arrows). The output/result of the quality risk management process should be appropriately communicated and documented (see Fig. 2.1: solid arrows). Communications might include those among interested parties; for example, regulators and industry, industry and the patient, within a company, industry or regulatory authority, etc. The included information might relate to the existence, nature, form, probability, severity, acceptability, control, treatment, detectability, or other aspects of risks to quality. Communication need not be carried out for each and every risk acceptance. Between the industry and regulatory authorities, communication concerning quality risk management decisions might be effected through existing channels as specified in regulations and guidances.

F. Risk Review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

The output/results of the risk management process should be reviewed to take into account new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be used for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall). The frequency of any review should be based upon the level of risk. Risk review might include reconsideration of risk acceptance decisions (section D).

V. RISK MANAGEMENT METHODOLOGY

Quality risk management supports a scientific and practical approach to decision making. It provides documented, transparent, and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity, and sometimes detectability of the risk.

Traditionally, risks to quality have been assessed and managed in a variety of informal ways (empirical and/or internal procedures) based on, for example, compilation of observations, trends, and other information. Such approaches continue to provide useful information that might support topics such as handling of complaints, quality defects, deviations, and allocation of resources.

Additionally, the pharmaceutical industry and regulators can assess and manage risk using recognized risk management tools and/or internal procedures (e.g., standard operating procedures). Below is a nonexhaustive list of some

of these tools (further details in Annex I and chapter 8):

- Basic risk management facilitation methods (flowcharts, check sheets, etc.)
- Failure Mode Effects Analysis (FMEA)
- Failure Mode, Effects, and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Preliminary Hazard Analysis (PHA)
- Risk ranking and filtering
- Supporting statistical tools

It might be appropriate to adapt these tools for use in specific areas pertaining to drug substance and drug (medicinal) product quality. Quality risk management methods and the supporting statistical tools can be used in combination (e.g., Probabilistic Risk Assessment). Combined use provides flexibility that can facilitate the application of quality risk management principles.

The degree of rigor and formality of quality risk management should reflect available knowledge and be commensurate with the complexity and/or criticality of the issue to be addressed.

VI. INTEGRATION OF QUALITY RISK MANAGEMENT INTO INDUSTRY AND REGULATORY OPERATIONS

Quality risk management is a process that supports science-based and practical decisions when integrated into quality systems (see Annex II). As outlined in the introduction, appropriate use of quality risk management does not obviate industry's obligation to comply with regulatory requirements. However, effective quality risk management can facilitate better and more informed decisions, can provide regulators with greater assurance of a company's ability to deal with potential risks, and might affect the extent and level of direct regulatory oversight. In addition, quality risk management can facilitate better use of resources by all parties.

Training of both industry and regulatory personnel in quality risk management processes provides for greater understanding of decision-making processes and builds confidence in quality risk management outcomes.

Quality risk management should be integrated into existing operations and documented appropriately. Annex II provides examples of situations in which the use of the quality risk management process might provide information that could then be used in a variety of pharmaceutical operations. These examples are provided for illustrative purposes only and should not be considered a definitive or exhaustive list. These examples are not intended to create any new expectations beyond the requirements laid out in the current regulations.

Examples for industry and regulatory operations (see Annex II):

- Quality management.

Examples for industry operations and activities (see Annex II):

- Development;
- Facility, equipment, and utilities;
- Materials management;
- Production;
- Laboratory control and stability testing;
- Packaging and labeling.

Examples for regulatory operations (see Annex II):

- Inspection and assessment activities.

While regulatory decisions will continue to be taken on a regional basis, a common understanding and application of quality risk management principles could facilitate mutual confidence and promote more consistent decisions among regulators on the basis of the same information. This collaboration could be important in the development of policies and guidelines that integrate and support quality risk management practices.

GLOSSARY

Decision Maker(s)—Person(s) with the competence and authority to make appropriate and timely quality risk management decisions.

Detectability—The ability to discover or determine the existence, presence, or fact of a hazard.

Harm—Damage to health, including the damage that can occur from loss of product quality or availability.

Hazard—The potential source of harm (ISO/IEC Guide 51).

Product Lifecycle—All phases in the life of the product from the initial development through marketing until the product's discontinuation.

Quality—The degree to which a set of inherent properties of a product, system, or process fulfills requirements [see ICH Q6A definition specifically for "quality" of drug substance and drug (medicinal) products].

Quality Risk Management—A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

Quality System—The sum of all aspects of a system that implements quality policy and ensures that quality objectives are met.

Requirements—The explicit or implicit needs or expectations of the patients or their surrogates (e.g., healthcare professionals, regulators, and legislators). In this document, "requirements" refers not only to statutory, legislative, or regulatory requirements, but also to such needs and expectations.

Risk—The combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).

Risk Acceptance—The decision to accept risk (ISO Guide 73).

Risk Analysis—The estimation of the risk associated with the identified hazards.

Risk Assessment—A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.

Risk Communication—The sharing of information about risk and risk management between the decision maker and other stakeholders.

Risk Control—Actions implementing risk management decisions (ISO Guide 73).

Risk Evaluation—The comparison of the estimated risk to given risk criteria using a quantitative or qualitative scale to determine the significance of the risk.

Risk Identification—The systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description.

Risk Management—The systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk.

Risk Reduction—Actions taken to lessen the probability of occurrence of harm and the severity of that harm.

Risk Review—Review or monitoring of output/results of the risk management process considering (if appropriate) new knowledge and experience about the risk.

Severity—A measure of the possible consequences of a hazard.

Stakeholder—Any individual, group, or organization that can affect, be affected by, or perceive itself to be affected by a risk. Decision makers might also be stakeholders. For the purposes of this guideline, the primary stakeholders are the patient, healthcare professional, regulatory authority, and industry.

Trend—A statistical term referring to the direction or rate of change of a variable(s).

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ANNEX I: RISK MANAGEMENT METHODS AND TOOLS

The purpose of this annex is to provide a general overview of and references for some of the primary tools that might be used in quality risk management by industry and regulators. The references are included as an aid to gain more knowledge and detail about the particular tool. This is not an exhaustive list. It is important to note that no one tool or set of tools is applicable to every situation in which a quality risk management procedure is used.

I.1 Basic Risk Management Facilitation Methods

Some of the simple techniques that are commonly used to structure risk management by organizing data and facilitating decision making are as follows:

- Flowcharts
- Check Sheets
- Process Mapping
- Cause and Effect Diagrams (also called an Ishikawa diagram or fish bone diagram)

I.2 Failure Mode Effects Analysis

FMEA (see IEC 60812) provides for an evaluation of potential failure modes for processes and their likely effect on outcomes and/or product performance. Once failure modes are established, risk reduction can be used to eliminate, contain, reduce, or control the potential failures. FMEA relies on product and process understanding. FMEA methodically breaks down the analysis of complex processes into manageable steps. It is a powerful tool for summarizing the important modes of failure, factors causing these failures, and the likely effects of these failures.

Potential Areas of Use(s)

FMEA can be used to prioritize risks and monitor the effectiveness of risk control activities.

FMEA can be applied to equipment and facilities and might be used to analyze a manufacturing operation and its effect on product or process. It identifies elements/operations within the system that render it vulnerable. The output/results of FMEA can be used as a basis for design or further analysis or to guide resource deployment.

I.3 Failure Mode, Effects, and Criticality Analysis

FMEA might be extended to incorporate an investigation of the degree of severity of the consequences, their respective probabilities of occurrence, and their detectability, thereby becoming a Failure Mode Effect and Criticality Analysis (FMECA; see IEC 60812). In order for such an analysis to be performed, the product or process specifications should be established. FMECA can identify places where additional preventive actions might be appropriate to minimize risks.

Potential Areas of Use(s)

FMECA application in the pharmaceutical industry should mostly be used for failures and risks associated with manufacturing processes; however, it is not limited to this application. The output of an FMECA is a relative risk "score" for each failure mode, which is used to rank the modes on a relative risk basis.

I.4 Fault Tree Analysis

The FTA tool (see IEC 61025) is an approach that assumes failure of the functionality of a product or process. This tool evaluates system (or subsystem) failures one at a time but can combine multiple causes of failure by identifying causal chains. The results are represented pictorially in the form of a tree of fault modes. At each level in the tree, combinations of fault modes are described with logical operators (AND, OR, etc.). FTA relies on the experts' process understanding to identify causal factors.

Potential Areas of Use(s)

FTA can be used to establish the pathway to the root cause of the failure. FTA can be used to investigate complaints or deviations in order to fully understand their root cause and to ensure that intended improvements will fully resolve the issue and not lead to other issues (i.e., solve one problem yet cause a different problem). FTA is an effective

tool for evaluating how multiple factors affect a given issue. The output of an FTA includes a visual representation of failure modes. It is useful both for risk assessment and in developing monitoring programs.

I.5 Hazard Analysis and Critical Control Points

HACCP is a systematic, proactive, and preventive tool for assuring product quality, reliability, and safety (see WHO Technical Report Series No 908, 2003, Annex 7). It is a structured approach that applies technical and scientific principles to analyze, evaluate, prevent, and control the risk or adverse consequence(s) of hazard(s) due to the design, development, production, and use of products.

HACCP consists of the following seven steps:

(1) conduct a hazard analysis and identify preventive measures for each step of the process;
(2) determine the critical control points;
(3) establish critical limits;
(4) establish a system to monitor the critical control points;
(5) establish the corrective action to be taken when monitoring indicates that the critical control points are not in a state of control;
(6) establish system to verify that the HACCP system is working effectively; and
(7) establish a record-keeping system.

Potential Areas of Use(s)

HACCP might be used to identify and manage risks associated with physical, chemical, and biological hazards (including microbiological contamination). HACCP is most useful when product and process understanding is sufficiently comprehensive to support identification of critical control points. The output of a HACCP analysis is risk management information that facilitates monitoring of critical points not only in the manufacturing process but also in other life cycle phases.

I.6 Hazard Operability Analysis

HAZOP (see IEC 61882) is based on a theory that assumes that risk events are caused by deviations from the design or operating intentions. It is a systematic brainstorming technique for identifying hazards using so-called "guide-words". "Guide-words" (e.g., No, More, Other Than, Part of, etc.) are applied to relevant parameters (e.g., contamination, temperature) to help identify potential deviations from normal use or design intentions. It often uses a team of people with expertise covering the design of the process or product and its application.

Potential Areas of Use(s)

HAZOP can be applied to manufacturing processes, including outsourced production and formulation as well as the upstream suppliers, equipment, and facilities for drug substances and drug (medicinal) products. It has also been used primarily in the pharmaceutical industry for evaluating process safety hazards. As is the case with HACCP, the output of a HAZOP analysis is a list of critical operations for risk management. This facilitates regular monitoring of critical points in the manufacturing process.

I.7 Preliminary Hazard Analysis

PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations, and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product, or system. The tool consists of (1) the identification of the possibilities that the risk event happens, (2) the qualitative evaluation of the extent of possible injury or damage to health that could result, (3) a relative ranking of the hazard using a combination of severity and likelihood of occurrence, and (4) the identification of possible remedial measures.

Potential Areas of Use(s)

PHA might be useful when analyzing existing systems or prioritizing hazards where circumstances prevent a more extensive technique from being used. It can be used for product, process, and facility design as well as to evaluate the types of hazards for the general product type, then the product class, and finally the specific product. PHA is most commonly used early in the development of a project when there is little information on design details or operating procedures; thus, it will often be a precursor to further studies. Typically, hazards identified in the PHA are further assessed with other risk management tools such as those in this section.

I.8 Risk Ranking and Filtering

Risk ranking and filtering is a tool for comparing and ranking risks. Risk ranking of complex systems typically requires evaluation of multiple diverse quantitative and qualitative factors for each risk. The tool involves breaking down a basic risk question into as many components as needed to capture factors involved in the risk. These factors are combined into a single relative risk score that can then be used for ranking risks. "Filters," in the form of weighting factors or cut-offs for risk scores, can be used to scale or fit the risk ranking to management or policy objectives.

Potential Areas of Use(s)

Risk ranking and filtering can be used to prioritize manufacturing sites for inspection/audit by regulators or industry. Risk ranking methods are particularly helpful in situations in which the portfolio of risks and the underlying consequences to be managed are diverse and difficult to compare using a single tool. Risk ranking is useful when management needs to evaluate both quantitatively assessed and qualitatively assessed risks within the same organizational framework.

I.9 Supporting Statistical Tools

Statistical tools can support and facilitate quality risk management. They can enable effective data assessment, aid in determining the significance of the data set(s), and facilitate more reliable decision making. A listing of some of the principal statistical tools commonly used in the pharmaceutical industry is provided below:

- Control Charts, for example
  - Acceptance Control Charts (see ISO 7966);
  - Control Charts with Arithmetic Average and Warning Limits (see ISO 7873);
  - Cumulative Sum Charts (see ISO 7871);
  - Shewhart Control Charts (see ISO 8258); and
  - Weighted Moving Average.
- Design of Experiments

- Histograms
- Pareto Charts
- Process Capability Analysis

ANNEX II: POTENTIAL APPLICATIONS FOR QUALITY RISK MANAGEMENT

This Annex is intended to identify potential uses of quality risk management principles and tools by industry and regulators. However, the selection of particular risk management tools is completely dependent upon specific facts and circumstances.

These examples are provided for illustrative purposes and only suggest potential uses of quality risk management. This annex is not intended to create any new expectations beyond the current regulatory requirements.

II.1 Quality Risk Management as Part of Integrated Quality Management

Documentation

To review current interpretations and application of regulatory expectations;

To determine the desirability of and/or develop the content for SOPs, guidelines, etc.

Training and education

To determine the appropriateness of initial and/or ongoing training sessions based on education, experience, and working habits of staff, as well as on a periodic assessment of previous training (e.g., its effectiveness);

To identify the training, experience, qualifications, and physical abilities that allow personnel to perform an operation reliably and with no adverse impact on the quality of the product.

Quality defects

To provide the basis for identifying, evaluating, and communicating the potential quality impact of a suspected quality defect, complaint, trend, deviation, investigation, out of specification result, etc;

To facilitate risk communications and determine appropriate action to address significant product defects, in conjunction with regulatory authorities (e.g., recall).

Auditing/Inspection

To define the frequency and scope of audits, both internal and external, taking into account factors such as

- existing legal requirements;
- overall compliance status and history of the company or facility;
- robustness of a company's quality risk management activities;
- complexity of the site;
- complexity of the manufacturing process;
- complexity of the product and its therapeutic significance;
- number and significance of quality defects (e.g., recall);
- results of previous audits/inspections;
- major changes of building, equipment, processes, key personnel;
- experience with manufacturing of a product (e.g., frequency, volume, number of batches); and
- test results of official control laboratories.

Periodic review

To select, evaluate, and interpret trend results of data within the product quality review;

To interpret monitoring data (e.g., to support an assessment of the appropriateness of revalidation or changes in sampling).

Change management/change control

To manage changes based on knowledge and information accumulated in pharmaceutical development and during manufacturing;

To evaluate the impact of the changes on the availability of the final product;

To evaluate the impact on product quality of changes to the facility, equipment, material, manufacturing process, or technical transfers;

To determine appropriate actions preceding the implementation of a change, for example, additional testing, (re)qualification, (re)validation, or communication with regulators.

Continual improvement

To facilitate continual improvement in processes throughout the product lifecycle.

II.2 Quality Risk Management as Part of Regulatory Operations

Inspection and assessment activities

To assist with resource allocation including, for example, inspection planning and frequency, and inspection and assessment intensity (see "Auditing" section in Annex II.1);

To evaluate the significance of, for example, quality defects, potential recalls, and inspectional findings;

To determine the appropriateness and type of postinspection regulatory follow-up;

To evaluate information submitted by industry including pharmaceutical development information;

To evaluate impact of proposed variations or changes;

To identify risks which should be communicated between inspectors and assessors to facilitate better understanding of how risks can be or are controlled [e.g., parametric release, Process Analytical Technology (PAT)].

II.3 Quality Risk Management as Part of development

To design a quality product and its manufacturing process to consistently deliver the intended performance of the product (see ICH Q8);

To enhance knowledge of product performance over a wide range of material attributes (e.g., particle size distribution, moisture content, flow properties), processing options and process parameters;

To assess the critical attributes of raw materials, solvents, active pharmaceutical ingredient (API) starting materials, APIs, excipients, or packaging materials;

To establish appropriate specifications, identify critical process parameters and establish manufacturing controls (e.g., using information from pharmaceutical development studies regarding the clinical significance of quality attributes and the ability to control them during processing);

To decrease variability of quality attributes:
- reduce product and material defects and
- reduce manufacturing defects.

To assess the need for additional studies (e.g., bioequivalence, stability) relating to scale up and technology transfer;
To make use of the "design space" concept (see ICH Q8).

II.4 Quality Risk Management for Facilities, Equipment, and Utilities

Design of facility/equipment

To determine appropriate zones when designing buildings and facilities, for example,
- flow of material and personnel;
- minimize contamination;
- pest control measures;
- prevention of mix-ups;
- open versus closed equipment;
- clean rooms versus isolator technologies; and
- dedicated or segregated facilities/equipment.

To determine appropriate product contact materials for equipment and containers (e.g., selection of stainless steel grade, gaskets, lubricants);
To determine appropriate utilities [e.g., steam, gases, power source, compressed air, HVAC (heating, ventilation, and air conditioning), water];
To determine appropriate preventive maintenance for associated equipment (e.g., inventory of necessary spare parts).

Hygiene aspects in facilities

To protect the product from environmental hazards, including chemical, microbiological, and physical hazards (e.g., determining appropriate clothing and gowning, hygiene concerns);
To protect the environment (e.g., personnel, potential for cross-contamination) from hazards related to the product being manufactured.

Qualification of facility/equipment/utilities

To determine the scope and extent of qualification of facilities, buildings, and production equipment and/or laboratory instruments (including proper calibration methods).

Cleaning of equipment and environmental control

To differentiate efforts and decisions based on the intended use (e.g., multi- versus single-purpose, batch versus continuous production);
To determine acceptable (specified) cleaning validation limits.

Calibration/preventive maintenance

To set appropriate calibration and maintenance schedules.

Computer systems and computer controlled equipment

To select the design of computer hardware and software (e.g., modular, structured, fault tolerance);
To determine the extent of validation, for example,
- identification of critical performance parameters;
- selection of the requirements and design;
- code review;
- the extent of testing and test methods; and
- reliability of electronic records and signatures.

II.5 Quality Risk Management as Part of Materials Management

Assessment and evaluation of suppliers and contract manufacturers

To provide a comprehensive evaluation of suppliers and contract manufacturers (e.g., auditing, supplier quality agreements).

Starting material

To assess differences and possible quality risks associated with variability in starting materials (e.g., age, route of synthesis).

Use of materials

To determine whether it is appropriate to use material under quarantine (e.g., for further internal processing);
To determine appropriateness of reprocessing, reworking, use of returned goods.

Storage, logistics, and distribution conditions

To assess the adequacy of arrangements to ensure maintenance of appropriate storage and transport conditions (e.g., temperature, humidity, container design);
To determine the effect on product quality of discrepancies in storage or transport conditions (e.g., cold chain management) in conjunction with other ICH guidelines;
To maintain infrastructure (e.g., capacity to ensure proper shipping conditions, interim storage, handling of hazardous materials and controlled substances, customs clearance);
To provide information for ensuring the availability of pharmaceuticals (e.g., ranking risks to the supply chain).

II.6 Quality Risk Management as Part of Production

Validation

To identify the scope and extent of verification, qualification and validation activities (e.g., analytical methods, processes, equipment and cleaning methods;
To determine the extent for follow-up activities (e.g., sampling, monitoring and revalidation);
To distinguish between critical and noncritical process steps to facilitate design of a validation study.

In-process sampling and testing

To evaluate the frequency and extent of in-process control testing (e.g., to justify reduced testing under conditions of proven control);
To evaluate and justify the use of PAT in conjunction with parametric and real time release.

Production planning

To determine appropriate production planning (e.g., dedicated, campaign and concurrent production process sequences).

II.7 Quality Risk Management as Part of Laboratory Control and Stability Studies

Out of specification results

To identify potential root causes and corrective actions during the investigation of out of specification results.

Retest period/expiration date

To evaluate adequacy of storage and testing of intermediates, excipients, and starting materials.

II.8 Quality Risk Management as Part of Packaging and Labeling

Design of packages

To design the secondary package for the protection of primary packaged product (e.g., to ensure product authenticity, label legibility).

Selection of container closure system

To determine the critical parameters of the container closure system.

Label controls

To design label control procedures based on the potential for mix-ups involving different product labels, including different versions of the same label.

3

Pharmaceutical Quality System

I. PHARMACEUTICAL QUALITY SYSTEM

A. Introduction

This document establishes a new ICH tripartite guideline describing a model for an effective *quality* management system for the pharmaceutical industry, referred to as the *Pharmaceutical Quality System*. Throughout this guideline, the term "pharmaceutical quality system" refers to the ICH Q10 model.

ICH Q10 describes one comprehensive model for an effective pharmaceutical quality system that is based on International Standards Organization (ISO) quality concepts, includes applicable Good Manufacturing Practice (GMP) regulations and complements ICH Q8 "Pharmaceutical Development" and ICH Q9 "Quality Risk Management". ICH Q10 is a model for a pharmaceutical quality system that can be implemented throughout the different stages of a product lifecycle. Much of the content of ICH Q10 applicable to manufacturing sites is currently specified by regional GMP requirements. ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional.

ICH Q10 demonstrates industry and regulatory authorities' support of an effective pharmaceutical quality system to enhance the quality and availability of medicines around the world in the interest of public health. Implementation of ICH Q10 throughout the product lifecycle should facilitate *innovation* and *continual improvement* and strengthen the link between pharmaceutical development and manufacturing activities.

B. Scope

This guideline applies to the systems supporting the development and manufacture of pharmaceutical drug substances (i.e., API) and drug products, including biotechnology and biological products, throughout the product lifecycle.

The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognizing the differences among, and the different goals of each stage (see section 3).

For the purposes of this guideline, the product lifecycle includes the following technical activities for new and existing products:

- Pharmaceutical development:
  - Drug substance development
  - Formulation development (including container/closure system)
  - Manufacture of investigational products
  - Delivery system development (where relevant)
  - Manufacturing process development and scale-up
  - Analytical method development
- Technology transfer:
  - New product transfers during development through manufacturing
  - Transfers within or between manufacturing and testing sites for marketed products
- Commercial manufacturing:
  - Acquisition and control of materials
  - Provision of facilities, utilities, and equipment
  - Production (including packaging and labeling)
  - Quality control and assurance
  - Release
  - Storage
  - Distribution (excluding wholesaler activities)
- Product discontinuation:
  - Retention of documentation
  - Sample retention
  - Continued product assessment and reporting

C. Relationship of ICH Q10 to Regional GMP Requirements, ISO Standards, and ICH Q7

Regional GMP requirements, the ICH Q7 Guideline, "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients," and ISO quality management system guidelines form the foundation for ICH Q10. To meet the objectives described below, ICH Q10 augments GMPs by describing specific quality system elements and management responsibilities. ICH Q10 provides a harmonized model for a pharmaceutical quality system throughout the lifecycle of a product and is intended to be used together with regional GMP requirements.

The regional GMPs do not explicitly address all stages of the product lifecycle (e.g., development). The quality system elements and management responsibilities described in this guideline are intended to encourage the use of science- and risk-based approaches at each lifecycle stage, thereby promoting continual improvement across the entire product lifecycle.

D. Relationship of ICH Q10 to Regulatory Approaches

Regulatory approaches for a specific product or manufacturing facility should be commensurate with the level of product and process understanding, the results of *quality risk management*, and the effectiveness of the pharmaceutical quality system. When implemented, the effectiveness of the pharmaceutical quality system can normally be evaluated during a regulatory inspection at the manufacturing site. Potential opportunities to enhance science- and risk-based regulatory approaches are identified in Annex 1. Regulatory processes will be determined by region.

E. ICH Q10 Objectives

Implementation of the Q10 model should result in achievement of three main objectives, which complement or enhance regional GMP requirements.

1. Achieve Product Realization

To establish, implement, and maintain a system that allows the delivery of products with the quality attributes

appropriate to meet the needs of patients, health care professionals, regulatory authorities (including compliance with approved regulatory filings), and other internal and external customers.

2. Establish and Maintain a State of Control

To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and *capability of processes*. Quality risk management can be useful in identifying the monitoring and control systems.

3. Facilitate Continual Improvement

To identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfil quality needs consistently. Quality risk management can be useful for identifying and prioritizing areas for continual improvement.

F. Enablers: Knowledge Management and Quality Risk Management

Use of *knowledge management* and quality risk management will enable a company to implement ICH Q10 effectively and successfully. These enablers will facilitate achievement of the objectives described in section IE above by providing the means for science- and risk-based decisions related to product quality.

1. Knowledge Management

Product and process knowledge should be managed from development through the commercial life of the product up to and including product discontinuation. For example, development activities using scientific approaches provide knowledge for product and process understanding. Knowledge management is a systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components. Sources of knowledge include, but are not limited to prior knowledge (public domain or internally documented), pharmaceutical development studies, technology transfer activities, process validation studies over the product lifecycle, manufacturing experience, innovation, continual improvement, and *change management* activities.

2. Quality Risk Management

Quality risk management is integral to an effective pharmaceutical quality system. It can provide a proactive approach to identifying, scientifically evaluating, and controlling potential risks to quality. It facilitates continual improvement of process performance and product quality throughout the product lifecycle. ICH Q9 provides principles and examples of tools for quality risk management that can be applied to different aspects of pharmaceutical quality.

G. Design and Content Considerations

(a) The design, organization, and documentation of the pharmaceutical quality system should be well structured and clear to facilitate common understanding and consistent application.

(b) The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognizing the different goals and knowledge available for each stage.

(c) The size and complexity of the company's activities should be taken into consideration when developing a new pharmaceutical quality system or modifying an existing one. The design of the pharmaceutical quality system should incorporate appropriate risk management principles. While some aspects of the pharmaceutical quality system can be company-wide and others site-specific, the effectiveness of the pharmaceutical quality system is normally demonstrated at the site level.

(d) The pharmaceutical quality system should include appropriate processes, resources, and responsibilities to provide assurance of the quality of *outsourced activities* and purchased materials.

(e) Management responsibilities, as described in section 2, should be identified within the pharmaceutical quality system.

(f) The pharmaceutical quality system should include the following elements, as described in section 3: process performance and product quality monitoring, *corrective* and *preventive action*, change management, and management review.

(g) *Performance indicators*, as described in section 4, should be identified and used to monitor the effectiveness of processes within the pharmaceutical quality system.

H. Quality Manual

A *Quality Manual* or equivalent documentation approach should be established and should contain the description of the pharmaceutical quality system. The description should include

(a) The *quality policy* (see section 2)

(b) The scope of the pharmaceutical quality system

(c) Identification of the pharmaceutical quality system processes, as well as their sequences, linkages, and interdependencies. Process maps and flow charts can be useful tools to facilitate depicting pharmaceutical quality system processes in a visual manner

(d) Management responsibilities within the pharmaceutical quality system (see section 2)

II. MANAGEMENT RESPONSIBILITY

Leadership is essential to establish and maintain a company-wide commitment to quality and for the performance of the pharmaceutical quality system.

A. Management Commitment

(a) *Senior management* has the ultimate responsibility to ensure an effective pharmaceutical quality system is in place to achieve the *quality objectives,* and that roles, responsibilities, and authorities are defined, communicated, and implemented throughout the company.

(b) Management should
  (1) participate in the design, implementation, monitoring, and maintenance of an effective pharmaceutical quality system;
  (2) demonstrate strong and visible support for the pharmaceutical quality system and ensure its implementation throughout their organization;
  (3) ensure a timely and effective communication and escalation process exists to raise quality issues to the appropriate levels of management;
  (4) define individual and collective roles, responsibilities, authorities, and interrelationships of all organizational units related to the pharmaceutical quality system. Ensure these interactions are communicated

and understood at all levels of the organization. An independent quality unit/structure with authority to fulfil certain pharmaceutical quality system responsibilities is required by regional regulations;
(5) conduct management reviews of process performance and product quality and of the pharmaceutical quality system;
(6) advocate continual improvement; and
(7) commit appropriate resources

B. Quality Policy

(a) Senior management should establish a quality policy that describes the overall intentions and direction of the company related to quality.
(b) The quality policy should include an expectation to comply with applicable regulatory requirements and should facilitate continual improvement of the pharmaceutical quality system.
(c) The quality policy should be communicated to and understood by personnel at all levels in the company.
(d) The quality policy should be reviewed periodically for continuing effectiveness.

C. Quality Planning

(a) Senior management should ensure the quality objectives needed to implement the quality policy are defined and communicated.
(b) Quality objectives should be supported by all relevant levels of the company.
(c) Quality objectives should align with the company's strategies and be consistent with the quality policy.
(d) Management should provide the appropriate resources and training to achieve the quality objectives.
(e) Performance indicators that measure progress against quality objectives should be established, monitored, communicated regularly, and acted upon as appropriate as described in section 4.1 of this document.

D. Resource Management

(a) Management should determine and provide adequate and appropriate resources (human, financial, materials, facilities, and equipment) to implement and maintain the pharmaceutical quality system and continually improve its effectiveness.
(b) Management should ensure that resources are appropriately applied to a specific product, process, or site.

E. Internal Communication

(a) Management should ensure appropriate communication processes are established and implemented within the organization.
(b) Communications processes should ensure the flow of appropriate information between all levels of the company.
(c) Communication processes should ensure the appropriate and timely escalation of certain product quality and pharmaceutical quality system issues.

F. Management Review

(a) Senior management should be responsible for pharmaceutical quality system governance through management review to ensure its continuing suitability and effectiveness.
(b) Management should assess the conclusions of periodic reviews of process performance and product quality and of the pharmaceutical quality system, as described in sections 3 and 4.

G. Management of Outsourced Activities and Purchased Materials

The pharmaceutical quality system, including the management responsibilities described in this section, extends to the control and review of any outsourced activities and quality of purchased materials. The pharmaceutical company is ultimately responsible to ensure processes are in place to assure the control of outsourced activities and quality of purchased materials. These processes should incorporate quality risk management and include

(a) assessing prior to outsourcing operations or selecting material suppliers, the suitability and competence of the other party to carry out the activity or provide the material using a defined supply chain (e.g., audits, material evaluations, qualification);
(b) defining the responsibilities and communication processes for quality-related activities of the involved parties. For outsourced activities, this should be included in a written agreement between the contract giver and contract acceptor;
(c) monitoring and review of the performance of the contract acceptor or the quality of the material from the provider, and the identification and implementation of any needed improvements; and
(d) monitoring incoming ingredients and materials to ensure they are from approved sources using the agreed supply chain.

H. Management of Change in Product Ownership

When product ownership changes (e.g., through acquisitions), management should consider the complexity of this and ensure:

(a) the ongoing responsibilities are defined for each company involved; and
(b) the necessary information is transferred

III. CONTINUAL IMPROVEMENT OF PROCESS PERFORMANCE AND PRODUCT QUALITY

This section describes the lifecycle stage goals and the four specific pharmaceutical quality system elements that augment regional requirements to achieve the ICH Q10 objectives, as defined in section IE. It does not restate all regional GMP requirements.

A. Lifecycle Stage Goals

The goals of each product lifecycle stage are described below.

1. Pharmaceutical Development

The goal of pharmaceutical development activities is to design a product and its manufacturing process to consistently deliver the intended performance and meet the needs of patients and health care professionals, and regulatory authorities and internal customers' requirements. Approaches to pharmaceutical development are described in ICH Q8. The results of exploratory and clinical development studies, while outside the scope of this guidance, are inputs to pharmaceutical development.

Table 3.1 Application of Process Performance and Product Quality Monitoring System Throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Process and product knowledge generated and process and product monitoring conducted throughout development can be used to establish a control strategy for manufacturing.	Monitoring during scale-up activities can provide a preliminary indication of process performance and the successful integration into manufacturing. Knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy.	A well-defined system for process performance and product quality monitoring should be applied to assure performance within a state of control and to identify improvement areas.	Once manufacturing ceases, monitoring such as stability testing should continue to completion of the studies. Appropriate action on marketed product should continue to be executed according to regional regulations.

2. Technology Transfer

The goal of technology transfer activities is to transfer product and process knowledge between development and manufacturing, and within or between manufacturing sites to achieve product realization. This knowledge forms the basis for the manufacturing process, *control strategy*, process validation approach, and ongoing continual improvement.

3. Commercial Manufacturing

The goals of manufacturing activities include achieving product realization, establishing, and maintaining a state of control and facilitating continual improvement. The pharmaceutical quality system should assure that the desired product quality is routinely met, suitable process performance is achieved, the set of controls are appropriate, improvement opportunities are identified and evaluated, and the body of knowledge is continually expanded.

4. Product Discontinuation

The goal of product discontinuation activities is to manage the terminal stage of the product lifecycle effectively. For product discontinuation, a predefined approach should be used to manage activities such as retention of documentation and samples and continued product assessment (e.g., complaint handling and stability) and reporting in accordance with regulatory requirements.

B. Pharmaceutical Quality System Elements

The elements described below might be required in part under regional GMP regulations. However, the Q10 model's intent is to enhance these elements in order to promote the lifecycle approach to product quality. These four elements are:

- Process performance and product quality monitoring system
- *Corrective action* and *preventive action* (CAPA) system
- Change management system
- Management review of process performance and product quality

These elements should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognizing the differences among, and the different goals of, each stage. Throughout the product lifecycle, companies are encouraged to evaluate opportunities for innovative approaches to improve product quality.

Each element is followed by a table of example applications of the element to the stages of the pharmaceutical lifecycle.

1. Process Performance and Product Quality Monitoring System (Table 3.1)

Pharmaceutical companies should plan and execute a system for the monitoring of process performance and product quality to ensure a state of control is maintained. An effective monitoring system provides assurance of the continued capability of processes and controls to produce a product of desired quality and to identify areas for continual improvement. The process performance and product quality monitoring system should:

(a) use quality risk management to establish the control strategy. This can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. The control strategy should facilitate timely *feedback/feedforward* and appropriate corrective action and preventive action;
(b) provide the tools for measurement and analysis of parameters and attributes identified in the control strategy (e.g., data management and statistical tools);
(c) analyze parameters and attributes identified in the control strategy to verify continued operation within a state of control;
(d) identify sources of variation affecting process performance and product quality for potential continual improvement activities to reduce or control variation;
(e) include feedback on product quality from both internal and external sources, for example, complaints, product rejections, nonconformances, recalls, deviations, audits and regulatory inspections, and findings; and
(f) provide knowledge to enhance process understanding, enrich the *design space* (where established), and enable innovative approaches to process validation.

2. Corrective Action and Preventive Action System (Table 3.2)

The pharmaceutical company should have a system for implementing corrective actions and preventive actions resulting from the investigation of complaints, product rejections, nonconformances, recalls, deviations, audits, regulatory inspections and findings, and trends from process performance, and product quality monitoring. A structured approach to the investigation process should be used with the objective of determining the root cause. The level of effort, formality, and documentation of the investigation should be commensurate with the level of risk, in line with ICH Q9. CAPA methodology

Table 3.2 Application of Corrective Action and Preventive Action System Throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Product or process variability is explored. CAPA methodology is useful where corrective actions and preventive actions are incorporated into the iterative design and development process.	CAPA can be used as an effective system for feedback, feedforward, and continual improvement.	CAPA should be used and the effectiveness of the actions should be evaluated.	CAPA should continue after the product is discontinued. The impact on product remaining on the market should be considered as well as other products, which might be impacted.

should result in product and process improvements and enhanced product and process understanding.

3. Change Management System (Table 3.3)

Innovation, continual improvement, the outputs of process performance, and product quality monitoring and CAPA drive change. In order to evaluate, approve, and implement these changes properly, a company should have an effective change management system. There is generally a difference in formality of change management processes prior to the initial regulatory submission and after submission, where changes to the regulatory filing might be required under regional requirements.

The change management system ensures continual improvement is undertaken in a timely and effective manner. It should provide a high degree of assurance there are no unintended consequences of the change.

The change management system should include the following, as appropriate for the stage of the lifecycle:

(a) Quality risk management should be utilized to evaluate proposed changes. The level of effort and formality of the evaluation should be commensurate with the level of risk.
(b) Proposed changes should be evaluated relative to the marketing authorization, including design space, where established, and/or current product and process understanding. There should be an assessment to determine whether a change to the regulatory filing is required under regional requirements. As stated in ICH Q8, working within the design space is not considered a change (from a regulatory filing perspective). However, from a pharmaceutical quality system standpoint, all changes should be evaluated by a company's change management system.
(c) Proposed changes should be evaluated by expert teams contributing the appropriate expertise and knowledge from relevant areas (e.g., Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs and Medical), to ensure the change is technically justified. Prospective evaluation criteria for a proposed change should be set.
(d) After implementation, an evaluation of the change should be undertaken to confirm the change objectives were achieved and that there was no deleterious impact on product quality.

4. Management Review of Process Performance and Product Quality (Table 3.4)

Management review should provide assurance that process performance and product quality are managed over the lifecycle. Depending on the size and complexity of the company, management review can be a series of reviews at various levels of management and should include a timely and effective communication and escalation process to raise appropriate quality issues to senior levels of management for review.

(a) The management review system should include
  (1) The results of regulatory inspections and findings, audits and other assessments, and commitments made to regulatory authorities.
  (2) Periodic quality reviews, that can include
    (i) measures of customer satisfaction such as product quality complaints and recalls;
    (ii) conclusions of process performance and product quality monitoring; and
    (iii) the effectiveness of process and product changes including those arising from corrective action and preventive actions
  (3) Any follow-up actions from previous management reviews.
(b) The management review system should identify appropriate actions, such as:
  (1) Improvements to manufacturing processes and products
  (2) Provision, training, and/or realignment of resources
  (3) Capture and dissemination of knowledge

IV. CONTINUAL IMPROVEMENT OF THE PHARMACEUTICAL QUALITY SYSTEM

This section describes activities that should be conducted to manage and continually improve the pharmaceutical quality system.

Table 3.3 Application of Change Management System Throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Change is an inherent part of the development process and should be documented; the formality of the change management process should be consistent with the stage of pharmaceutical development.	The change management system should provide management and documentation of adjustments made to the process during technology transfer activities.	A formal change management system should be in place for commercial manufacturing. Oversight by the quality unit should provide assurance of appropriate science- and risk-based assessments.	Any changes after product discontinuation should go through an appropriate change management system.

Table 3.4 Application of Management Review of Process Performance and Product Quality Throughout the Product Lifecycle

Pharmaceutical Development	Technology Transfer	Commercial Manufacturing	Product Discontinuation
Aspects of management review can be performed to ensure adequacy of the product and process design.	Aspects of management review should be performed to ensure the developed product and process can be manufactured at commercial scale.	Management review should be a structured system, as described above, and should support continual improvement.	Management review should include such items as product stability and product quality complaints.

A. Management Review of the Pharmaceutical Quality System

Management should have a formal process for reviewing the pharmaceutical quality system on a periodic basis. The review should include

(a) Measurement of achievement of pharmaceutical quality system objectives
(b) Assessment of performance indicators that can be used to monitor the effectiveness of processes within the pharmaceutical quality system, such as:
  (1) Complaint, deviation, CAPA, and change management processes
  (2) Feedback on outsourced activities
  (3) Self-assessment processes including risk assessments, trending, and audits
  (4) External assessments such as regulatory inspections and findings and customer audits

B. Monitoring of Internal and External Factors Impacting the Pharmaceutical Quality System

Factors monitored by management can include

(a) Emerging regulations, guidance, and quality issues that can impact the Pharmaceutical Quality System
(b) Innovations that might enhance the pharmaceutical quality system
(c) Changes in business environment and objectives
(d) Changes in product ownership

C. Outcomes of Management Review and Monitoring

The outcome of management review of the pharmaceutical quality system and monitoring of internal and external factors can include

(a) Improvements to the pharmaceutical quality system and related processes
(b) Allocation or reallocation of resources and/or personnel training
(c) Revisions to quality policy and quality objectives
(d) Documentation and timely and effective communication of the results of the management review and actions, including escalation of appropriate issues to senior management

GLOSSARY

ICH and ISO definitions are used in ICH Q10 where they exist. For the purpose of ICH Q10, where the words "requirement," "requirements," or "necessary" appear in an ISO definition, they do not necessarily reflect a regulatory requirement. The source of the definition is identified in parentheses after the definition. Where no appropriate ICH or ISO definition was available, an ICH Q10 definition was developed.

Capability of a Process—Ability of a process to realize a product that will fulfil the requirements of that product. The concept of process capability can also be defined in statistical terms. (ISO 9000:2005)

Change Management—A systematic approach to proposing, evaluating, approving, implementing, and reviewing changes. (ICH Q10)

Continual Improvement—Recurring activity to increase the ability to fulfil requirements. (ISO 9000:2005)

Control Strategy—A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Corrective Action—Action to eliminate the cause of a detected nonconformity or other undesirable situation. *Note*: Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence. (ISO 9000:2005)

Design Space—The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. (ICH Q8)

Enabler—A tool or process which provides the means to achieve an objective. (ICH Q10)

Feedback/Feedforward—Feedback: The modification or control of a process or system by its results or effects.
Feedforward: The modification or control of a process using its anticipated results or effects. (Oxford Dictionary of English. Oxford University Press; 2003)
Feedback/feedforward can be applied technically in process control strategies and conceptually in quality management. (ICH Q10)

Innovation—The introduction of new technologies or methodologies. (ICH Q10)

Knowledge Management—Systematic approach to acquiring, analyzing, storing, and disseminating information related to products, manufacturing processes, and components. (ICH Q10)

Outsourced Activities—Activities conducted by a contract acceptor under a written agreement with a contract giver. (ICH Q10)

Performance Indicators—Measurable values used to quantify quality objectives to reflect the performance of an organisation, process or system, also known as "performance metrics" in some regions. (ICH Q10)

Pharmaceutical Quality System (PQS)—Management system to direct and control a pharmaceutical company with regard to quality. (ICH Q10 based upon ISO 9000:2005)

Preventive Action—Action to eliminate the cause of a potential nonconformity or other undesirable potential situation. *Note*: Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence. (ISO 9000:2005)

Product Realization—Achievement of a product with the quality attributes appropriate to meet the needs of patients, health care professionals, and regulatory authorities (including compliance with marketing authorisation) and internal customers requirements. (ICH Q10)

Quality—The degree to which a set of inherent properties of a product, system, or process fulfils requirements. (ICH Q9)

Quality Manual—Document specifying the quality management system of an organization. (ISO 9000:2005)

Quality Objectives—A means to translate the quality policy and strategies into measurable activities. (ICH Q10)

Quality Planning—Part of quality management focused on setting quality objectives and specifying necessary operational processes and related resources to fulfil the quality objectives. (ISO 9000:2005)

Quality Policy—Overall intentions and direction of an organisation related to quality as formally expressed by senior management. (ISO 9000:2005)

Quality Risk Management—A systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle. (ICH Q9)

Senior Management—Person(s) who direct and control a company or site at the highest levels with the authority and responsibility to mobilise resources within the company or site. (ICH Q10 based in part on ISO 9000:2005)

State of Control—A condition in which the set of controls consistently provides assurance of continued process performance and product quality. (ICH Q10)

Annex 1

Potential Opportunities to Enhance Science- and Risk-Based Regulatory Approaches[a]

Scenario	Potential Opportunity
1. Comply with GMPs	Compliance–status quo
2. Demonstrate effective pharmaceutical quality system, including effective use of quality risk management principles (e.g., ICH Q9 and ICH Q10).	Opportunity to • Increase use of risk-based approaches for regulatory inspections.
3. Demonstrate product and process understanding, including effective use of quality risk management principles (e.g., ICH Q8 and ICH Q9).	Opportunity to • facilitate science-based pharmaceutical quality assessment, • enable innovative approaches to process validation, and • establish real-time release mechanisms.
4. Demonstrate effective pharmaceutical quality system and product and process understanding, including the use of quality risk management principles (e.g., ICH Q8, ICH Q9, and ICH Q10).	Opportunity to • increase use of risk-based approaches for regulatory inspections, • facilitate science-based pharmaceutical quality assessment, • optimize science- and risk-based postapproval change processes to maximize benefits from innovation and continual improvement, • enable innovative approaches to process validation, and • establish real-time release mechanisms.

[a]*Note*: This annex reflects potential opportunities to enhance regulatory approaches. The actual regulatory process will be determined by region.

Annex 2

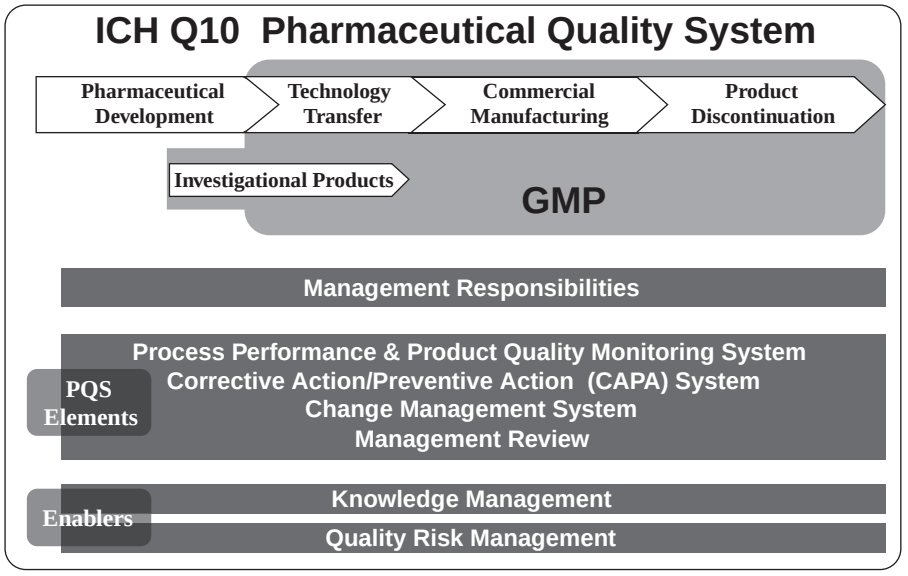


Diagram of the ICH Q10 Pharmaceutical Quality System Model

This diagram illustrates the major features of the ICH Q10 Pharmaceutical Quality System (PQS) model. The PQS covers the entire lifecycle of a product including pharmaceutical development, technology transfer, commercial manufacturing, and product discontinuation as illustrated by the upper portion of the diagram. The PQS augments regional GMPs as illustrated in the diagram. The diagram also illustrates that regional GMPs apply to the manufacture of investigational products.

The next horizontal bar illustrates the importance of management responsibilities explained in section 2 to all stages of the product lifecycle. The following horizontal bar lists the PQS elements, which serve as the major pillars under the PQS model. These elements should be applied appropriately and proportionally to each lifecycle stage recognizing opportunities to identify areas for continual improvement.

The bottom set of horizontal bars illustrates the enablers: knowledge management and quality risk management, which are applicable throughout the lifecycle stages. These enablers support the PQS goals of achieving product realization, establishing and maintaining a state of control, and facilitating continual improvement.

4

Pharmaceutical Development

I. INTRODUCTION

Where a company chooses to apply quality by design and quality risk management (ICH Q9, Quality Risk Management), linked to an appropriate pharmaceutical quality system, then opportunities arise to enhance science- and risk-based regulatory approaches, which is the subject of this chapter.

A. Approaches to Pharmaceutical Development

In all cases, the product should be designed to meet patients' needs and the intended product performance. Strategies for product development vary from company to company and from product to product. The approach to, and extent of, development can also vary and should be outlined in the submission. An applicant might choose either an empirical approach or a more systematic approach to product development. An illustration of the potential contrasts of these approaches is shown in Appendix 1. A more systematic approach to development (also defined as quality by design) can include, for example, incorporation of prior knowledge, results of studies using design of experiments, use of quality risk management, and use of knowledge management (see ICH Q10) throughout the lifecycle of the product. Such a systematic approach can enhance the process to achieve quality and help the regulators to better understand a company's strategy. Product and process understanding can be updated with the knowledge gained over the product lifecycle.

A greater understanding of the product and its manufacturing process can create a basis for more flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided in the registration application. It is the knowledge gained and submitted to the authorities, and not the volume of data collected, that forms the basis for science- and risk-based submissions and regulatory evaluations. Nevertheless, appropriate data demonstrating that this knowledge is based on sound scientific principles should be presented with each application.

Pharmaceutical development should include, at a minimum, the following elements:

- Defining the target product profile as it relates to quality, safety, and efficacy, considering for example, the route of administration, dosage form, bioavailability, dosage, and stability
- Identifying critical quality attributes (CQAs) of the drug product, so that those product characteristics having an impact on product quality can be studied and controlled
- Determining the quality attributes of the drug substance, excipients etc., and selecting the type and amount of excipients to deliver drug product of the desired quality
- Selecting an appropriate manufacturing process
- Identifying a control strategy

An enhanced, quality by design approach to product development would additionally include the following elements:

- A systematic evaluation, understanding, and refining of the formulation and manufacturing process, including
  - identifying, through for example, prior knowledge, experimentation, and risk assessment, the material attributes and process parameters that can have an effect on product CQAs; and
  - determining the functional relationships that link material attributes and process parameters to product CQAs.
- Using the enhanced process understanding in combination with quality risk management to establish an appropriate control strategy, which can, for example, include a proposal for design space(s) and/or real-time release.

As a result, this more systematic approach could facilitate continual improvement and innovation throughout the product lifecycle (see ICH Q10 Pharmaceutical Quality System).

II. ELEMENTS OF PHARMACEUTICAL DEVELOPMENT

The section that follows elaborates, by means of description and example, possible approaches to gaining a more systematic, enhanced understanding of the product and process under development. The examples given are purely illustrative and are not intended to create new regulatory requirements.

A. Target Product Profile

A target product profile is a prospective and dynamic summary of the quality characteristics of a drug product that ideally will be achieved to ensure that the desired quality, and hence the safety and efficacy, of a drug product is realized. The target product profile forms the basis of design for the development of the product.

Considerations for the target product profile should include

- Dosage form and route of administration
- Dosage form strength(s)
- Therapeutic moiety release or delivery and pharmacokinetic characteristics (e.g., dissolution; aerodynamic performance) appropriate to the drug product dosage form being developed
- Drug product quality criteria (e.g., sterility, purity) appropriate for the intended marketed product

B. Critical Quality Attributes

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates, and drug product.

Drug product CQAs include the properties that impart the desired quality, safety, and efficacy. CQAs of solid oral dosage forms are typically those aspects affecting product purity, potency, stability, and drug release. CQAs for other delivery systems can additionally include more product specific aspects, such as aerodynamic properties for inhaled products, sterility for parenterals, and adhesive force for transdermal patches. For drug substances or intermediates, the CQAs can additionally include those properties (e.g., particle size distribution, bulk density) that affect downstream processability.

Drug product CQAs are used to guide the product and process development. Potential drug product CQAs can be identified from the target product profile and/or prior knowledge. The list of potential CQAs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase. Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product.

C. Linking Material Attributes and Process Parameters to CQAs—Risk Assessment

Risk assessment is a valuable science-based process used in quality risk management (see ICH Q9) that can aid in identifying which material attributes and process parameters have an effect on product CQAs. While the risk assessment is typically performed early in the pharmaceutical development, it can be helpful to repeat the risk assessment as information and greater knowledge become available.

Risk assessment tools can be used to identify and rank parameters (e.g., operational, equipment, input material) with potential to have an impact on product quality based on prior knowledge and initial experimental data. For an illustrative example, see Appendix 2. The initial list of potential parameters can be quite extensive, but is likely to be narrowed as process understanding is increased. The list can be refined further through experimentation to determine the significance of individual variables and potential interactions. Once the significant parameters are identified, they can be further studied (e.g., through a combination of design of experiments, mathematical models, or studies that lead to mechanistic understanding) to achieve a higher level of process understanding.

D. Design Space

The linkage between the process inputs (input variables and process parameters) and the critical quality attributes can be described in the design space.

1. Selection of Variables

The risk assessment and process development experiments described in section 2.3 can not only lead to an understanding of the linkage and effect of process inputs on product CQAs, but also help identify the variables and their ranges within which consistent quality can be achieved. These input variables can thus be selected for inclusion in the design space.

An explanation should be provided in the application to describe what variables were considered, how they affect the process and product quality, and which parameters were included or excluded in the design space. An input variable or process parameter need not be included in the design space if it has no effect on delivering CQAs when the input variable or parameter is varied over the full potential range of operation. The control of these variables would be under good manufacturing practices (GMP). However, the knowledge gained from studies should be described in the submission.

2. Defining and Describing a Design Space in a Submission

A design space can be defined in terms of ranges of input variables or parameters, or through more complex mathematical relationships. It is possible to define a design space as a time-dependent function (e.g., temperature and pressure cycle of a lyophilization cycle), or as a combination of variables such as principal components of a multivariate model. Scaling factors can also be included if the design space is intended to span multiple operational scales. Analysis of historical data can provide the basis for establishing a design space. Regardless of how a design space is developed, it is expected that operation within the design space will result in a product meeting the defined quality attributes.

Examples of different potential approaches to presentation of a design space are presented in Appendix 2.

3. Unit Operation Design Space(s)

The applicant can choose to establish independent design spaces for one or more unit operations, or to establish a single design space that spans multiple operations. While a separate design space for each unit operation is often simpler to develop, a design space that spans the entire process can provide more operational flexibility. For example, in the case of a drug product that undergoes degradation in solution before lyophilization, the design space to control the extent of degradation (e.g., concentration, time, temperature) could be expressed for each unit operation, or as a sum overall unit operations.

4. Relationship of Design Space to Scale and Equipment

When defining a design space, the applicant should keep in mind the type of operational flexibility desired. A design space can be developed at small scale or pilot scale. The applicant should justify the relevance of a design space developed at small or pilot scale to the proposed production scale manufacturing process and discuss the potential risks in the scale-up operation.

If the applicant wishes the design space to be applicable to multiple operational scales, the design space should be described in terms of relevant scale-independent parameters. For example, if a product was determined to be shear sensitive in a mixing operation, the design space could include shear rate, rather than agitation rate. Dimensionless numbers and/or models for scaling also can be included as part of the design space description.

The creation of a design space can be helpful for technology transfer or site changes. The subsequent regulatory processes will be region-specific.

5. Design Space vs. Proven Acceptable Ranges

A combination of proven acceptable ranges does not constitute a design space. However, proven acceptable ranges based on univariate experimentation can provide some knowledge about the process.

6. Design Space and Edge of Failure

It can be helpful to know where edges of failure could be, or to determine potential failure modes. However, it is not an essential part of establishing a design space.

E. Control Strategy

A control strategy is designed to consistently ensure product quality.

The elements of the control strategy discussed in section P.2 of the dossier should describe and justify how in-process controls and the controls of input materials (drug substance and excipients), container closure system, intermediates and end products contribute to the final product quality. These controls should be based on product, formulation, and process understanding and should include, at a minimum, control of the critical parameters and attributes.

A comprehensive pharmaceutical development approach will generate process and formulation understanding that identifies sources of variability. Critical sources of variability that can lead to product failures should be identified, appropriately understood, and managed or controlled. Understanding sources of variability and their impact on downstream processes or processing, intermediate products, and finished product quality can provide flexibility for shifting of controls upstream and minimize the need for end product testing. This process understanding, in combination with quality risk management (see ICH Q9), will support the control of process parameters so that the variability of raw materials can be compensated for in an adaptable process to deliver consistent product quality.

This process understanding enables an alternative, manufacturing paradigm where the variability of input materials might not need to be tightly constrained. Instead, it can be possible to design an adaptive process step (a step that is responsive to the input materials) to ensure consistent product quality.

Enhanced understanding of product performance can justify the use of surrogate tests or support real-time release in lieu of end-product testing. For example, disintegration could serve as a surrogate for dissolution for fast-disintegrating solid forms with highly soluble drug substances. Unit dose uniformity performed in-process [e.g., using weight variation coupled with near infrared (NIR) assay] can enable real-time release and provide an increased level of quality assurance compared to the traditional end-product testing using compendial content uniformity standards.

Elements of a control strategy can include, but are not limited to, the following:

- Control of input material attributes (e.g., drug substance, excipients, primary packaging materials) based on an understanding of their impact on processability or product quality;
- Product specification(s);
- Controls for unit operations that have an impact on downstream processing or end-product quality (e.g., the impact of drying on degradation, particle size distribution of the granulate on dissolution);
- In-process or real-time release in lieu of end-product testing;
- A monitoring program (e.g., full product testing at regular intervals) for verifying multivariate prediction models.

A control strategy can include redundant or alternative elements, if justified. For example, one element of the control strategy could rely on end-product testing, whereas an additional or alternative element could depend on real-time release using process analytical technology (PAT). The use of these alternative elements should be described in the submission.

Adoption of the principles in this guideline can support the justification of alternative approaches to the setting of specification attributes and acceptance criteria as described in Q6A and Q6B.

F. Product Lifecycle Management and Continual Improvement

Throughout the product lifecycle, companies have opportunities to evaluate innovative approaches to improve product quality (see ICH Q10).

For example, once approved, a design space provides the applicant flexibility to optimize and adjust a process as managed under their quality system. A design space is not necessarily static in nature and should be periodically reassessed to ensure that the process is working as anticipated to deliver product quality attributes. For certain design spaces using mathematical models (e.g., chemometrics models of NIR) periodic maintenance could be essential to ensure the models' performance (e.g., checking calibration), or to update the model based upon additional data. Expansion, reduction, or redefinition of the design space could be desired upon gaining additional process information.

III. SUBMISSION OF PHARMACEUTICAL DEVELOPMENT AND RELATED INFORMATION IN CTD FORMAT

Pharmaceutical development information is submitted in section P.2 of the Common Technical Document (CTD). Other information resulting from pharmaceutical development studies could be accommodated by the CTD format in a number of different ways and some specific suggestions are provided below. Certain aspects (e.g., product lifecycle management, continual improvement) of this guidance are handled under the applicant's pharmaceutical quality system (see ICH Q10) and need not be submitted in the registration application.

A. Quality Risk Management and Product and Process Development

Quality risk management can be used at many different stages during product and process development and manufacturing implementation. The assessments used to guide and justify development decisions can be included in the relevant sections of P.2. For example, risk analyses and functional relationships linking material attributes to product CQAs can be included in P.2.1, P.2.2, and P.2.3. Risk analyses linking the design of the manufacturing process to product quality can be included in P.2.3.

B. Design Space

As an element of the proposed manufacturing process, the design space(s) can be described in the section of the application that includes the description of the manufacturing process and process controls (P.3.3). If appropriate, additional information can be provided in the section of the application that addresses the controls of critical steps and intermediates (P.3.4). The relationship of the design space(s) to the overall control strategy can be explained in the section of the application that includes the justification of the drug product specification (P.5.6). The product and manufacturing process development sections of the application (P.2.1, P.2.2, and P.2.3) are appropriate places to summarize and describe product and process development studies that provide the basis for the design space(s).

C. Control Strategy

The section of the application that includes the justification of the drug product specification (P.5.6) is a good place to summarize the control strategy. The summary should be clear about the various roles played by different components of the control strategy. However, detailed information about input material controls, and process controls should still be provided in the appropriate CTD format sections [e.g., drug substance section (S), control of excipients (P.4), description of manufacturing process and process controls (P.3.3), controls of critical steps and intermediates (P.3.4)].

D. Drug Substance Related Information

If drug substance CQAs have the potential to affect the CQAs or manufacturing process of the drug product, some discussion of drug substance CQAs can be appropriate in the pharmaceutical development section of the application (e.g., P.2.1).

GLOSSARY

Control Strategy—A planned set of controls, derived from current product and process understanding, that assures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control. (ICH Q10)

Critical Quality Attribute (CQA)—A physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Critical Process Parameter—A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.

Edge of Failure—The boundary to a variable or parameter, beyond which the relevant quality attributes or specification cannot be met.

Proven Acceptable Range—A characterized range of a process parameter for which operation within this range, while keeping other parameters constant, will result in producing a material meeting relevant quality criteria.

Quality by Design—A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.

Real-time release—The ability to evaluate and ensure the acceptable quality of in-process and/or final product based on process data, which typically include a valid combination of assessed material attributes and process controls.

Appendix 1: Differing Approaches to Pharmaceutical Development[a]

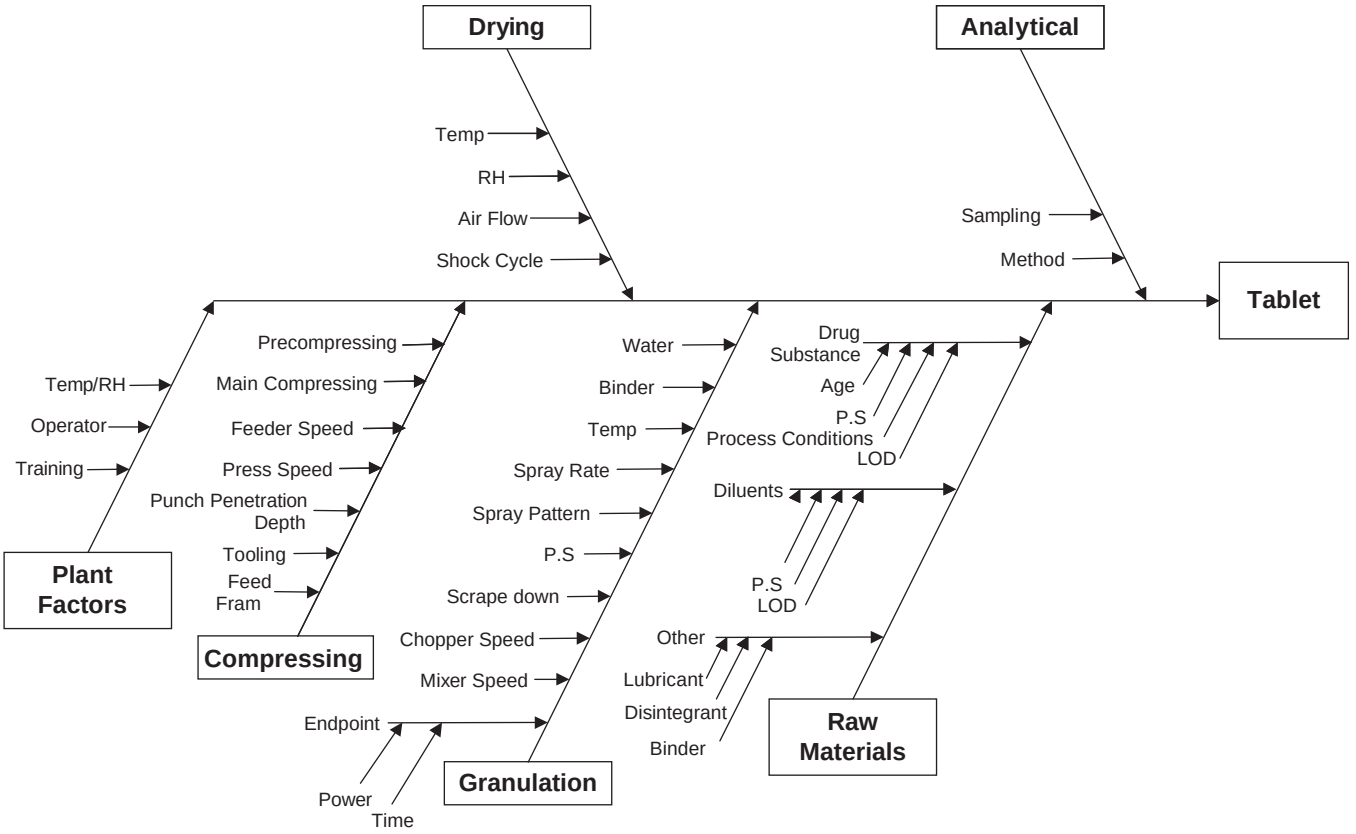
Aspect	Minimal Approach	Enhanced, Quality by Design Approach
Overall pharmaceutical development	• Mainly empirical • Developmental research often conducted one variable at a time	• Systematic, relating mechanistic understanding of input material attributes and process parameters to drug product CQAs • Multivariate experiments to understand product and process • Establishment of design space • PAT tools utilized
Manufacturing process	• Fixed • Validation primarily based on initial full-scale batches • Focus on optimization and reproducibility	• Adjustable within design space • Lifecycle approach to validation and, ideally, continuous process verification • Focus on control strategy and robustness • Use of statistical process control methods
Process controls	• In-process tests primarily for go/no go decisions • Off-line analysis	• PAT tools utilized with appropriate feedforward and feedback controls • Process operations tracked and trended to support continual improvement efforts postapproval
Product specifications	• Primary means of control • Based on batch data available at time of registration	• Part of the overall quality control strategy • Based on desired product performance with relevant supportive data
Control strategy	• Drug product quality controlled primarily by intermediate and end-product testing	• Drug product quality ensured by risk-based control strategy for well understood product and process • Quality controls shifted upstream, with the possibility of real-time release or reduced end-product testing
Lifecycle management	• Reactive (i.e., problem solving and corrective action)	• Preventive action • Continual improvement facilitated

[a]*Note*: This table is intended only to illustrate some potential contrasts between what might be considered a minimal approach and an enhanced approach regarding different aspects of pharmaceutical development and lifecycle management. It is not intended to specifically define the approach. Current practices in the pharmaceutical industry vary and typically lie between these approaches.

Appendix 2: Illustrative Examples

Example of Use of a Risk Assessment Tool

For example, a cross-functional team of experts could work together to develop an Ishikawa (fishbone) diagram that identifies all potential variables, which can have an impact on the desired quality attribute. The team could then rank the variables based on probability, severity, and detectability using failure mode effect analysis (FMEA) or similar tools based on prior knowledge and initial experimental data. Design of experiments or other experimental approaches could then be used to evaluate the impact of the higher ranked variables, to gain greater understanding of the process, and to develop a proper control strategy.



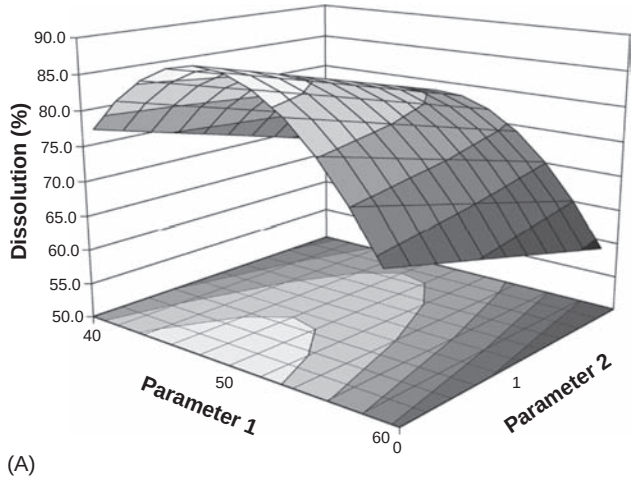
Ishikawa Diagram

Example of Depiction of Interactions

The figure below depicts the effect of interactions, or lack thereof, between three process parameters on the level of degradation product Y. The figure shows a series of two-dimensional plots showing the effect of interactions among three process parameters (initial moisture content, temperature, mean particle size) of the drying operation of a granulate (drug product intermediate) on degradation product Y. The relative slopes of the lines or curves within a plot indicate if interaction is present. In this example, initial moisture content and temperature are interacting; but initial moisture content and mean particle size are not, nor are temperature and mean particle size.

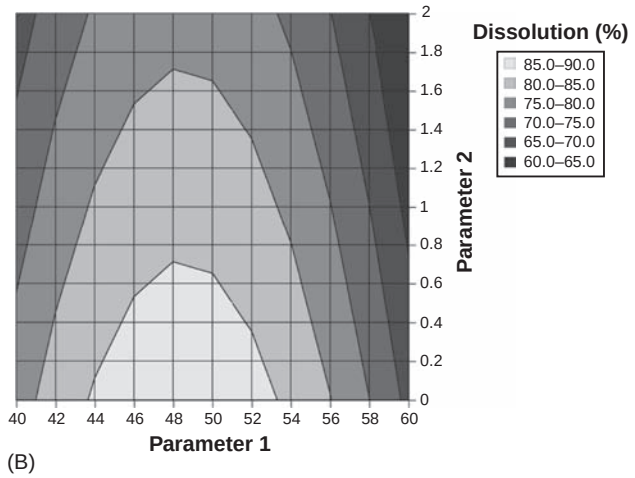
Illustrative Examples of Presentation of Design Space

Figure 4.1 Design space described with the aid of response surface plot [Fig. 4.1(A)] or contour plot [Fig. 4.1(B)] and defined by nonlinear [Fig. 4.1(C)] or linear combination [Fig. 4.1(D)] of process parameter ranges. In this example, the effects of the two parameters are additive, but the two parameters do not interact.



(A)

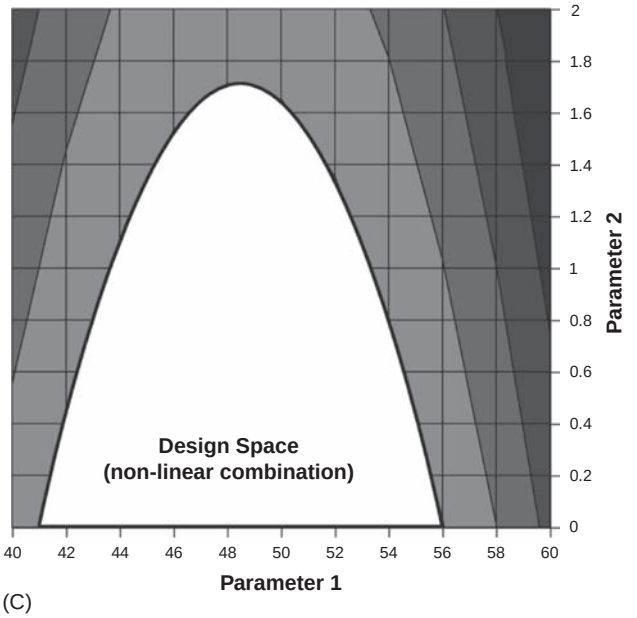
Figure 4.1(A) Response surface plot of dissolution as a function of two parameters of a granulation operation. Dissolution above 80% is desired.



(B)

Figure 4.1(B) Contour plot of dissolution from example 1A.

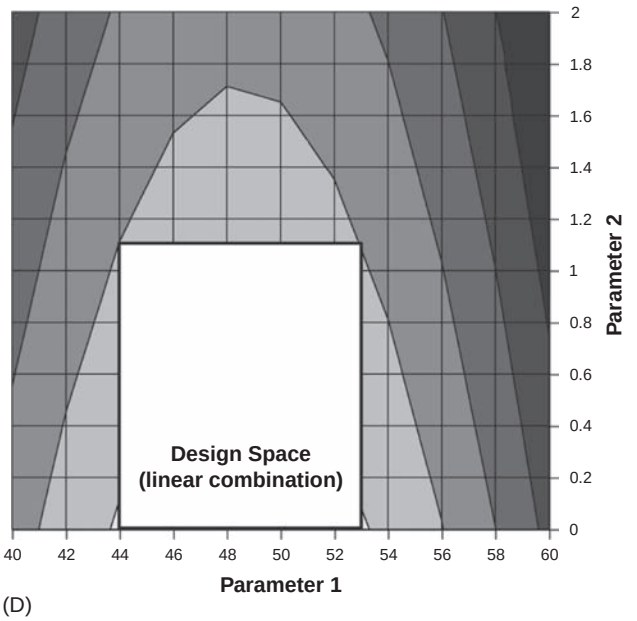
Where multiple parameters are involved, the design space can be presented for two parameters, in a manner similar to the examples shown above, at different values (e.g., high, middle, low) within the range of the third parameter, the fourth parameter, and so on. A stacked plot of these design spaces can be considered, if appropriate.



(C)

Figure 4.1(C) Design space for granulation parameters, defined by a nonlinear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%). In this example, the design space can be optionally expressed by equations that describe the boundaries, that is.,

- Parameter 1 has a range of 41 to 56
- Parameter 2 has a lower limit of 0 and an upper limit that is a function of parameter



(D)

Figure 4.1(D) Design space for granulation parameters, defined by a linear combination of their ranges, that delivers satisfactory dissolution (i.e., >80%). This design space is a subset of the nonlinear design space from example 1C, and can be optionally expressed as the following:

- Parameter 1 has a range of 44 to 53
- Parameter 2 has a range of 0 to 1.1

Figure 4.2 Design space determined from the common region of successful operating ranges for multiple CQAs. The relations of two CQAs, that is, friability and dissolution, to two process parameters of a granulation operation are shown in Figures 2(A) and 2(B). Figure 2(C) shows the overlap of these regions and the maximum ranges of the potential design space.

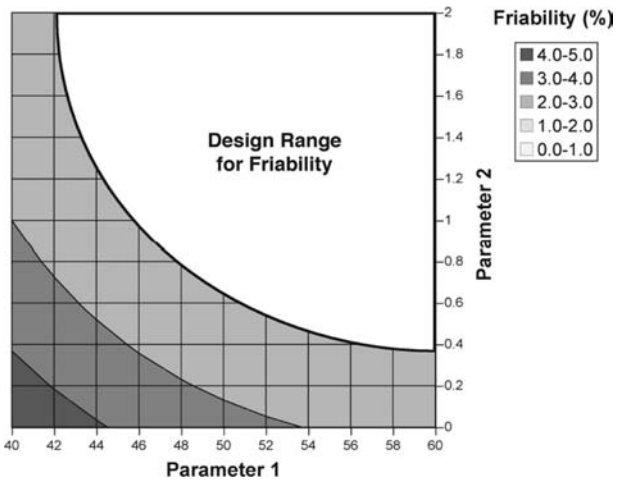


Figure 4.2(A) Contour plot of friability as a function of parameters 1 and 2.

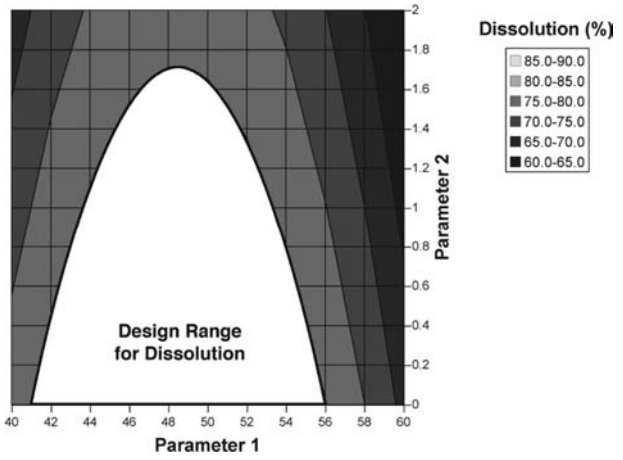


Figure 4.2(B) Contour plot of dissolution as a function of parameters 1 and 2.

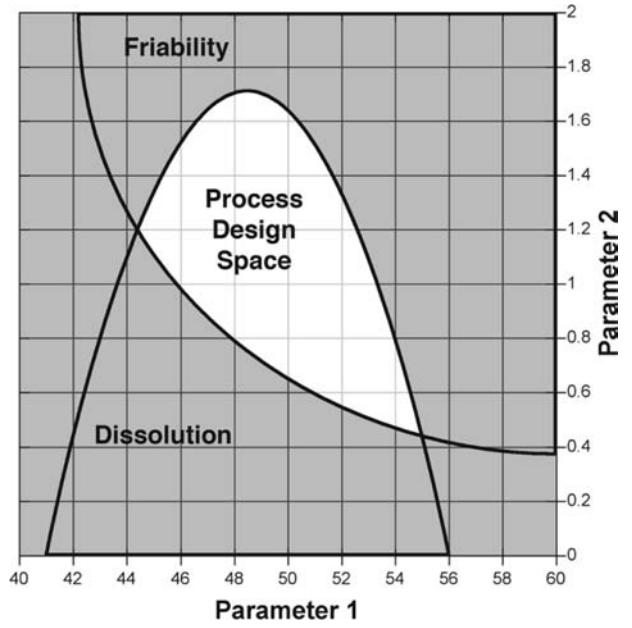


Figure 4.2(C) Potential process design space, comprised of the overlap region of design ranges for friability and or dissolution.

Figure 4.3 The design space for a drying operation that is dependent upon the path of temperature and/or pressure overtime. The end point for moisture content is 1–2%. Operating above the upper limit of the design space can cause excessive impurity formation, while operating below the lower limit of the design space can result in excessive particle attrition.

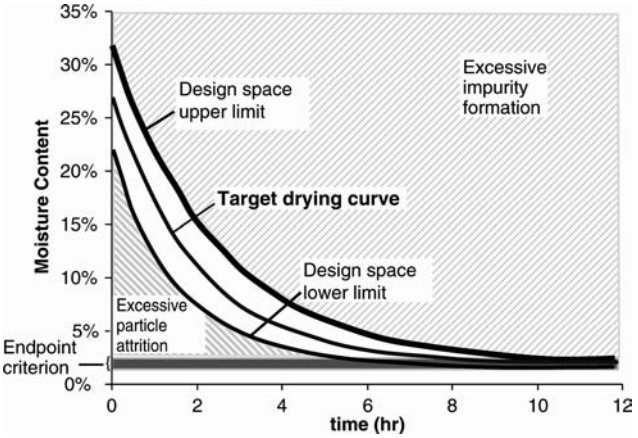


Figure 4.3

5

Pharmaceutical Development in CTD

I. INTRODUCTION

A. Objective of the Guideline

This guideline describes the suggested contents for the 3.2.P.2 (Pharmaceutical Development) section of a regulatory submission in the ICH M4 CTD format.

The Pharmaceutical Development section provides an opportunity to present the knowledge gained through the application of scientific approaches and quality risk management (for definition, see ICH Q9) to the development of a product and its manufacturing process. It is first produced for the original marketing application and can be updated to support new knowledge gained over the lifecycle* of a product. The Pharmaceutical Development section is intended to provide a comprehensive understanding of the product and manufacturing process for reviewers and inspectors. The guideline also indicates areas where the demonstration of greater understanding of pharmaceutical and manufacturing sciences can create a basis for flexible regulatory approaches. The degree of regulatory flexibility is predicated on the level of relevant scientific knowledge provided.

B. Scope

This guideline is intended to provide guidance on the contents of section 3.2.P.2 (Pharmaceutical Development) for drug products as defined in the scope of Module 3 of the CTD (ICH guideline M4). The guideline does not apply to contents of submissions for drug products during the clinical research stages of drug development. However, the principles in this guideline are important to consider during those stages as well. This guideline might also be appropriate for other types of products. To determine the applicability of this guideline to a particular type of product, applicants can consult with the appropriate regulatory authorities.

II. PHARMACEUTICAL DEVELOPMENT

The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. The information and knowledge gained from pharmaceutical development studies and manufacturing experience provide scientific understanding to support the establishment of the design space, specifications, and manufacturing controls.

Information from pharmaceutical development studies can be a basis for quality risk management. It is important to recognize that quality* cannot be tested into products; that is, quality should be built in by design. Changes in formulation and manufacturing processes during development and lifecycle management should be looked upon as opportunities to gain additional knowledge and further support establishment of the design space. Similarly, inclusion of relevant knowledge gained from experiments giving unexpected results can also be useful. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory postapproval change process.

The Pharmaceutical Development section should describe the knowledge that establishes that the type of dosage form selected and the formulation proposed are suitable for the intended use. This section should include sufficient information in each part to provide an understanding of the development of the drug product and its manufacturing process. Summary tables and graphs are encouraged where they add clarity and facilitate review.

At a minimum, those aspects of drug substances, excipients, container closure systems, and manufacturing processes that are critical to product quality should be determined and control strategies justified. Critical formulation attributes and process parameters are generally identified through an assessment of the extent to which their variation can have impact on the quality of the drug product.

In addition, the applicant can choose to conduct pharmaceutical development studies that can lead to an enhanced knowledge of product performance over a wider range of material attributes, processing options, and process parameters. Inclusion of this additional information in this section provides an opportunity to demonstrate a higher degree of understanding of material attributes, manufacturing processes, and their controls. This scientific understanding facilitates establishment of an expanded design space. In these situations, opportunities exist to develop more flexible regulatory approaches, for example, to facilitate:

- risk-based regulatory decisions (reviews and inspections);
- manufacturing process improvements, within the approved design space described in the dossier, without further regulatory review;
- reduction of postapproval submissions; and
- real-time quality control, leading to a reduction of end-product release testing.

To realize this flexibility, the applicant should demonstrate an enhanced knowledge of product performance over a range of material attributes, manufacturing process options, and process parameters. This understanding can be gained by application of, for example, formal experimental designs; process analytical technology (PAT); and/or prior knowledge. Appropriate use of quality risk management principles can be helpful in prioritising the additional pharmaceutical development studies to collect such knowledge.

The design and conduct of pharmaceutical development studies should be consistent with their intended scientific purpose. It should be recognized that the level of knowledge gained, and not the volume of data, provides

* See Glossary for definition

the basis for science-based submissions and their regulatory evaluation.

A. Components of the Drug Product

1. Drug Substance

The physicochemical and biological properties of the drug substance that can influence the performance of the drug product and its manufacturability, or were specifically designed into the drug substance (e.g., solid state properties), should be identified and discussed. Examples of physicochemical and biological properties that might need to be examined include solubility, water content, particle size, crystal properties, biological activity, and permeability. These properties could be interrelated and might need to be considered in combination.

To evaluate the potential effect of drug substance physicochemical properties on the performance of the drug product, studies on drug product might be warranted. For example, the ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* describes some of the circumstances in which drug product studies are recommended [e.g., Decision Tree 3 and 4 (Part 2)]. This approach applies equally for the ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products*. The knowledge gained from the studies investigating the potential effect of drug substance properties on drug product performance can be used, as appropriate, to justify elements of the drug substance specification (3.2.S.4.5).

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be evaluated. For products that contain more than one drug substance, the compatibility of the drug substances with each other should also be evaluated.

2. Excipients

The excipients chosen, their concentration, and the characteristics that can influence the drug product performance (e.g., stability, bioavailability) or manufacturability should be discussed relative to the respective function of each excipient. This should include all substances used in the manufacture of the drug product, whether they appear in the finished product or not (e.g., processing aids). Compatibility of excipients with other excipients, where relevant (e.g., combination of preservatives in a dual preservative system), should be established. The ability of excipients (e.g., antioxidants, penetration enhancers, disintegrants, release controlling agents) to provide their intended functionality, and to perform throughout the intended drug product shelf life, should also be demonstrated. The information on excipient performance can be used, as appropriate, to justify the choice and quality attributes of the excipient, and to support the justification of the drug product specification (3.2.P.5.6).

Information to support the safety of excipients, when appropriate, should be cross-referenced (3.2.P.4.6).

B. Drug Product

1. Formulation Development

A summary should be provided describing the development of the formulation, including identification of those attributes that are critical to the quality of the drug product, taking into consideration intended usage and route of administration. Information from formal experimental designs can be useful in identifying critical or interacting variables that might be important to ensure the quality of the drug product.

The summary should highlight the evolution of the formulation design from initial concept up to the final design. This summary should also take into consideration the choice of drug product components (e.g., the properties of the drug substance, excipients, container closure system, any relevant dosing device), the manufacturing process, and, if appropriate, knowledge gained from the development of similar drug product(s).

Any excipient ranges included in the batch formula (3.2.P.3.2) should be justified in this section of the application; this justification can often be based on the experience gained during development or manufacture.

A summary of formulations used in clinical safety and efficacy and in any relevant bioavailability or bioequivalence studies should be provided. Any changes between the proposed commercial formulation and those formulations used in pivotal clinical batches and primary stability batches should be clearly described and the rationale for the changes provided.

Information from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) that links clinical formulations to the proposed commercial formulation described in 3.2.P.1 should be summarized and a cross-reference to the studies (with study numbers) should be provided. Where attempts have been made to establish an in vitro/in vivo correlation, the results of those studies, and a cross-reference to the studies (with study numbers), should be provided in this section. A successful correlation can assist in the selection of appropriate dissolution acceptance criteria, and can potentially reduce the need for further bioequivalence studies following changes to the product or its manufacturing process.

Any special design features of the drug product (e.g., tablet score line, overfill, anticounterfeiting measure as it affects the drug product) should be identified and a rationale provided for their use.

2. Overages

In general, use of an overage of a drug substance to compensate for degradation during manufacture or a product's shelf life, or to extend shelf life, is discouraged.

Any overages in the manufacture of the drug product, whether they appear in the final formulated product or not, should be justified considering the safety and efficacy of the product. Information should be provided on (1) amount of overage, (2) reason for the overage (e.g., to compensate for expected and documented manufacturing losses), and (3) justification for the amount of overage. The overage should be included in the amount of drug substance listed in the batch formula (3.2.P.3.2).

3. Physicochemical and Biological Properties

The physicochemical and biological properties relevant to the safety, performance, or manufacturability of the drug product should be identified and discussed. This includes the physiological implications of drug substance and formulation attributes. Studies could include, for example, the development of a test for respirable fraction of an inhaled product. Similarly, information supporting the selection of dissolution versus disintegration testing, or other means to assure drug release, and the development and suitability of the chosen test, could be provided in this section. See also ICH *Q6A Specifications: Test Procedures And Acceptance Criteria For New Drug Substances And New Drug Products: Chemical Substances*; Decision Tree 4 (Part 3) and Decision Tree 7 (Part 1) or ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for*

Biotechnology/Biological Products. The discussion should cross-reference any relevant stability data in 3.2.P.8.3.

C. Manufacturing Process Development

The selection, the control, and any improvement of the manufacturing process described in 3.2.P.3.3 (i.e., intended for commercial production batches) should be explained. It is important to consider the critical formulation attributes, together with the available manufacturing process options, in order to address the selection of the manufacturing process and confirm the appropriateness of the components. Appropriateness of the equipment used for the intended products should be discussed. Process development studies should provide the basis for process improvement, process validation, continuous process verification* (where applicable), and any process control requirements. Where appropriate, such studies should address microbiological as well as physical and chemical attributes. The knowledge gained from process development studies can be used, as appropriate, to justify the drug product specification (3.2.P.5.6).

The manufacturing process development programme or process improvement programme should identify any critical process parameters that should be monitored or controlled (e.g., granulation end point) to ensure that the product is of the desired quality.

For those products intended to be sterile an appropriate method of sterilization for the drug product and primary packaging material should be chosen and the choice justified.

Significant differences between the manufacturing processes used to produce batches for pivotal clinical trials (safety, efficacy, bioavailability, bioequivalence) or primary stability studies and the process described in 3.2.P.3.3 should be discussed. The discussion should summarize the influence of the differences on the performance, manufacturability, and quality of the product. The information should be presented in a way that facilitates comparison of the processes and the corresponding batch analyses information (3.2.P.5.4). The information should include, for example, (1) the identity (e.g., batch number) and use of the batches produced (e.g., bioequivalence study batch number), (2) the manufacturing site, (3) the batch size, and (4) any significant equipment differences (e.g., different design, operating principle, size).

In order to provide flexibility for future process improvement, when describing the development of the manufacturing process, it is useful to describe measurement systems that allow monitoring of critical attributes or process end points. Collection of process monitoring data during the development of the manufacturing process can provide useful information to enhance process understanding. The process control strategies that provide process adjustment capabilities to ensure control of all critical attributes should be described.

An assessment of the ability of the process to reliably produce a product of the intended quality (e.g., the performance of the manufacturing process under different operating conditions, at different scales, or with different equipment) can be provided. An understanding of process robustness* can be useful in risk assessment and risk reduction (see ICH *Q9 Quality Risk Management* glossary for definition) and to support future manufacturing and process improvement, especially in conjunction with the use of risk management tools (see ICH *Q9 Quality Risk Management*).

* See Glossary for definition

D. Container Closure System

The choice and rationale for selection of the container closure system for the commercial product (described in 3.2.P.7) should be discussed. Consideration should be given to the intended use of the drug product and the suitability of the container closure system for storage and transportation (shipping), including the storage and shipping container for bulk drug product, where appropriate.

The choice of materials for primary packaging should be justified. The discussion should describe studies performed to demonstrate the integrity of the container and closure. A possible interaction between product and container or label should be considered.

The choice of primary packaging materials should consider, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching), and safety of materials of construction. Justification for secondary packaging materials should be included, when relevant.

If a dosing device is used (e.g., dropper pipette, pen injection device, dry powder inhaler), it is important to demonstrate that a reproducible and accurate dose of the product is delivered under testing conditions, which, as far as possible, simulate the use of the product.

E. Microbiological Attributes

Where appropriate, the microbiological attributes of the drug product should be discussed in this section (3.2.P.2.5). The discussion should include, for example:

- The rationale for performing or not performing microbial limits testing for nonsterile drug products (e.g., Decision Tree 8 in ICH *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* and ICH *Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnology/Biological Products)*
- The selection and effectiveness of preservative systems in products containing antimicrobial preservative or the antimicrobial effectiveness of products that are inherently antimicrobial
- For sterile products, the integrity of the container closure system as it relates to preventing microbial contamination

Although chemical testing for preservative content is the attribute normally included in the drug product specification, antimicrobial preservative effectiveness should be demonstrated during development. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using an antimicrobial preservative effectiveness test. The concentration used should be justified in terms of efficacy and safety, such that the minimum concentration of preservative that gives the required level of efficacy throughout the intended shelf life of the product is used. Where relevant, microbial challenge testing under testing conditions that, as far as possible, simulate patient use should be performed during development and documented in this section.

F. Compatibility

The compatibility of the drug product with reconstitution diluents (e.g., precipitation, stability) should be addressed to provide appropriate and supportive information for the

labelling. This information should cover the recommended in-use shelf life, at the recommended storage temperature and at the likely extremes of concentration. Similarly, admixture or dilution of products prior to administration (e.g., product added to large volume infusion containers) might need to be addressed.

GLOSSARY

Continuous Process Verification—An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.

Design Space—The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval.

Formal Experimental Design—A structured, organized method for determining the relationship between factors affecting a process and the output of that process. Also known as "Design of Experiments".

Lifecycle—All phases in the life of a product from the initial development through marketing until the product's discontinuation.

Process Analytical Technology (PAT)—A system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality.

Process Robustness—Ability of a process to tolerate variability of materials and changes of the process and equipment without negative impact on quality.

Quality—The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity.

6

Scale-Up and Postapproval Changes for Nonsterile Semisolid Dosage Forms: Manufacturing Equipment

To ensure continuing product quality and performance characteristics of the semisolid topical formulations, regulatory approvals are required for changes to

1. components or composition,
2. manufacturing (process and equipment),
3. scale-up/scale-down of manufacture, and
4. site of manufacture of a semisolid formulation during the postapproval period.

It is important to define

1. the levels of change;
2. recommended chemistry, manufacturing, and controls tests to support each level of change;
3. recommended in vitro release tests or in vivo bioequivalence tests to support each level of change; and
4. documentation to support the change.

The effect that scale-up and postapproval changes may have on the stability of the drug product should be evaluated. For general guidance on conducting stability studies, see the FDA *Guideline for Submitting Documentation for the Stability of Human Drugs and Biologics*. For scale-up and postapproval changes submissions, the following points should also be considered:

A. In most cases, except those involving scale-up, stability data from pilot scale batches will be acceptable to support the proposed change.
B. Where stability data show a trend toward potency loss or degradant increase under accelerated conditions, it is recommended that historical accelerated stability data from a representative prechange batch be submitted for comparison. It is also recommended that under these circumstances, all available long-term data on test batches from ongoing studies be provided in the supplement. Submission of historical accelerated and available long-term data would facilitate review and approval of the supplement.
C. A commitment should be included to conduct long-term stability studies through the expiration dating period, according to the approved protocol, on either the first or first three (see below for details) production batches and to report the results in subsequent annual reports.

Definition of level 1 changes are those that are unlikely to have any detectable effect on formulation quality and performance. Examples:

A. Deletion or partial deletion of an ingredient intended to affect the color, fragrance, or flavor of the drug product.
B. Any change in an excipient up to 5% of approved amount of that excipient. The total additive effect of all excipient changes should not be more than 5%. Changes in the composition should be based on the approved target composition and not on previous level 1changes in the composition. A change in diluent (q.s. excipient) caused by component and composition changes in excipient may be made and is excluded from the 5% change limit.
C. Change in a supplier of a structure forming excipient that is primarily a single chemical entity (purity 95%) or change in a supplier or technical grade of any other excipient.

Definition of level 2 changes are those that could have a significant effect on formulation quality and performance. Examples:

A. Changes of >5% and <10% of approved amount of an individual excipient; the total additive effect of all excipient changes should not be more than 10%.
B. Changes in the composition should be based on the approved target composition and not on previous level 1 or level 2 changes in the composition.
C. Changes in diluent (q.s. excipient) caused by component and composition changes in excipients are acceptable and are excluded from the10% change limit.
D. Change in supplier of a structure forming excipient not covered under level 1.
E. Change in the technical grade of structure-forming excipient.
F. Change in particle size distribution of the drug substance if the drug is in suspension.

Definition of level 3 changes are those that are likely to have a significant effect on formulation quality and performance. Examples:

A. Any qualitative and quantitative changes in an excipient beyond the ranges noted in level 2 change.
B. Change in crystalline form of the drug substance, if the drug is in suspension.

I. PRESERVATIVE

For semisolid products, any change in the preservative may affect the quality of the product. If any quantitative or qualitative changes are made in the formulation, additional testing should be performed. No in vitro release documentation or in vivo bioequivalence documentation is needed for preservative changes.

II. MANUFACTURING CHANGES

Manufacturing changes may affect both equipment used in the manufacturing process and the process itself. A level 1 change is a change from nonautomated or nonmechanical equipment to automated or mechanical equipment to transfer ingredients or a change to alternative equipment of the same design and operating principles. A level 2 change is a

change in equipment to a different design or different operating principles or a change in type of mixing equipment, such as high shear to low shear and vice versa. No level 3 changes are anticipated in this category.

III. PROCESS

Level 1 changes include changes such as rate of mixing, mixing times, operating speeds, and holding times within approved application ranges, in addition to the order of addition of components (excluding actives) to either the oil or water phase. Level 2 changes include changes such as rate of mixing, mixing times, rate of cooling, operating speeds, and holding times outside approved application ranges for all dosage forms in addition to any changes in the process of combining the phases. No level 3 changes are anticipated in this category.

A. Batch Size (Scale-Up or Scale-Down)

The minimum batch size for the NDA pivotal clinical trial batch or the ANDA/AADA biobatch is at least 100 kg or 10% of a production batch, whichever is larger. All scale changes should be properly validated and may be inspected by appropriate agency personnel. Level 1 changes in batch size are those up to and including a factor of 10 times the size of the pivotal clinical trial or biobatch, where the equipment used to produce the test batch or batches is of the same design and operating principles, the batch or batches are manufactured in full compliance with current good manufacturing practice (cGMPs), and the same standard operating procedures (SOPs) and controls, as well as the same formulation and manufacturing procedures, are used on the test batch or batches and on the full-scale production batch or batches. Level 2 changes in batch size are those from beyond a factor of 10 times the size of the pivotal clinical trial or biobatch, where the equipment used to produce the test batch or batches is of the same design and operating principles, the batch or batches is manufactured in full compliance with cGMPs, and the same SOPs and controls, as well as the same formulation and manufacturing procedures, are used on the test batch or batches and on the full-scale production batch or batches. No level 3 changes are anticipated in this category.

IV. MANUFACTURING SITE

Manufacturing site changes consist of changes in location in the site of manufacture, packaging and filling operations, or testing for both company-owned and contract manufacturing facilities, and they do not include any other level 2 or 3 changes; for example, changes in scale, manufacturing (including process or equipment), and components or composition. New manufacturing locations should have had a satisfactory cGMP inspection within the past 2 years. A stand-alone analytical testing laboratory site change may be submitted as a Changes Being Effected Supplement if the new facility has a current and satisfactory cGMP compliance profile with the FDA for the type of testing operation in question. The supplement should contain a commitment to use the same test methods employed in the approved application, written certification from the testing laboratory stating that they are in conformance with cGMPs, and a full description of the testing to be performed by the testing laboratory. If the facility has not received a satisfactory cGMP inspection for the type of testing involved, a prior approval supplement is recommended. No stability data are needed for a change in a stand-alone analytical facility. Level 1 changes consist of site changes within a single facility where the same equipment, SOPs, environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility. "Common" is defined as employees already working on the campus who have suitable experience with the manufacturing process.

Level 2 changes consist of site changes within a contiguous campus, or between facilities in adjacent city blocks, where similar equipment, SOPs, environmental conditions (e.g., temperature and humidity) and controls, and personnel common to both manufacturing sites are used, and where no changes are made to the manufacturing batch records, except for administrative information and the location of the facility. Level 3 changes consist of a site change in manufacturing site to a different campus. A different campus is defined as one that is not on the same original contiguous site or where the facilities are not in adjacent city blocks. To qualify as a level 3 change, similar equipment, SOPs, environmental conditions, and controls should be used in the manufacturing process at the new site. Changes should not be made to the manufacturing batch records except when consistent with other level 1 changes. Administrative information, location, and language translation may be revised as needed. Any change to a new contract manufacturer also constitutes a level 3 change.

I. INTRODUCTION

Any equipment changes should be validated in accordance with cGMPs. The resulting data will be subject to examination by field investigators during routine GMP inspections. The information here is presented in broad categories of unit operation (particle size reduction or separation, mixing, emulsification, deaeration, transfer, and packaging).

Under scale-up and postapproval changes (semisolid) (SUPAC-SS), equipment within the same class and subclass are considered to have the same design and operating principle. For example, a change from a planetary mixer from manufacturer A to another planetary mixer from manufacturer B would not represent a change in design or operating principle and would be considered the same.

A change from equipment in one class to equipment in a different class would usually be considered a change in design and operating principle. For example, a change from a planetary mixer to a dispersator mixer demonstrates a change in operating principle from low-shear convection mixing to high-shear convection mixing. These types of equipment would be considered different under SUPAC-SS.

Applicants should carefully consider and evaluate on a case-by-case basis changes in equipment that are in the same class but different subclasses. In many situations, these changes in equipment would be considered similar. For example, in section III, Mixing, under the convection mixers, low shear, a change from an impeller mixer (subclass) to a planetary mixer (subclass) represents a change within a class and between subclasses. Provided the manufacturing process with the new equipment is validated, this change would likely not need a Changes Being Effected Supplement. At the time of such a change the applicant should have available the scientific data and rationale used to make this determination. It is up to the applicant to determine the filing category.

II. PARTICLE SIZE REDUCTION AND SEPARATION

A. Definitions

1. Unit Operations

a. Particle Size Reduction

Particle size reduction is the mechanical process of breaking particles into smaller pieces via one or more size-reduction mechanisms. The mechanical process used is generally referred to as milling.

i. *Particle*
A particle is either a discrete crystal or a grouping of crystals, generally known as an agglomerate.

ii. *Particle Size Reduction Mechanisms*
- Impact—Particle size reduction caused by applying an instantaneous force perpendicular to the particle or agglomerate surface; the force can result from particle-to-particle or particle-to-mill surface collision
- Attrition—Particle size reduction by applying force parallel to the particle surface
- Compression—Particle size reduction by applying a force slowly (as compared with impact) to the particle surface toward the center of the particle
- Cutting—Particle size reduction by applying a shearing force to a material

b. Particle Separation

Particle separation is particle size classification according to particle size alone.

2. Operating Principles

a. Fluid Energy Milling

Fluid energy milling is particle size reduction by high speed particle-to-particle impact or attrition (also known as micronizing).

b. Impact Milling

Particle size reduction by high-speed mechanical impact or impact with other particles (also known as milling, pulverizing, or comminuting) is known as impact milling.

c. Cutting

Cutting is particle size reduction by mechanical shearing.

d. Compression Milling

Particle size reduction by compression stress and shear between two surfaces is known as compression milling.

e. Screening

Particle size reduction by mechanically induced attrition through a screen (commonly referred to as milling or deagglomeration) is called screening.

f. Tumble Milling

Tumble milling is particle size reduction by attrition, using grinding media.

g. Separating

Particle segregation based on size alone, without any significant particle size reduction (commonly referred to as screening or bolting), is also known as separating.

B. Equipment Classifications

1. Fluid Energy Mills

Fluid energy mill subclasses have no moving parts and primarily differ in the configuration or shape of their chambers, nozzles, and classifiers.

- Fixed target
- Fluidized bed
- Loop or oval
- Moving target
- Opposed jet
- Opposed jet with dynamic classifier
- Tangential jet

2. Impact Mills

Impact mill subclasses primarily differ in the configuration of the grinding heads, chamber grinding liners (if any), and classifiers.

- Cage
- Hammer air swept
- Hammer conventional
- Pin or disc

3. Cutting Mills

Although cutting mills can differ in whether the knives are movable or fixed, and in classifier configuration, no cutting mill subclasses have been identified.

4. Compression Mills

Although compression mills, also known as roller mills, can differ in whether one or both surfaces move, no compression mill subclasses have been identified.

5. Screening Mills

Screening mill subclasses primarily differ in the rotating element.

- Oscillating bar
- Rotating impeller
- Rotating screen

6. Tumbling Mills

Tumbling mill subclasses primarily differ in the grinding media used and whether the mill is vibrated.

- Ball media
- Rod media
- Vibrating

7. Separators

Separator subclasses primarily differ in the mechanical means used to induce particle movement.

- Centrifugal
- Vibratory or shaker

Note that if a single piece of equipment is capable of performing multiple discrete unit operations, it has been evaluated solely for its ability to affect particle size or separation.

III. MIXING

A. Definitions

1. Unit Operation

Mixing is the reorientation of particles relative to one another to achieve uniformity or randomness. This process can include wetting of solids by a liquid phase, dispersion of discrete particles, or deagglomeration into a continuous phase. Heating and cooling via indirect conduction may be used in this operation to facilitate phase mixing or stabilization.

2. Operating Principles

a. Convection Mixing, Low Shear

Convection mixing, low shear, is a mixing process with a repeated pattern of cycling material from top to bottom in which dispersion occurs under low power per unit mass through rotating low shear forces.

b. Convection Mixing, High Shear

Convection mixing, high shear, is a mixing process with a repeated pattern of cycling material from top to bottom in which dispersion occurs under high power per unit mass through rotating high shear forces.

c. Roller Mixing (Milling)

Also known as milling, roller mixing is a mixing process by high mechanical shearing action where compression stress is achieved by passing material between a series of rotating rolls. This is commonly referred to as compression or roller milling.

d. Static Mixing

In static mixing, material passes through a tube with stationary baffles. The mixer is generally used in conjunction with an in-line pump.

B. Equipment Classification

1. Convection Mixers, Low Shear

This group of mixers normally operates under low-shear conditions and is broken down by impeller design and movement. Design can also include a jacketed vessel to facilitate heat transfer.

- Anchor or sweepgate
- Impeller
- Planetary

2. Convection Mixers, High Shear

These mixers normally operate only under high-shear conditions. Subclasses are differentiated by how the high shear is introduced into the material, such as by a dispersator with serrated blades or homogenizer with rotor stator.

- Dispersator
- Rotor stator

3. Roller Mixers (Mills)

No roller mixer subclasses have been identified.

4. Static Mixers

No static mixer subclasses have been identified.

Note that if a single piece of equipment is capable of performing multiple discrete unit operations, it has been evaluated solely for its ability to mix materials.

5. Low-Shear Emulsifiers

Although low-shear emulsification equipment (mechanical stirrers or impellers) can differ in the type of fluid flow imparted to the mixture (axial-flow propeller or radial-flow turbines), no subclasses have been defined.

IV. TRANSFER

A. Definitions

1. Unit Operation

Transfer is the controlled movement or transfer of materials from one location to another.

2. Operating Principles

a. Passive

Passive transfer is the movement of materials across a non-mechanically induced pressure gradient, usually through a conduit or pipe.

b. Active

The movement of materials across a mechanically induced pressure gradient, usually through conduit or pipe, is known as active transfer.

B. Equipment Classification

1. Low Shear

Equipment used for active or passive material transfer, with a low degree of induced shear, is classified as "low-shear" equipment:

- Diaphragm
- Gravity
- Peristaltic
- Piston
- Pneumatic
- Rotating lobe
- Screw or helical screw

2. High Shear

Active or mechanical material transfer with a high degree of induced shear is performed by what is known as "high-shear" equipment:

- Centrifugal or turbine
- Piston
- Rotating gear

A single piece of equipment can be placed in either a low-or high-shear class, depending on its operating parameters. If a single piece of equipment is capable of performing multiple discrete unit operations, the unit has been evaluated solely for its ability to transfer materials.

V. PACKAGING

A. Definitions

1. Unit Operation

a. Holding

The process of storing product after completion of manufacturing process and before filling final primary packs is known as holding.

b. Transfer

Transfer is the process of relocating bulk finished product from holding to filling equipment using pipe, hose, pumps, or other associated components.

c. Filling

Filling is the delivery of target weight or volume of bulk finished product to primary pack containers.

d. Sealing
A device or process for closing or sealing primary pack containers, known collectively as sealing, follows the filling process.

2. Operating Principles

a. Holding
The storage of liquid, semisolids, or product materials in a vessel that may or may not have temperature control or agitation is called holding.

b. Transfer
The controlled movement or transfer of materials from one location to another is known as transfer.

c. Filling
Filling operating principles involve several associated subprinciples. The primary package can be precleaned to remove particulates or other materials by the use of ionized air, vacuum, or inversion. A holding vessel equipped with an auger, gravity, or pressure material feeding system should be used. The vessel may or may not be able to control temperature or agitation. Actual filling of the dosage form into primary containers can involve a metering system based on an auger, gear, orifice, peristaltic, or piston pump. A headspace blanketing system can also be used.

d. Sealing
Primary packages can be sealed using a variety of methods, including conducted heat and electromagnetic (induction or microwave) or mechanical manipulation (crimping or torquing).

B. Equipment Classification

1. Holders

Although holding vessels can differ in their geometry and ability to control temperature or agitation, their primary differences are based on how materials are fed. Feeding devices include the following:

- Auger
- Gravity
- Pneumatic (nitrogen, air, etc.)

2. Fillers

The primary differences in filling equipment are based on how materials are metered. Different varieties of filling equipment include the following:

- Auger
- Gear pump
- Orifice
- Peristaltic pump
- Piston

3. Sealers

The differences in primary container sealing are based on how energy is transferred or applied. Energy transfer can be accomplished via the following:

- Heat
- Induction
- Microwave
- Mechanical or crimping
- Torque

7

GOOD Manufacturing Practice Guide for Active Pharmaceutical Ingredients

1. INTRODUCTION

1.1. Objective

This document (Guide) is intended to provide guidance regarding good manufacturing practice (GMP) for the manufacturing of active pharmaceutical ingredients (APIs) under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the requirements for quality and purity that they purport or are represented to possess.

In this Guide "manufacturing" is defined to include all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control (QC), release, storage and distribution of APIs, and the related controls. In this Guide the term "should" indicates recommendations that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality assurance (QA). For the purposes of this Guide, the terms "current good manufacturing practices" and "good manufacturing practices" are equivalent.

The Guide as a whole does not cover safety aspects for the personnel engaged in the manufacture, nor aspects of protection of the environment. These controls are inherent responsibilities of the manufacturer and are governed by national laws.

This Guide is not intended to define registration/filing requirements or modify pharmacopoeial requirements. This Guide does not affect the ability of the responsible regulatory agency to establish specific registration/filing requirements regarding APIs within the context of marketing/manufacturing authorizations or drug applications. All commitments in registration/filing documents must be met.

1.2. Regulatory Applicability

Within the world community, materials may vary as to the legal classification as an API. When a material is classified as an API in the region or country in which it is manufactured or used in a drug product, it should be manufactured according to this Guide.

1.3. Scope

This Guide applies to the manufacture of APIs for use in human drug (medicinal) products. It applies to the manufacture of sterile APIs only up to the point immediately prior to the APIs being rendered sterile. The sterilization and aseptic processing of sterile APIs are not covered by this guidance, but should be performed in accordance with GMP guidelines for drug (medicinal) products as defined by local authorities.

This Guide covers APIs that are manufactured by chemical synthesis, extraction, cell culture/fermentation, by recovery from natural sources, or by any combination of these processes. Specific guidance for APIs manufactured by cell culture/fermentation is described in section 18.

This Guide excludes all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives (plasma fractionation), and gene therapy APIs. However, it does include APIs that are produced using blood or plasma as raw materials. Note that cell substrates (mammalian, plant, insect or microbial cells, tissue or animal sources including transgenic animals) and early process steps may be subject to GMP but are not covered by this Guide. In addition, the Guide does not apply to medical gases, bulk-packaged drug (medicinal) products, and manufacturing/control aspects specific to radiopharmaceuticals.

Section 19 contains guidance that only applies to the manufacture of APIs used in the production of drug (medicinal) products specifically for clinical trials (investigational medicinal products).

An "API Starting Material" is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials normally have defined chemical properties and structure.

The company should designate and document the rationale for the point at which production of the API begins. For synthetic processes, this is known as the point at which "API Starting Materials" are entered into the process. For other processes (e.g., fermentation, extraction, purification), this rationale should be established on a case-by-case basis. Table 7.1 gives guidance on the point at which the API Starting Material is normally introduced into the process.

From this point on, appropriate GMP as defined in this Guide should be applied to these intermediate and/or API manufacturing steps. This would include the validation of critical process steps determined to impact the quality of the API. However, it should be noted that the fact that a company chooses to validate a process step does not necessarily define that step as critical.

The guidance in this document would normally be applied to the steps shown in gray in Table 7.1. It does not imply that all steps shown should be completed. The stringency of GMP in API manufacturing should increase as the process proceeds from early API steps to final steps, purification, and packaging. Physical processing of APIs, such as granulation, coating, or physical manipulation of particle size (e.g., milling, micronizing), should be conducted at least to the standards of this Guide.

This GMP Guide does not apply to steps prior to the introduction of the defined "API Starting Material."

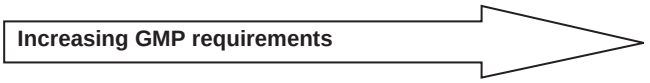
2. QUALITY MANAGEMENT

2.1. Principles

- 2.10 Quality should be the responsibility of all persons involved in manufacturing.
- 2.11 Each manufacturer should establish, document, and implement an effective system for managing quality that

Table 7.1 Application of this Guide to API Manufacturing

Type of Manufacturing	Application of This Guide to Steps (Shown in Gray) Used in This Type of Manufacturing				
Chemical manufacturing	Production of the API starting material	Introduction of the API starting material into process	Production of intermediate(s)	Isolation and purification	Physical processing and packaging
API derived from animal sources	Collection of organ, fluid, or tissue	Cutting, mixing, and/or initial processing	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
API extracted from plant sources	Collection of plants	Cutting and initial extraction(s)	Introduction of the API starting material into process	Isolation and purification	Physical processing and packaging
Herbal extracts used as API	Collection of plants	Cutting and initial extraction		Further extraction	Physical processing and packaging
API consisting of comminuted or powdered herbs	Collection of plants and/or cultivation and harvesting	Cutting/comminuting			Physical processing and packaging
Biotechnology: fermentation/cell culture	Establishment of master cell bank and working cell bank	Maintenance of working cell bank	Cell culture and/or fermentation	Isolation and purification	Physical processing and packaging
"Classical" fermentation to produce an API	Establishment of cell bank	Maintenance of the cell bank	Introduction of the cells into fermentation	Isolation and purification	Physical processing and packaging



involves the active participation of management and appropriate manufacturing personnel.

- 2.12 The system for managing quality should encompass the organizational structure, procedures, processes, and resources, as well as activities necessary to ensure confidence that the API will meet its intended specifications for quality and purity. All quality-related activities should be defined and documented.
- 2.13 There should be a quality unit(s) that is independent of production and that fulfills both QA and QC responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.
- 2.14 The persons authorized to release intermediates and APIs should be specified.
- 2.15 All quality-related activities should be recorded at the time they are performed.
- 2.16 Any deviation from established procedures should be documented and explained. Critical deviations should be investigated, and the investigation and its conclusions should be documented.
- 2.17 No materials should be released or used before the satisfactory completion of evaluation by the quality unit(s) unless there are appropriate systems in place to allow for such use (e.g., release under quarantine as described in section 10.20 or the use of raw materials or intermediates pending completion of evaluation).
- 2.18 Procedures should exist for notifying responsible management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects, and related actions (e.g., quality-related complaints, recalls, regulatory actions, etc.).

2.2. Responsibilities of the Quality Unit(s)

- 2.20 The quality unit(s) should be involved in all quality-related matters.
- 2.21 The quality unit(s) should review and approve all appropriate quality-related documents.
- 2.22 The main responsibilities of the independent quality unit(s) should not be delegated. These responsibilities should be described in writing and should include but not necessarily be limited to
  - 1. releasing or rejecting all APIs. Releasing or rejecting intermediates for use outside the control of the manufacturing company;
  - 2. establishing a system to release or reject raw materials, intermediates, packaging, and labeling materials;
  - 3. reviewing completed batch production and laboratory control records of critical process steps before release of the API for distribution;
  - 4. making sure that critical deviations are investigated and resolved;
  - 5. approving all specifications and master production instructions;
  - 6. approving all procedures impacting the quality of intermediates or APIs;
  - 7. making sure that internal audits (self-inspections) are performed;
  - 8. approving intermediate and API contract manufacturers;
  - 9. approving changes that potentially impact intermediate or API quality;
  - 10. reviewing and approving validation protocols and reports;
  - 11. making sure that quality-related complaints are investigated and resolved;
  - 12. making sure that effective systems are used for maintaining and calibrating critical equipment;
  - 13. making sure that materials are appropriately tested and the results are reported;
  - 14. making sure that there is stability data to support retest or expiry dates and storage conditions on APIs and/or intermediates where appropriate; and
  - 15. performing product quality reviews (as defined in section 2.5).

2.3. Responsibility for Production Activities

- The responsibility for production activities should be described in writing, and should include but not necessarily

be limited to
- 1. preparing, reviewing, approving, and distributing the instructions for the production of intermediates or APIs according to written procedures;
- 2. producing APIs and, when appropriate, intermediates according to preapproved instructions;
- 3. reviewing all production batch records and ensuring that these are completed and signed;
- 4. making sure that all production deviations are reported and evaluated and that critical deviations are investigated and the conclusions are recorded;
- 5. making sure that production facilities are clean and when appropriate disinfected;
- 6. making sure that the necessary calibrations are performed and records kept;
- 7. making sure that the premises and equipment are maintained and records kept;
- 8. making sure that validation protocols and reports are reviewed and approved;
- 9. evaluating proposed changes in product, process, or equipment; and
- 10. making sure that new and, when appropriate, modified facilities and equipment are qualified.

2.4. Internal Audits (Self-Inspection)
- 2.40 In order to verify compliance with the principles of GMP for APIs, regular internal audits should be performed in accordance with an approved schedule.
- 2.41 Audit findings and corrective actions should be documented and brought to the attention of responsible management of the firm. Agreed corrective actions should be completed in a timely and effective manner.

2.5. Product Quality Review
- 2.50 Regular quality reviews of APIs should be conducted with the objective of verifying the consistency of the process. Such reviews should normally be conducted and documented annually and should include at least
  - a review of critical in-process control and critical API test results;
  - a review of all batches that failed to meet established specification(s);
  - a review of all critical deviations or nonconformances and related investigations;
  - a review of any changes carried out to the processes or analytical methods;
  - a review of results of the stability monitoring program;
  - a review of all quality-related returns, complaints and recalls; and
  - a review of adequacy of corrective actions.
- 2.51 The results of this review should be evaluated and an assessment made of whether corrective action or any revalidation should be undertaken. Reasons for such corrective action should be documented. Agreed corrective actions should be completed in a timely and effective manner.

3. PERSONNEL

3.1. Personnel Qualifications
- 3.10 There should be an adequate number of personnel qualified by appropriate education, training, and/or experience to perform and supervise the manufacture of intermediates and APIs.
- 3.11 The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.
- 3.12 Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.

3.2. Personnel Hygiene
- 3.20 Personnel should practice good sanitation and health habits.
- 3.21 Personnel should wear clean clothing suitable for the manufacturing activity with which they are involved and this clothing should be changed when appropriate. Additional protective apparel, such as head, face, hand, and arm coverings, should be worn when necessary, to protect intermediates and APIs from contamination.
- 3.22 Personnel should avoid direct contact with intermediates or APIs.
- 3.23 Smoking, eating, drinking, chewing, and the storage of food should be restricted to certain designated areas separate from the manufacturing areas.
- 3.24 Personnel suffering from an infectious disease or having open lesions on the exposed surface of the body should not engage in activities that could result in compromising the quality of APIs. Any person shown at any time (either by medical examination or supervisory observation) to have an apparent illness or open lesions should be excluded from activities where the health condition could adversely affect the quality of the APIs until the condition is corrected or qualified medical personnel determine that the person's inclusion would not jeopardize the safety or quality of the APIs.

3.3. Consultants
- 3.30 Consultants advising on the manufacture and control of intermediates or APIs should have sufficient education, training, and experience, or any combination thereof, to advise on the subject for which they are retained.
- 3.31 Records should be maintained stating the name, address, qualifications, and type of service provided by these consultants.

4. BUILDINGS AND FACILITIES

4.1. Design and Construction
- 4.10 Buildings and facilities used in the manufacture of intermediates and APIs should be located, designed, and constructed to facilitate cleaning, maintenance, and operations as appropriate to the type and stage of manufacture. Facilities should also be designed to minimize potential contamination. Where microbiological specifications have been established for the intermediate or API, facilities should also be designed to limit exposure to objectionable microbiological contaminants as appropriate.
- 4.11 Buildings and facilities should have adequate space for the orderly placement of equipment and materials to prevent mix-ups and contamination.
- 4.12 Where the equipment itself (e.g., closed or contained systems) provides adequate protection of the material, such equipment can be located outdoors.
- 4.13 The flow of materials and personnel through the building or facilities should be designed to prevent mix-ups or contamination.

- 4.14 There should be defined areas or other control systems for the following activities:
  - Receipt, identification, sampling, and quarantine of incoming materials, pending release, or rejection
  - Quarantine before release or rejection of intermediates and APIs
  - Sampling of intermediates and APIs
  - Holding rejected materials before further disposition (e.g., return, reprocessing or destruction)
  - Storage of released materials
  - Production operations
  - Packaging and labeling operations
  - Laboratory operations
- 4.15 Adequate, clean washing and toilet facilities should be provided for personnel. These washing facilities should be equipped with hot and cold water as appropriate, soap or detergent, air driers or single service towels. The washing and toilet facilities should be separate from, but easily accessible to, manufacturing areas. Adequate facilities for showering and/or changing clothes should be provided, when appropriate.
- 4.16 Laboratory areas/operations should normally be separated from production areas. Some laboratory areas, in particular those used for in-process controls, can be located in production areas, provided the operations of the production process do not adversely affect the accuracy of the laboratory measurements, and the laboratory and its operations do not adversely affect the production process or intermediate or API.

4.2. Utilities

- 4.20 All utilities that could impact on product quality (e.g., steam, gases, compressed air, and heating, ventilation and air conditioning) should be qualified and appropriately monitored and action should be taken when limits are exceeded. Drawings for these utility systems should be available.
- 4.21 Adequate ventilation, air filtration, and exhaust systems should be provided, where appropriate. These systems should be designed and constructed to minimize risks of contamination and cross-contamination and should include equipment for control of air pressure, microorganisms (if appropriate), dust, humidity, and temperature, as appropriate to the stage of manufacture. Particular attention should be given to areas where APIs are exposed to the environment.
- 4.22 If air is recirculated to production areas, appropriate measures should be taken to control risks of contamination and cross-contamination.
- 4.23 Permanently installed pipework should be appropriately identified. This can be accomplished by identifying individual lines, documentation, computer control systems, or alternative means. Pipework should be located to avoid risks of contamination of the intermediate or API.
- 4.24 Drains should be of adequate size and should be provided with an air break or a suitable device to prevent back-siphonage, when appropriate.

4.3. Water

- 4.30 Water used in the manufacture of APIs should be demonstrated to be suitable for its intended use.
- 4.31 Unless otherwise justified, process water should, at a minimum, meet World Health Organization (WHO) guidelines for drinking (potable) water quality.
- 4.32 If drinking (potable) water is insufficient to assure API quality, and tighter chemical and/or microbiological water quality specifications are called for, appropriate specifications for physical/chemical attributes, total microbial counts, objectionable organisms and/or endotoxins should be established.
- 4.33 Where water used in the process is treated by the manufacturer to achieve a defined quality, the treatment process should be validated and monitored with appropriate action limits.
- 4.34 Where the manufacturer of a nonsterile API either intends or claims that it is suitable for use in further processing to produce a sterile drug (medicinal) product, water used in the final isolation and purification steps should be monitored and controlled for total microbial counts, objectionable organisms, and endotoxins.

4.4. Containment

- 4.40 Dedicated production areas, which can include facilities, air handling equipment, and/or process equipment, should be employed in the production of highly sensitizing materials, such as penicillins or cephalosporins.
- 4.41 Dedicated production areas should also be considered when material of an infectious nature or high pharmacological activity or toxicity is involved (e.g., certain steroids or cytotoxic anticancer agents) unless validated inactivation and/or cleaning procedures are established and maintained.
- 4.42 Appropriate measures should be established and implemented to prevent cross-contamination from personnel, materials, etc. moving from one dedicated area to another.
- 4.43 Any production activities (including weighing, milling, or packaging) of highly toxic nonpharmaceutical materials such as herbicides and pesticides should not be conducted using the buildings and/or equipment being used for the production of APIs. Handling and storage of these highly toxic nonpharmaceutical materials should be separate from APIs.

4.5. Lighting

- 4.50 Adequate lighting should be provided in all areas to facilitate cleaning, maintenance, and proper operations.

4.6. Sewage and Refuse

- 4.60 Sewage, refuse, and other waste (e.g., solids, liquids, or gaseous by-products from manufacturing) in and from buildings and the immediate surrounding area should be disposed of in a safe, timely, and sanitary manner. Containers and/or pipes for waste material should be clearly identified.

4.7. Sanitation and Maintenance

- 4.70 Buildings used in the manufacture of intermediates and APIs should be properly maintained and repaired and kept in a clean condition.
- 4.71 Written procedures should be established assigning responsibility for sanitation and describing the cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities.
- 4.72 When necessary, written procedures should also be established for the use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents to prevent the contamination of equipment, raw materials, packaging/labeling materials, intermediates, and APIs.

5. PROCESS EQUIPMENT

5.1. Design and Construction

- 5.10 Equipment used in the manufacture of intermediates and APIs should be of appropriate design and adequate size, and suitably located for its intended use, cleaning, sanitization (where appropriate), and maintenance.
- 5.11 Equipment should be constructed so that surfaces that contact raw materials, intermediates, or APIs do not alter the quality of the intermediates and APIs beyond the official or other established specifications.
- 5.12 Production equipment should only be used within its qualified operating range.
- 5.13 Major equipment (e.g., reactors, storage containers) and permanently installed processing lines used during the production of an intermediate or API should be appropriately identified.
- 5.14 Any substances associated with the operation of equipment, such as lubricants, heating fluids, or coolants, should not contact intermediates or APIs so as to alter their quality beyond the official or other established specifications. Any deviations from this should be evaluated to ensure that there are no detrimental effects upon the fitness for purpose of the material. Wherever possible, food grade lubricants and oils should be used.
- 5.15 Closed or contained equipment should be used whenever appropriate. Where open equipment is used, or equipment is opened, appropriate precautions should be taken to minimize the risk of contamination.
- 5.16 A set of current drawings should be maintained for equipment and critical installations (e.g., instrumentation and utility systems).

5.2. Equipment Maintenance and Cleaning

- 5.20 Schedules and procedures (including assignment of responsibility) should be established for the preventative maintenance of equipment.
- 5.21 Written procedures should be established for cleaning of equipment and its subsequent release for use in the manufacture of intermediates and APIs. Cleaning procedures should contain sufficient details to enable operators to clean each type of equipment in a reproducible and effective manner. These procedures should include
  - assignment of responsibility for cleaning of equipment;
  - cleaning schedules, including, where appropriate, sanitizing schedules;
  - a complete description of the methods and materials, including dilution of cleaning agents used to clean equipment;
  - when appropriate, instructions for disassembling and reassembling each article of equipment to ensure proper cleaning;
  - instructions for the removal or obliteration of previous batch identification;
  - instructions for the protection of clean equipment from contamination prior to use;
  - inspection of equipment for cleanliness immediately before use, if practical; and
  - establishing the maximum time that may elapse between the completion of processing and equipment cleaning, when appropriate.
- 5.22 Equipment and utensils should be cleaned, stored, and, where appropriate, sanitized or sterilized to prevent contamination or carryover of a material that would alter the quality of the intermediate or API beyond the official or other established specifications.
- 5.23 Where equipment is assigned to continuous production or campaign production of successive batches of the same intermediate or API, equipment should be cleaned at appropriate intervals to prevent buildup and carryover of contaminants (e.g., degradants or objectionable levels of microorganisms).
- 5.24 Nondedicated equipment should be cleaned between production of different materials to prevent cross-contamination.
- 5.25 Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be defined and justified.
- 5.26 Equipment should be identified as to its contents and its cleanliness status by appropriate means.

5.3. Calibration

- 5.30 Control, weighing, measuring, monitoring, and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.
- 5.31 Equipment calibrations should be performed using standards traceable to certified standards, if existing.
- 5.32 Records of these calibrations should be maintained.
- 5.33 The current calibration status of critical equipment should be known and verifiable.
- 5.34 Instruments that do not meet calibration criteria should not be used.
- 5.35 Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.

5.4. Computerized Systems

- 5.40 GMP-related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity, and criticality of the computerized application.
- 5.41 Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.
- 5.42 Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.
- 5.43 Computerized systems should have sufficient controls to prevent unauthorized access or changes to data. There should be controls to prevent omissions in data (e.g., system turned off and data not captured). There should be a record of any data change made, the previous entry, who made the change, and when the change was made.
- 5.44 Written procedures should be available for the operation and maintenance of computerized systems.
- 5.45 Where critical data are being entered manually, there should be an additional check on the accuracy of the entry. This can be done by a second operator or by the system itself.
- 5.46 Incidents related to computerized systems that could affect the quality of intermediates or APIs or the reliability of records or test results should be recorded and investigated.
- 5.47 Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented, and tested. Records should be kept of all changes, including modifications and

enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.

- 5.48 If system breakdowns or failures would result in the permanent loss of records, a backup system should be provided. A means of ensuring data protection should be established for all computerized systems.
- 5.49 Data can be recorded by a second means in addition to the computer system.

6. DOCUMENTATION AND RECORDS

6.1. Documentation System and Specifications

- 6.10 All documents related to the manufacture of intermediates or APIs should be prepared, reviewed, approved, and distributed according to written procedures. Such documents can be in paper or electronic form.
- 6.11 The issuance, revision, superseding, and withdrawal of all documents should be controlled with maintenance of revision histories.
- 6.12 A procedure should be established for retaining all appropriate documents (e.g., development history reports, scale-up reports, technical transfer reports, process validation reports, training records, production records, control records, and distribution records). The retention periods for these documents should be specified.
- 6.13 All production, control, and distribution records should be retained for at least 1 year after the expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.
- .14 When entries are made in records, these should be made indelibly in spaces provided for such entries, directly after performing the activities, and should identify the person making the entry. Corrections to entries should be dated and signed and leave the original entry still readable.
- 6.15 During the retention period, originals or copies of records should be readily available at the establishment where the activities described in such records occurred. Records that can be promptly retrieved from another location by electronic or other means are acceptable.
- 6.16 Specifications, instructions, procedures, and records can be retained either as originals or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records. Where reduction techniques such as microfilming or electronic records are used, suitable retrieval equipment and a means to produce a hard copy should be readily available.
- 6.17 Specifications should be established and documented for raw materials, intermediates where necessary, APIs, and labeling and packaging materials. In addition, specifications may be appropriate for certain other materials, such as process aids, gaskets, or other materials used during the production of intermediates or APIs that could critically impact on quality. Acceptance criteria should be established and documented for in-process controls.
- 6.18 If electronic signatures are used on documents, they should be authenticated and secure.

6.2. Equipment Cleaning and Use Record

- 6.20 Records of major equipment use, cleaning, sanitization and/or sterilization, and maintenance should show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed the cleaning and maintenance.
- 6.21 If equipment is dedicated to manufacturing one intermediate or API, then individual equipment records are not necessary if batches of the intermediate or API follow in traceable sequence. In cases where dedicated equipment is employed, the records of cleaning, maintenance, and use can be part of the batch record or maintained separately.

6.3. Records of Raw Materials, Intermediates, API Labeling and Packaging Materials

- 6.30 Records should be maintained including
  - the name of the manufacturer, identity and quantity of each shipment of each batch of raw materials, intermediates, or labeling and packaging materials for API's; the name of the supplier; the supplier's control number(s), if known, or other identification number; the number allocated on receipt; and the date of receipt;
  - the results of any test or examination performed and the conclusions derived from this;
  - records tracing the use of materials;
  - documentation of the examination and review of API labeling and packaging materials for conformity with established specifications; and
  - the final decision regarding rejected raw materials, intermediates or API labeling and packaging materials.
- 6.31 Master (approved) labels should be maintained for comparison to issued labels.

6.4. Master Production Instructions (Master Production and Control Records)

- 6.40 To ensure uniformity from batch to batch, master production instructions for each intermediate and API should be prepared, dated, and signed by one person and independently checked, dated, and signed by a person in the quality unit(s).
- 6.41 Master production instructions should include
  - the name of the intermediate or API being manufactured and an identifying document reference code, if applicable;
  - a complete list of raw materials and intermediates designated by names or codes sufficiently specific to identify any special quality characteristics;
  - an accurate statement of the quantity or ratio of each raw material or intermediate to be used, including the unit of measure. Where the quantity is not fixed, the calculation for each batch size or rate of production should be included. Variations to quantities should be included where they are justified;
  - the production location and major production equipment to be used;
  - detailed production instructions, including the
    - sequences to be followed;
    - ranges of process parameters to be used;
    - sampling instructions and in-process controls with their acceptance criteria, where appropriate;
    - time limits for completion of individual processing steps and/or the total process, where appropriate; and
    - expected yield ranges at appropriate phases of processing or time;
  - where appropriate, special notations and precautions to be followed, or cross-references to these; and
  - the instructions for storage of the intermediate or API to assure its suitability for use, including the labeling and packaging materials and special storage conditions with time limits, where appropriate.

6.5. Batch Production Records (Batch Production and Control Records)

- 6.50 Batch production records should be prepared for each intermediate and API and should include complete information relating to the production and control of each batch. The batch production record should be checked before issuance to assure that it is the correct version and a legible accurate reproduction of the appropriate master production instruction. If the batch production record is produced from a separate part of the master document, that document should include a reference to the current master production instruction being used.
- 6.51 These records should be numbered with a unique batch or identification number, dated, and signed when issued. In continuous production, the product code together with the date and time can serve as the unique identifier until the final number is allocated.
- 6.52 Documentation of completion of each significant step in the batch production records (batch production and control records) should include
  - dates and, when appropriate, times;
  - identity of major equipment (e.g., reactors, driers, mills, etc.) used;
  - specific identification of each batch, including weights, measures, and batch numbers of raw materials, intermediates, or any reprocessed materials used during manufacturing;
  - actual results recorded for critical process parameters;
  - any sampling performed;
  - signatures of the persons performing and directly supervising or checking each critical step in the operation;
  – in-process and laboratory test results;
  – actual yield at appropriate phases or times;
  – description of packaging and label for intermediate or API;
  – representative label of API or intermediate if made commercially available;
  – any deviation noted, its evaluation, investigation conducted (if appropriate), or reference to that investigation if stored separately; and
  – results of release testing.
- 6.53 Written procedures should be established and followed for investigating critical deviations or the failure of a batch of intermediate or API to meet specifications. The investigation should extend to other batches that may have been associated with the specific failure or deviation.

6.6. Laboratory Control Records

- 6.60 Laboratory control records should include complete data derived from all tests conducted to ensure compliance with established specifications and standards, including examinations and assays, as follows:
  - A description of samples received for testing, including the material name or source, batch number or other distinctive code, date sample was taken, and, where appropriate, the quantity and date the sample was received for testing.
  - A statement of or reference to each test method used.
  - A statement of the weight or measure of sample used for each test as described by the method; data on or cross-reference to the preparation and testing of reference standards, reagents, and standard solutions.
  - A complete record of all raw data generated during each test, in addition to graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific material and batch tested.
  - A record of all calculations performed in connection with the test, including, for example, units of measure, conversion factors, and equivalency factors.
  - A statement of the test results and how they compare with established acceptance criteria.
  - The signature of the person who performed each test and the date(s) the tests were performed.
  - The date and signature of a second person showing that the original records have been reviewed for accuracy, completeness, and compliance with established standards.
- 6.61 Complete records should also be maintained for

- any modifications to an established analytical method;
- periodic calibration of laboratory instruments, apparatus, gauges, and recording devices;
- all stability testing performed on APIs; and
- out-of-specification (OOS) investigations.

6.7. Batch Production Record Review

- 6.70 Written procedures should be established and followed for the review and approval of batch production and laboratory control records, including packaging and labeling, to determine compliance of the intermediate or API with established specifications before a batch is released or distributed.
- 6.71 Batch production and laboratory control records of critical process steps should be reviewed and approved by the quality unit(s) before an API batch is released or distributed. Production and laboratory control records of noncritical process steps can be reviewed by qualified production personnel or other units following procedures approved by the quality unit(s).
- 6.72 All deviation, investigation, and OOS reports should be reviewed as part of the batch record review before the batch is released.
- 6.73 The quality unit(s) can delegate to the production unit the responsibility and authority for release of intermediates, except for those shipped outside the control of the manufacturing company.

7. MATERIALS MANAGEMENT

7.1. General Controls

- 7.10 There should be written procedures describing the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials.
- 7.11 Manufacturers of intermediates and/or APIs should have a system for evaluating the suppliers of critical materials.
- 7.12 Materials should be purchased against an agreed specification, from a supplier or suppliers approved by the quality unit(s).
- 7.13 If the supplier of a critical material is not the manufacturer of that material, the name and address of that manufacturer should be known by the intermediate and/or API manufacturer.
- 7.14 Changing the source of supply of critical raw materials should be treated according to section 13, Change Control.

7.2. Receipt and Quarantine

- 7.20 Upon receipt and before acceptance, each container or grouping of containers of materials should be examined visually for correct labeling (including correlation between the name used by the supplier and the in-house name, if these are different), container damage, broken seals, and

evidence of tampering or contamination. Materials should be held under quarantine until they have been sampled, examined, or tested as appropriate, and released for use.

- 7.21 Before incoming materials are mixed with existing stocks (e.g., solvents or stocks in silos), they should be identified as correct, tested, if appropriate, and released. Procedures should be available to prevent discharging incoming materials wrongly into the existing stock.
- 7.22 If bulk deliveries are made in nondedicated tankers, there should be assurance of no cross-contamination from the tanker. Means of providing this assurance could include one or more of the following:
  - Certificate of cleaning
  - Testing for trace impurities
  - Audit of the supplier
- 7.23 Large storage containers, and their attendant manifolds, filling and discharge lines should be appropriately identified.
- 7.24 Each container or grouping of containers (batches) of materials should be assigned and identified with a distinctive code, batch, or receipt number. This number should be used in recording the disposition of each batch. A system should be in place to identify the status of each batch.

7.3. Sampling and Testing of Incoming Production Materials

- 7.30 At least one test to verify the identity of each batch of material should be conducted, with the exception of the materials described below in section 7.32. A supplier's Certificate of Analysis can be used in place of performing other tests, provided that the manufacturer has a system in place to evaluate suppliers.
- 7.31 Supplier approval should include an evaluation that provides adequate evidence (e.g., past quality history) that the manufacturer can consistently provide material meeting specifications. Full analyses should be conducted on at least three batches before reducing in-house testing. However, as a minimum, a full analysis should be performed at appropriate intervals and compared with the Certificates of Analysis. Reliability of Certificates of Analysis should be checked at regular intervals.
- 7.32 Processing aids, hazardous or highly toxic raw materials, other special materials, or materials transferred to another unit within the company's control do not need to be tested if the manufacturer's Certificate of Analysis is obtained, showing that these raw materials conform to established specifications. Visual examination of containers, labels, and recording of batch numbers should help in establishing the identity of these materials. The lack of on-site testing for these materials should be justified and documented.
- 7.33 Samples should be representative of the batch of material from which they are taken. Sampling methods should specify the number of containers to be sampled, which part of the container to sample, and the amount of material to be taken from each container. The number of containers to sample and the sample size should be based upon a sampling plan that takes into consideration the criticality of the material, material variability, past quality history of the supplier, and the quantity needed for analysis.
- 7.34 Sampling should be conducted at defined locations and by procedures designed to prevent contamination of the material sampled and contamination of other materials.
- 7.35 Containers from which samples are withdrawn should be opened carefully and subsequently reclosed. They should be marked to indicate that a sample has been taken.

7.4. Storage

- 7.40 Materials should be handled and stored in a manner to prevent degradation, contamination, and cross-contamination.
- 7.41 Materials stored in fiber drums, bags, or boxes should be stored off the floor and, when appropriate, suitably spaced to permit cleaning and inspection.
- 7.42 Materials should be stored under conditions and for a period that have no adverse effect on their quality, and should normally be controlled so that the oldest stock is used first.
- 7.43 Certain materials in suitable containers can be stored outdoors, provided identifying labels remain legible, and containers are appropriately cleaned before opening and use.
- 7.44 Rejected materials should be identified and controlled under a quarantine system designed to prevent their unauthorized use in manufacturing.

7.5. Reevaluation

- 7.50 Materials should be reevaluated as appropriate to determine their suitability for use (e.g., after prolonged storage or exposure to heat or humidity).

8. PRODUCTION AND IN-PROCESS CONTROLS

8.1. Production Operations

- 8.10 Raw materials for intermediate and API manufacturing should be weighed or measured under appropriate conditions that do not affect their suitability for use. Weighing and measuring devices should be of suitable accuracy for the intended use.
- 8.11 If a material is subdivided for later use in production operations, the container receiving the material should be suitable and should be so identified that the following information is available:
  - Material name and/or item code;
  - Receiving or control number;
  - Weight or measure of material in the new container; and
  - Reevaluation or retest date if appropriate.
- 8.12 Critical weighing, measuring, or subdividing operations should be witnessed or subjected to an equivalent control. Prior to use, production personnel should verify that the materials are those specified in the batch record for the intended intermediate or API.
- 8.13 Other critical activities should be witnessed or subjected to an equivalent control.
- 8.14 Actual yields should be compared with expected yields at designated steps in the production process. Expected yields with appropriate ranges should be established based on previous laboratory, pilot scale, or manufacturing data. Deviations in yield associated with critical process steps should be investigated to determine their impact or potential impact on the resulting quality of affected batches.
- 8.15 Any deviation should be documented and explained. Any critical deviation should be investigated.
- 8.16 The processing status of major units of equipment should be indicated either on the individual units of equipment or by appropriate documentation, computer control systems, or alternative means.
- 8.17 Materials to be reprocessed or reworked should be appropriately controlled to prevent unauthorized use.

8.2. Time Limits

- 8.20 If time limits are specified in the master production instruction (see section 6.41), these time limits should be met to ensure the quality of intermediates and APIs. Deviations should be documented and evaluated. Time limits may be inappropriate when processing to a target value (e.g., pH adjustment, hydrogenation, drying to predetermined specification) because completion of reactions or processing steps are determined by in-process sampling and testing.
- 8.21 Intermediates held for further processing should be stored under appropriate conditions to ensure their suitability for use.

8.3. In-process Sampling and Controls

- 8.30 Written procedures should be established to monitor the progress and control the performance of processing steps that cause variability in the quality characteristics of intermediates and APIs. In-process controls and their acceptance criteria should be defined based on the information gained during the development stage or historical data.
- 8.31 The acceptance criteria and type and extent of testing can depend on the nature of the intermediate or API being manufactured, the reaction or process step being conducted, and the degree to which the process introduces variability in the product's quality. Less stringent in-process controls may be appropriate in early processing steps, whereas tighter controls may be appropriate for later processing steps (e.g., isolation and purification steps).
- 8.32 Critical in-process controls (and critical process monitoring), including the control points and methods, should be stated in writing and approved by the quality unit(s).
- 8.33 In-process controls can be performed by qualified production department personnel and the process adjusted without prior quality unit(s) approval if the adjustments are made within preestablished limits approved by the quality unit(s). All tests and results should be fully documented as part of the batch record.
- 8.34 Written procedures should describe the sampling methods for in-process materials, intermediates, and APIs. Sampling plans and procedures should be based on scientifically sound sampling practices.
- 8.35 In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material and other intermediates or APIs. Procedures should be established to ensure the integrity of samples after collection.
- 8.36 OOS investigations are not normally needed for in-process tests that are performed for the purpose of monitoring and/or adjusting the process.

8.4. Blending Batches of Intermediates or APIs

- 8.40 For the purpose of this document, blending is defined as the process of combining materials within the same specification to produce a homogeneous intermediate or API. In-process mixing of fractions from single batches (e.g., collecting several centrifuge loads from a single crystallization batch) or combining fractions from several batches for further processing is considered to be part of the production process and is not considered to be blending.
- 8.41 OOS batches should not be blended with other batches for the purpose of meeting specifications. Each batch incorporated into the blend should have been manufactured using an established process and should have been individually tested and found to meet appropriate specifications prior to blending.
- 8.42 Acceptable blending operations include but are not limited to
  - blending of small batches to increase batch size; and
  - blending of tailings (i.e., relatively small quantities of isolated material) from batches of the same intermediate or API to form a single batch.
- 8.43 Blending processes should be adequately controlled and documented and the blended batch should be tested for conformance to established specifications where appropriate.
- 8.44 The batch record of the blending process should allow traceability back to the individual batches that make up the blend.
- 8.45 Where physical attributes of the API are critical (e.g., APIs intended for use in solid oral dosage forms or suspensions), blending operations should be validated to show homogeneity of the combined batch. Validation should include testing of critical attributes (e.g., particle size distribution, bulk density, and tap density) that may be affected by the blending process.
- 8.46 If the blending could adversely affect stability, stability testing of the final blended batches should be performed.
- 8.47 The expiry or retest date of the blended batch should be based on the manufacturing date of the oldest tailings or batch in the blend.

8.5. Contamination Control

- 8.50 Residual materials can be carried over into successive batches of the same intermediate or API if there is adequate control. Examples include residue adhering to the wall of a micronizer, residual layer of damp crystals remaining in a centrifuge bowl after discharge, and incomplete discharge of fluids or crystals from a processing vessel upon transfer of the material to the next step in the process. Such carryover should not result in the carryover of degradants or microbial contamination that may adversely alter the established API impurity profile.
- 8.51 Production operations should be conducted in a manner that will prevent contamination of intermediates or APIs by other materials.
- 8.52 Precautions to avoid contamination should be taken when APIs are handled after purification.

9. PACKAGING AND IDENTIFICATION LABELING OF APIs AND INTERMEDIATES

9.1. General

- 9.10 There should be written procedures describing the receipt, identification, quarantine, sampling, examination and/or testing and release, and handling of packaging and labeling materials.
- 9.11 Packaging and labeling materials should conform to established specifications. Those that do not comply with such specifications should be rejected to prevent their use in operations for which they are unsuitable.
- 9.12 Records should be maintained for each shipment of labels and packaging materials showing receipt, examination, or testing, and whether accepted or rejected.

9.2. Packaging Materials

- 9.20 Containers should provide adequate protection against deterioration or contamination of the intermediate or API that may occur during transportation and recommended storage.

- 9.21 Containers should be clean and, where indicated by the nature of the intermediate or API, sanitized to ensure that they are suitable for their intended use. These containers should not be reactive, additive, or absorptive so as to alter the quality of the intermediate or API beyond the specified limits.
- 9.22 If containers are reused, they should be cleaned in accordance with documented procedures and all previous labels should be removed or defaced.

9.3. Label Issuance and Control

- 9.30 Access to the label storage areas should be limited to authorized personnel.
- 9.31 Procedures should be used to reconcile the quantities of labels issued, used, and returned and to evaluate discrepancies found between the number of containers labeled and the number of labels issued. Such discrepancies should be investigated, and the investigation should be approved by the quality unit(s).
- 9.32 All excess labels bearing batch numbers or other batch-related printing should be destroyed. Returned labels should be maintained and stored in a manner that prevents mix-ups and provides proper identification.
- 9.33 Obsolete and outdated labels should be destroyed.
- 9.34 Printing devices used to print labels for packaging operations should be controlled to ensure that all imprinting conforms to the print specified in the batch production record.
- 9.35 Printed labels issued for a batch should be carefully examined for proper identity and conformity to specifications in the master production record. The results of this examination should be documented.
- 9.36 A printed label representative of those used should be included in the batch production record.

9.4. Packaging and Labeling Operations

- 9.40 There should be documented procedures designed to ensure that correct packaging materials and labels are used.
- 9.41 Labeling operations should be designed to prevent mix-ups. There should be physical or spatial separation from operations involving other intermediates or APIs.
- 9.42 Labels used on containers of intermediates or APIs should indicate the name or identifying code, the batch number of the product, and storage conditions, when such information is critical to assure the quality of intermediate or API.
- 9.43 If the intermediate or API is intended to be transferred outside the control of the manufacturer's material management system, the name and address of the manufacturer, quantity of contents, and special transport conditions and any special legal requirements should also be included on the label. For intermediates or APIs with an expiry date, the expiry date should be indicated on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.
- 9.44 Packaging and labeling facilities should be inspected immediately before use to ensure that all materials not needed for the next packaging operation have been removed. This examination should be documented in the batch production records, the facility log, or other documentation system.
- 9.45 Packaged and labeled intermediates or APIs should be examined to ensure that containers and packages in the batch have the correct label. This examination should be part of the packaging operation. Results of these examinations should be recorded in the batch production or control records.
- 9.46 Intermediate or API containers that are transported outside of the manufacturer's control should be sealed in a manner such that, if the seal is breached or missing, the recipient will be alerted to the possibility that the contents may have been altered.

10. STORAGE AND DISTRIBUTION

10.1. Warehousing Procedures

- 10.10 Facilities should be available for the storage of all materials under appropriate conditions (e.g., controlled temperature and humidity when necessary). Records should be maintained of these conditions if they are critical for the maintenance of material characteristics.
- 10.11 Unless there is an alternative system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials, separate storage areas should be assigned for their temporary storage until the decision as to their future use has been taken.

10.2. Distribution Procedures

- 10.20 APIs and intermediates should only be released for distribution to third parties after they have been released by the quality unit(s). APIs and intermediates can be transferred under quarantine to another unit under the company's control when authorized by the quality unit(s) and if appropriate controls and documentation are in place.
- 10.21 APIs and intermediates should be transported in a manner that does not adversely affect their quality.
- 10.22 Special transport or storage conditions for an API or intermediate should be stated on the label.
- 10.23 The manufacturer should ensure that the contract acceptor (contractor) for transportation of the API or intermediate knows and follows the appropriate transport and storage conditions.
- 10.24 A system should be in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall.

11. LABORATORY CONTROLS

11.1. General Controls

- 11.10 The independent quality unit(s) should have at its disposal adequate laboratory facilities.
- 11.11 There should be documented procedures describing sampling, testing, approval or rejection of materials, and recording and storage of laboratory data. Laboratory records should be maintained in accordance with section 6.6.
- 11.12 All specifications, sampling plans, and test procedures should be scientifically sound and appropriate to ensure that raw materials, intermediates, APIs, and labels and packaging materials conform to established standards of quality and/or purity. Specifications and test procedures should be consistent with those included in the registration/filing. There can be specifications in addition to those in the registration/filing. Specifications, sampling plans, and test procedures, including changes to them, should be drafted by the appropriate organizational unit and reviewed and approved by the quality unit(s).
- 11.13 Appropriate specifications should be established for APIs in accordance with accepted standards and consistent with the manufacturing process. The specifications should include a control of the impurities (e.g., organic impurities,

inorganic impurities, and residual solvents). If the API has a specification for microbiological purity, appropriate action limits for total microbial counts and objectionable organisms should be established and met. If the API has a specification for endotoxins, appropriate action limits should be established and met.

- 11.14 Laboratory controls should be followed and documented at the time of performance. Any departures from the above described procedures should be documented and explained.
- 11.15 Any OOS result obtained should be investigated and documented according to a procedure. This procedure should require analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure.
- 11.16 Reagents and standard solutions should be prepared and labeled following written procedures. "Use by" dates should be applied as appropriate for analytical reagents or standard solutions.
- 11.17 Primary reference standards should be obtained as appropriate for the manufacture of APIs. The source of each primary reference standard should be documented. Records should be maintained of each primary reference standard's storage and use in accordance with the supplier's recommendations. Primary reference standards obtained from an officially recognized source are normally used without testing if stored under conditions consistent with the supplier's recommendations.
- 11.18 Where a primary reference standard is not available from an officially recognized source, an "in-house primary standard" should be established. Appropriate testing should be performed to establish fully the identity and purity of the primary reference standard. Appropriate documentation of this testing should be maintained.
- 11.19 Secondary reference standards should be appropriately prepared, identified, tested, approved, and stored. The suitability of each batch of secondary reference standard should be determined prior to first use by comparing against a primary reference standard. Each batch of secondary reference standard should be periodically requalified in accordance with a written protocol.

11.2. Testing of Intermediates and APIs

- 11.20 For each batch of intermediate and API, appropriate laboratory tests should be conducted to determine conformance to specifications.
- 11.21 An impurity profile describing the identified and unidentified impurities present in a typical batch produced by a specific controlled production process should normally be established for each API. The impurity profile should include the identity or some qualitative analytical designation (e.g., retention time), the range of each impurity observed, and classification of each identified impurity (e.g., inorganic, organic, solvent). The impurity profile is normally dependent upon the production process and origin of the API. Impurity profiles are normally not necessary for APIs from herbal or animal tissue origin. Biotechnology considerations are covered in ICH Guideline Q6B.
- 11.22 The impurity profile should be compared at appropriate intervals against the impurity profile in the regulatory submission or compared against historical data in order to detect changes to the API resulting from modifications in raw materials, equipment operating parameters, or the production process.
- 11.23 Appropriate microbiological tests should be conducted on each batch of intermediate and API where microbial quality is specified.

11.3. Validation of Analytical Procedures (see Section 12)

11.4. Certificates of Analysis

- 11.40 Authentic Certificates of Analysis should be issued for each batch of intermediate or API on request.
- 11.41 Information on the name of the intermediate or API including where appropriate its grade, the batch number, and the date of release should be provided on the Certificate of Analysis. For intermediates or APIs with an expiry date, the expiry date should be provided on the label and Certificate of Analysis. For intermediates or APIs with a retest date, the retest date should be indicated on the label and/or Certificate of Analysis.
- 11.42 The Certificate should list each test performed in accordance with compendial or customer requirements, including the acceptance limits, and the numerical results obtained (if test results are numerical).
- 11.43 Certificates should be dated and signed by authorized personnel of the quality unit(s) and should show the name, address, and telephone number of the original manufacturer. Where the analysis has been carried out by a repacker or reprocessor, the Certificate of Analysis should show the name, address, and telephone number of the repacker/reprocessor and a reference to the name of the original manufacturer.
- 11.44 If new Certificates are issued by or on behalf of repackers/reprocessors, agents, or brokers, these Certificates should show the name, address, and telephone number of the laboratory that performed the analysis. They should also contain a reference to the name and address of the original manufacturer and to the original batch Certificate, a copy of which should be attached.

11.5. Stability Monitoring of APIs

- 11.50 A documented, ongoing testing program should be designed to monitor the stability characteristics of APIs, and the results should be used to confirm appropriate storage conditions and retest or expiry dates.
- 11.51 The test procedures used in stability testing should be validated and be stability indicating.
- 11.52 Stability samples should be stored in containers that simulate the market container. For example, if the API is marketed in bags within fiber drums, stability samples can be packaged in bags of the same material and in smaller-scale drums of similar or identical material composition to the market drums.
- 11.53 Normally the first three commercial production batches should be placed on the stability monitoring program to confirm the retest or expiry date. However, where data from previous studies show that the API is expected to remain stable for at least 2 years, fewer than three batches can be used.
- 11.54 Thereafter, at least one batch per year of API manufactured (unless none is produced that year) should be added to the stability monitoring program and tested at least annually to confirm the stability.
- 11.55 For APIs with short shelf lives, testing should be done more frequently. For example, for those biotechnological/biological and other APIs with shelf lives of 1 year or less, stability samples should be obtained and should be tested monthly for the first 3 months, and at 3 month

intervals after that. When data exist that confirm that the stability of the API is not compromised, elimination of specific test intervals (e.g., 9 month testing) can be considered.
- 11.56 Where appropriate, the stability storage conditions should be consistent with the ICH guidelines on stability.

11.6. Expiry and Retest Dating
- 11.60 When an intermediate is intended to be transferred outside the control of the manufacturer's material management system and an expiry or retest date is assigned, supporting stability information should be available (e.g., published data, test results).
- 11.61 An API expiry or retest date should be based on an evaluation of data derived from stability studies. Common practice is to use a retest date, not an expiration date.
- 11.62 Preliminary API expiry or retest dates can be based on pilot scale batches if (1) the pilot batches employ a method of manufacture and procedure that simulates the final process to be used on a commercial manufacturing scale and (2) the quality of the API represents the material to be made on a commercial scale.
- 11.63 A representative sample should be taken for the purpose of performing a retest.

11.7. Reserve/Retention Samples
- 11.70 The packaging and holding of reserve samples is for the purpose of potential future evaluation of the quality of batches of API and not for future stability testing purposes.
- 11.71 Appropriately identified reserve samples of each API batch should be retained for 1 year after the expiry date of the batch assigned by the manufacturer, or for 3 years after distribution of the batch, whichever is the longer. For APIs with retest dates, similar reserve samples should be retained for 3 years after the batch is completely distributed by the manufacturer.
- 11.72 The reserve sample should be stored in the same packaging system in which the API is stored or in one that is equivalent to or more protective than the marketed packaging system. Sufficient quantities should be retained to conduct at least two full compendial analyses or, when there is no pharmacopoeial monograph, two full specification analyses.

12. VALIDATION

12.1. Validation Policy
- 12.10 The company's overall policy, intentions, and approach to validation, including the validation of production processes, cleaning procedures, analytical methods, in-process control test procedures, computerized systems, and persons responsible for design, review, approval, and documentation of each validation phase, should be documented.
- 12.11 The critical parameters/attributes should normally be identified during the development stage or from historical data, and the ranges necessary for the reproducible operation should be defined. This should include:
  - defining the API in terms of its critical product attributes;
  - identifying process parameters that could affect the critical quality attributes of the API; and
  - determining the range for each critical process parameter expected to be used during routine manufacturing and process control.
- 12.12 Validation should extend to those operations determined to be critical to the quality and purity of the API.

12.2. Validation Documentation
- 12.20 A written validation protocol should be established that specifies how validation of a particular process will be conducted. The protocol should be reviewed and approved by the quality unit(s) and other designated units.
- 12.21 The validation protocol should specify critical process steps and acceptance criteria as well as the type of validation to be conducted (e.g., retrospective, prospective, concurrent) and the number of process runs.
- 12.22 A validation report that cross-references the validation protocol should be prepared, summarizing the results obtained, commenting on any deviations observed, and drawing the appropriate conclusions, including recommending changes to correct deficiencies.
- 12.23 Any variations from the validation protocol should be documented with appropriate justification.

12.3. Qualification
- 12.30 Before starting process validation activities, appropriate qualification of critical equipment and ancillary systems should be completed. Qualification is usually carried out by conducting the following activities, individually or combined:
  - Design Qualification (DQ): documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.
  - Installation Qualification (IQ): documented verification that the equipment or systems, as installed or modified, comply with the approved design, the manufacturer's recommendations and/or user requirements.
  - Operational Qualification (OQ): documented verification that the equipment or systems, as installed or modified, perform as intended throughout the anticipated operating ranges.
  - Performance Qualification (PQ): documented verification that the equipment and ancillary systems, as connected together, can perform effectively and reproducibly based on the approved process method and specifications.

12.4. Approaches to Process Validation
- 12.40 Process Validation is the documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce an intermediate or API meeting its predetermined specifications and quality attributes.
- 12.41 There are three approaches to validation. Prospective validation is the preferred approach, but there are exceptions where the other approaches can be used. These approaches and their applicability are listed below.
- 12.42 Prospective validation should normally be performed for all API processes as defined in section 12.12. Prospective validation performed on an API process should be completed before the commercial distribution of the final drug product manufactured from that API.
- 12.43 Concurrent validation can be conducted when data from replicate production runs are unavailable because only a limited number of API batches have been produced, API batches are produced infrequently, or API batches are produced by a validated process that has been modified. Prior to the completion of concurrent validation, batches can be released and used in final drug product for commercial distribution based on thorough monitoring and testing of the API batches.

- 12.44 An exception can be made for retrospective validation for well-established processes that have been used without significant changes to API quality due to changes in raw materials, equipment, systems, facilities, or the production process. This validation approach may be used where
  (1) critical quality attributes and critical process parameters have been identified;
  (2) appropriate in-process acceptance criteria and controls have been established;
  (3) there have not been significant process/product failures attributable to causes other than operator error or equipment failures unrelated to equipment suitability; and
  (4) impurity profiles have been established for the existing API.
- 12.45 Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Retained samples can be tested to obtain data to retrospectively validate the process.

12.5. Process Validation Program

- 12.50 The number of process runs for validation should depend on the complexity of the process or the magnitude of the process change being considered. For prospective and concurrent validation, three consecutive successful production batches should be used as a guide, but there may be situations where additional process runs are warranted to prove consistency of the process (e.g., complex API processes or API processes with prolonged completion times). For retrospective validation, generally data from 10 to 30 consecutive batches should be examined to assess process consistency, but fewer batches can be examined if justified.
- 12.51 Critical process parameters should be controlled and monitored during process validation studies. Process parameters unrelated to quality, such as variables controlled to minimize energy consumption or equipment use, need not be included in the process validation.
- 12.52 Process validation should confirm that the impurity profile for each API is within the limits specified. The impurity profile should be comparable to or better than historical data and, where applicable, the profile determined during process development or for batches used for pivotal clinical and toxicological studies.

12.6. Periodic Review of Validated Systems

- 12.60 Systems and processes should be periodically evaluated to verify that they are still operating in a valid manner. Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specifications, there is normally no need for revalidation.

12.7. Cleaning Validation

- 12.70 Cleaning procedures should normally be validated. In general, cleaning validation should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality. For example, in early production it may be unnecessary to validate equipment cleaning procedures where residues are removed by subsequent purification steps.
- 12.71 Validation of cleaning procedures should reflect actual equipment usage patterns. If various APIs or intermediates are manufactured in the same equipment and the equipment is cleaned by the same process, a representative intermediate or API can be selected for cleaning validation. This selection should be based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.
- 12.72 The cleaning validation protocol should describe the equipment to be cleaned, procedures, materials, acceptable cleaning levels, parameters to be monitored and controlled, and analytical methods. The protocol should also indicate the type of samples to be obtained and how they are collected and labeled.
- 12.73 Sampling should include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring levels of residues remaining on the equipment surfaces after cleaning. Swab sampling may be impractical when product contact surfaces are not easily accessible due to equipment design and/or process limitations (e.g., inner surfaces of hoses, transfer pipes, reactor tanks with small ports or handling toxic materials, and small intricate equipment such as micronizers and microfluidizers).
- 12.74 Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant. The method's attainable recovery level should be established. Residue limits should be practical, achievable, verifiable and based on the most deleterious residue. Limits can be established based on the minimum known pharmacological, toxicological, or physiological activity of the API or its most deleterious component.
- 12.75 Equipment cleaning/sanitization studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API, or other processes where such contamination could be of concern (e.g., nonsterile APIs used to manufacture sterile products).
- 12.76 Cleaning procedures should be monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production. Equipment cleanliness can be monitored by analytical testing and visual examination, where feasible. Visual inspection can allow detection of gross contamination concentrated in small areas that could otherwise go undetected by sampling and/or analysis.

12.8. Validation of Analytical Methods

- 12.80 Analytical methods should be validated unless the method employed is included in the relevant pharmacopoeia or other recognized standard reference. The suitability of all testing methods used should nonetheless be verified under actual conditions of use and documented.
- 12.81 Methods should be validated to include consideration of characteristics included within the ICH guidelines on validation of analytical methods. The degree of analytical validation performed should reflect the purpose of the analysis and the stage of the API production process.
- 12.82 Appropriate qualification of analytical equipment should be considered before starting validation of analytical methods.
- 12.83 Complete records should be maintained of any modification of a validated analytical method. Such records should include the reason for the modification and

appropriate data to verify that the modification produces results that are as accurate and reliable as the established method.

13. CHANGE CONTROL

- 13.10 A formal change control system should be established to evaluate all changes that may affect the production and control of the intermediate or API.
- 13.11 Written procedures should provide for the identification, documentation, appropriate review, and approval of changes in raw materials, specifications, analytical methods, facilities, support systems, equipment (including computer hardware), processing steps, labeling and packaging materials, and computer software.
- 13.12 Any proposals for GMP relevant changes should be drafted, reviewed, and approved by the appropriate organizational units, and reviewed and approved by the quality unit(s).
- 13.13 The potential impact of the proposed change on the quality of the intermediate or API should be evaluated. Classification procedure may help in determining the level of testing, validation, and documentation needed to justify changes to a validated process. Changes can be classified (e.g., as minor or major) depending on the nature and extent of the changes, and the effects these changes may impart on the process. Scientific judgment should determine what additional testing and validation studies are appropriate to justify a change in a validated process.
- 13.14 When implementing approved changes, measures should be taken to ensure that all documents affected by the changes are revised.
- 13.15 After the change has been implemented, there should be an evaluation of the first batches produced or tested under the change.
- 13.16 The potential for critical changes to affect established retest or expiry dates should be evaluated. If necessary, samples of the intermediate or API produced by the modified process can be placed on an accelerated stability program and/or can be added to the stability monitoring program.
- 13.17 Current dosage form manufacturers should be notified of changes from established production and process control procedures that can impact the quality of the API.

14. REJECTION AND REUSE OF MATERIALS

14.1. Rejection

- 14.10 Intermediates and APIs failing to meet established specifications should be identified as such and quarantined. These intermediates or APIs can be reprocessed or reworked as described below. The final disposition of rejected materials should be recorded.

14.2. Reprocessing

- 14.20 Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and reprocessing by repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process is generally considered acceptable. However, if such reprocessing is used for a majority of batches, such reprocessing should be included as part of the standard manufacturing process.
- 14.21 Continuation of a process step after an in-process control test has shown that the step is incomplete is considered to be part of the normal process. This is not considered to be reprocessing.
- 14.22 Introducing unreacted material back into a process and repeating a chemical reaction is considered to be reprocessing unless it is part of the established process. Such reprocessing should be preceded by careful evaluation to ensure that the quality of the intermediate or API is not adversely impacted due to the potential formation of by-products and overreacted materials.

14.3. Reworking

- 14.30 Before a decision is taken to rework batches that do not conform to established standards or specifications, an investigation into the reason for nonconformance should be performed.
- 14.31 Batches that have been reworked should be subjected to appropriate evaluation, testing, stability testing if warranted, and documentation to show that the reworked product is of equivalent quality to that produced by the original process. Concurrent validation is often the appropriate validation approach for rework procedures. This allows a protocol to define the rework procedure, how it will be carried out, and the expected results. If there is only one batch to be reworked, then a report can be written and the batch released once it is found to be acceptable.
- 14.32 Procedures should provide for comparing the impurity profile of each reworked batch against batches manufactured by the established process. Where routine analytical methods are inadequate to characterize the reworked batch, additional methods should be used.

14.4. Recovery of Materials and Solvents

- 14.40 Recovery (e.g., from mother liquor or filtrates) of reactants, intermediates, or the API is considered acceptable, provided that approved procedures exist for the recovery and the recovered materials meet specifications suitable for their intended use.
- 14.41 Solvents can be recovered and reused in the same processes or in different processes, provided that the recovery procedures are controlled and monitored to ensure that solvents meet appropriate standards before reuse or comingling with other approved materials.
- 14.42 Fresh and recovered solvents and reagents can be combined if adequate testing has shown their suitability for all manufacturing processes in which they may be used.
- 14.43 The use of recovered solvents, mother liquors, and other recovered materials should be adequately documented.

14.5. Returns

- 14.50 Returned intermediates or APIs should be identified as such and quarantined.
- 14.51 If the conditions under which returned intermediates or APIs have been stored or shipped before or during their return or the condition of their containers casts doubt on their quality, the returned intermediates or APIs should be reprocessed, reworked, or destroyed, as appropriate.
- 14.52 Records of returned intermediates or APIs should be maintained. For each return, documentation should include the following:
  - Name and address of the consignee
  - Intermediate or API, batch number, and quantity returned

- Reason for return
- Use or disposal of the returned intermediate or API

15. COMPLAINTS AND RECALLS

- 15.10 All quality-related complaints, whether received orally or in writing, should be recorded and investigated according to a written procedure.
- 15.11 Complaint records should include
  - name and address of complainant;
  - name (and, where appropriate, title) and phone number of person submitting the complaint;
  - complaint nature (including name and batch number of the API);
  - date complaint is received;
  - action initially taken (including dates and identity of person taking the action);
  - any follow-up action taken;
  - response provided to the originator of complaint (including date response sent); and
  - final decision on intermediate or API batch or lot.
- 15.12 Records of complaints should be retained in order to evaluate trends, product-related frequencies, and severity with a view to taking additional, and if appropriate, immediate corrective action.
- 15.13 There should be a written procedure that defines the circumstances under which a recall of an intermediate or API should be considered.
- 15.14 The recall procedure should designate who should be involved in evaluating the information, how a recall should be initiated, who should be informed about the recall, and how the recalled material should be treated.
- 15.15 In the event of a serious or potentially life-threatening situation, local, national, and/or international authorities should be informed and their advice sought.

16. CONTRACT MANUFACTURERS (INCLUDING LABORATORIES)

- 16.10 All contract manufacturers (including laboratories) should comply with the GMP defined in this Guide. Special consideration should be given to the prevention of cross-contamination and to maintaining traceability.
- 16.11 Contract manufacturers (including laboratories) should be evaluated by the contract giver to ensure GMP compliance of the specific operations occurring at the contract sites.
- 16.12 There should be a written and approved contract or formal agreement between the contract giver and the contract acceptor that defines in detail the GMP responsibilities, including the quality measures, of each party.
- 16.13 The contract should permit the contract giver to audit the contract acceptor's facilities for compliance with GMP.
- 16.14 Where subcontracting is allowed, the contract acceptor should not pass to a third party any of the work entrusted to him under the contract without the contract giver's prior evaluation and approval of the arrangements.
- 16.15 Manufacturing and laboratory records should be kept at the site where the activity occurs and be readily available.
- 16.16 Changes in the process, equipment, test methods, specifications, or other contractual requirements should not be made unless the contract giver is informed and approves the changes.

17. AGENTS, BROKERS, TRADERS, DISTRIBUTORS, REPACKERS, AND RELABELERS

17.1. Applicability

- 17.10 This section applies to any party other than the original manufacturer who may trade and/or take possession, repack, relabel, manipulate, distribute, or store an API or intermediate.
- 17.11 All agents, brokers, traders, distributors, repackers, and relabelers should comply with GMP as defined in this Guide.

17.2. Traceability of Distributed APIs and Intermediates

- 17.20 Agents, brokers, traders, distributors, repackers, or relabelers should maintain complete traceability of APIs and intermediates that they distribute. Documents that should be retained and available include the following:
  - Identity of original manufacturer
  - Address of original manufacturer
  - Purchase orders
  - Bills of lading (transportation documentation)
  - Receipt documents
  - Name or designation of API or intermediate
  - Manufacturer's batch number
  - Transportation and distribution records
  - All authentic Certificates of Analysis, including those of the original manufacturer
  - Retest or expiry date

17.3. Quality Management

- 17.30 Agents, brokers, traders, distributors, repackers, or relabelers should establish, document, and implement an effective system of managing quality, as specified in section 2.

17.4. Repackaging, Relabeling and Holding of APIs and Intermediates

- 17.40 Repackaging, relabeling and holding of APIs and intermediates should be performed under appropriate GMP controls, as stipulated in this Guide, to avoid mix-ups and loss of API or intermediate identity or purity.
- 17.41 Repackaging should be conducted under appropriate environmental conditions to avoid contamination and cross-contamination.

17.5. Stability

- 17.50 Stability studies to justify assigned expiration or retest dates should be conducted if the API or intermediate is repackaged in a different type of container than that used by the API or intermediate manufacturer.

17.6. Transfer of Information

- 17.60 Agents, brokers, distributors, repackers, or relabelers should transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer.
- 17.61 The agent, broker, trader, distributor, repacker, or relabeler who supplies the API or intermediate to the customer should provide the name of the original API or intermediate manufacturer and the batch number(s) supplied.
- 17.62 The agent should also provide the identity of the original API or intermediate manufacturer to regulatory authorities upon request. The original manufacturer can respond to the regulatory authority directly or through its authorized agents, depending on the legal relationship

between the authorized agents and the original API or intermediate manufacturer. (In this context "authorized" refers to authorized by the manufacturer.)
- 17.63 The specific guidance for Certificates of Analysis included in section 11.4 should be met.

17.7. Handling of Complaints and Recalls
- 17.70 Agents, brokers, traders, distributors, repackers, or relabelers should maintain records of complaints and recalls, as specified in section 15, for all complaints and recalls that come to their attention.
- 17.71 If the situation warrants, the agents, brokers, traders, distributors, repackers, or relabelers should review the complaint with the original API or intermediate manufacturer in order to determine whether any further action, either with other customers who may have received this API or intermediate or with the regulatory authority, or both, should be initiated. The investigation into the cause for the complaint or recall should be conducted and documented by the appropriate party.
- 17.72 Where a complaint is referred to the original API or intermediate manufacturer, the record maintained by the agents, brokers, traders, distributors, repackers, or relabelers should include any response received from the original API or intermediate manufacturer (including date and information provided).

17.8. Handling of Returns
- 17.80 Returns should be handled as specified in section 14.52. The agents, brokers, traders, distributors, repackers, or relabelers should maintain documentation of returned APIs and intermediates.

18. SPECIFIC GUIDANCE FOR APIs MANUFACTURED BY CELL CULTURE/FERMENTATION

18.1. General
- 18.10 Section 18 is intended to address specific controls for APIs or intermediates manufactured by cell culture or fermentation using natural or recombinant organisms and that have not been covered adequately in the previous sections. It is not intended to be a stand-alone section. In general, the GMP principles in the other sections of this document apply. Note that the principles of fermentation for "classical" processes for production of small molecules and for processes using recombinant and nonrecombinant organisms for production of proteins and/or polypeptides are the same, although the degree of control will differ. Where practical, this section will address these differences. In general, the degree of control for biotechnological processes used to produce proteins and polypeptides is greater than that for classical fermentation processes.
- 18.11 The term "biotechnological process" (biotech) refers to the use of cells or organisms that have been generated or modified by recombinant DNA, hybridoma or other technology to produce APIs. The APIs produced by biotechnological processes normally consist of high molecular weight substances, such as proteins and polypeptides, for which specific guidance is given in this section. Certain APIs of low molecular weight, such as antibiotics, amino acids, vitamins, and carbohydrates, can also be produced by recombinant DNA technology. The level of control for these types of APIs is similar to that employed for classical fermentation.
- 18.12 The term "classical fermentation" refers to processes that use microorganisms existing in nature and/or modified by conventional methods (e.g., irradiation or chemical mutagenesis) to produce APIs. APIs produced by "classical fermentation" are normally low molecular weight products such as antibiotics, amino acids, vitamins, and carbohydrates.
- 18.13 Production of APIs or intermediates from cell culture or fermentation involves biological processes such as cultivation of cells or extraction and purification of material from living organisms. Note that there may be additional process steps, such as physicochemical modification, that are part of the manufacturing process. The raw materials used (media, buffer components) may provide the potential for growth of microbiological contaminants. Depending on the source, method of preparation, and the intended use of the API or intermediate, control of bioburden, viral contamination, and/or endotoxins during manufacturing and monitoring of the process at appropriate stages may be necessary.
- 18.14 Appropriate controls should be established at all stages of manufacturing to assure intermediate and/or API quality. While this Guide starts at the cell culture/fermentation step, prior steps (e.g., cell banking) should be performed under appropriate process controls. This Guide covers cell culture/fermentation from the point at which a vial of the cell bank is retrieved for use in manufacturing.
- 18.15 Appropriate equipment and environmental controls should be used to minimize the risk of contamination. The acceptance criteria for quality of the environment and the frequency of monitoring should depend on the step in production and the production conditions (open, closed, or contained systems).
- 18.16 In general, process controls should take into account:
  - Maintenance of the Working Cell Bank (where appropriate);
  - Proper inoculation and expansion of the culture;
  - Control of the critical operating parameters during fermentation/cell culture;
  - Monitoring of the process for cell growth, viability (for most cell culture processes) and productivity where appropriate;
  - Harvest and purification procedures that remove cells, cellular debris, and media components while protecting the intermediate or API from contamination (particularly of a microbiological nature) and from loss of quality;
  - Monitoring of bioburden and, where needed, endotoxin levels at appropriate stages of production; and
  - Viral safety concerns as described in ICH Guideline Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin*.
- 18.17 Where appropriate, the removal of media components, host cell proteins, other process-related impurities, product-related impurities and contaminants should be demonstrated.

18.2. Cell Bank Maintenance and Record Keeping
- 18.20 Access to cell banks should be limited to authorized personnel.
- 18.21 Cell banks should be maintained under storage conditions designed to maintain viability and prevent contamination.
- 18.22 Records of the use of the vials from the cell banks and storage conditions should be maintained.
- 18.23 Where appropriate, cell banks should be periodically monitored to determine suitability for use.

- 18.24 See ICH Guideline Q5D *Quality of Biotechnological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products* for a more complete discussion of cell banking.

18.3. Cell Culture/Fermentation

- 18.30 Where aseptic addition of cell substrates, media, buffers, and gases is needed, closed or contained systems should be used where possible. If the inoculation of the initial vessel or subsequent transfers or additions (media, buffers) are performed in open vessels, there should be controls and procedures in place to minimize the risk of contamination.
- 18.31 Where the quality of the API can be affected by microbial contamination, manipulations using open vessels should be performed in a biosafety cabinet or similarly controlled environment.
- 18.32 Personnel should be appropriately gowned and take special precautions handling the cultures.
- 18.33 Critical operating parameters (e.g., temperature, pH, agitation rates, addition of gases, pressure) should be monitored to ensure consistency with the established process. Cell growth, viability (for most cell culture processes), and, where appropriate, productivity should also be monitored. Critical parameters will vary from one process to another, and for classical fermentation, certain parameters (cell viability, for example) may not need to be monitored.
- 18.34 Cell culture equipment should be cleaned and sterilized after use. As appropriate, fermentation equipment should be cleaned, and sanitized or sterilized.
- 18.35 Culture media should be sterilized before use when appropriate to protect the quality of the API.
- 18.36 There should be appropriate procedures in place to detect contamination and determine the course of action to be taken. This should include procedures to determine the impact of the contamination on the product and those to decontaminate the equipment and return it to a condition to be used in subsequent batches. Foreign organisms observed during fermentation processes should be identified as appropriate and the effect of their presence on product quality should be assessed, if necessary. The results of such assessments should be taken into consideration in the disposition of the material produced.
- 18.37 Records of contamination events should be maintained.
- 18.38 Shared (multiproduct) equipment may warrant additional testing after cleaning between product campaigns, as appropriate, to minimize the risk of cross-contamination.

18.4. Harvesting, Isolation, and Purification

- 18.40 Harvesting steps, either to remove cells or cellular components or to collect cellular components after disruption, should be performed in equipment and areas designed to minimize the risk of contamination.
- 18.41 Harvest and purification procedures that remove or inactivate the producing organism, cellular debris, and media components (while minimizing degradation, contamination, and loss of quality) should be adequate to ensure that the intermediate or API is recovered with consistent quality.
- 18.42 All equipment should be properly cleaned and, as appropriate, sanitized after use. Multiple successive batching without cleaning can be used if intermediate or API quality is not compromised.
- 18.43 If open systems are used, purification should be performed under environmental conditions appropriate for the preservation of product quality.
- 18.44 Additional controls, such as the use of dedicated chromatography resins or additional testing, may be appropriate if equipment is to be used for multiple products.

18.5. Viral Removal/Inactivation Steps

- 18.50 See the ICH Guideline Q5A *Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin* for more specific information.
- 18.51 Viral removal and viral inactivation steps are critical processing steps for some processes and should be performed within their validated parameters.
- 18.52 Appropriate precautions should be taken to prevent potential viral contamination from previral to postviral removal/inactivation steps. Therefore, open processing should be performed in areas that are separate from other processing activities and have separate air handling units.
- 18.53 The same equipment is not normally used for different purification steps. However, if the same equipment is to be used, the equipment should be appropriately cleaned and sanitized before reuse. Appropriate precautions should be taken to prevent potential virus carryover (e.g., through equipment or environment) from previous steps.

19. APIs FOR USE IN CLINICAL TRIALS

19.1. General

- 19.10 Not all the controls in the previous sections of this Guide are appropriate for the manufacture of a new API for investigational use during its development. Section 19 provides specific guidance unique to these circumstances.
- 19.11 The controls used in the manufacture of APIs for use in clinical trials should be consistent with the stage of development of the drug product incorporating the API. Process and test procedures should be flexible to provide for changes as knowledge of the process increases and clinical testing of a drug product progresses from preclinical stages through clinical stages. Once drug development reaches the stage where the API is produced for use in drug products intended for clinical trials, manufacturers should ensure that APIs are manufactured in suitable facilities using appropriate production and control procedures to ensure the quality of the API.

19.2. Quality

- 19.20 Appropriate GMP concepts should be applied in the production of APIs for use in clinical trials with a suitable mechanism of approval of each batch.
- 19.21 A quality unit(s) independent from production should be established for the approval or rejection of each batch of API for use in clinical trials.
- 19.22 Some of the testing functions commonly performed by the quality unit(s) can be performed within other organizational units.
- 19.23 Quality measures should include a system for testing of raw materials, packaging materials, intermediates, and APIs.
- 19.24 Process and quality problems should be evaluated.

- 19.25 Labeling for APIs intended for use in clinical trials should be appropriately controlled and should identify the material as being for investigational use.

19.3. Equipment and Facilities

- 19.30 During all phases of clinical development, including the use of small-scale facilities or laboratories to manufacture batches of APIs for use in clinical trials, procedures should be in place to ensure that equipment is calibrated, clean, and suitable for its intended use.
- 19.31 Procedures for the use of facilities should ensure that materials are handled in a manner that minimizes the risk of contamination and cross-contamination.

19.4. Control of Raw Materials

- 19.40 Raw materials used in production of APIs for use in clinical trials should be evaluated by testing, or received with a supplier's analysis and subjected to identity testing. When a material is considered hazardous, a supplier's analysis should suffice.
- 19.41 In some instances, the suitability of a raw material can be determined before use based on acceptability in small-scale reactions (i.e., use testing) rather than on analytical testing alone.

19.5. Production

- 19.50 The production of APIs for use in clinical trials should be documented in laboratory notebooks, batch records, or by other appropriate means. These documents should include information on the use of production materials, equipment, processing, and scientific observations.
- 19.51 Expected yields can be more variable and less defined than the expected yields used in commercial processes. Investigations into yield variations are not expected.

19.6. Validation

- 19.60 Process validation for the production of APIs for use in clinical trials is normally inappropriate, where a single API batch is produced or where process changes during API development make batch replication difficult or inexact. The combination of controls, calibration, and, where appropriate, equipment qualification assures API quality during this development phase.
- 19.61 Process validation should be conducted in accordance with section 12 when batches are produced for commercial use, even when such batches are produced on a pilot or small scale.

19.7. Changes

- 19.70 Changes are expected during development, as knowledge is gained and the production is scaled up. Every change in the production, specifications, or test procedures should be adequately recorded.

19.8. Laboratory Controls

- 19.80 While analytical methods performed to evaluate a batch of API for clinical trials may not yet be validated, they should be scientifically sound.
- 19.81 A system for retaining reserve samples of all batches should be in place. This system should ensure that a sufficient quantity of each reserve sample is retained for an appropriate length of time after approval, termination, or discontinuation of an application.
- 19.82 Expiry and retest dating as defined in section 11.6 applies to existing APIs used in clinical trials. For new APIs, section 11.6 does not normally apply in early stages of clinical trials.

19.9. Documentation

- 19.90 A system should be in place to ensure that information gained during the development and the manufacture of APIs for use in clinical trials is documented and available.
- 19.91 The development and implementation of the analytical methods used to support the release of a batch of API for use in clinical trials should be appropriately documented.
- 19.92 A system for retaining production and control records and documents should be used. This system should ensure that records and documents are retained for an appropriate length of time after the approval, termination, or discontinuation of an application.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (or Drug Substance)—Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

API Starting Material—A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

Batch (or Lot)—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval.

Batch Number (or Lot Number)—A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined.

Bioburden—The level and type (e.g., objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates, or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Calibration—The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements.

Computer System—A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions.

Computerized System—A process or operation integrated with a computer system.

Contamination—The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage or transport.

Contract Manufacturer—A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical—Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Cross-Contamination—Contamination of a material or product with another material or product.

Deviation—Departure from an approved instruction or established standard.

Drug (Medicinal) Product—The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance—See Active Pharmaceutical Ingredient

Expiry Date (or Expiration Date)—The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Impurity—Any component present in the intermediate or API that is not the desired entity.

Impurity Profile—A description of the identified and unidentified impurities present in an API.

In-Process Control (or Process Control)—Checks performed during production in order to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

Intermediate—A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. (*Note*: this Guide only addresses those intermediates produced after the point that the company has defined as the point at which the production of the API begins.)

Lot—See Batch

Lot Number—See Batch Number

Manufacture—All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Material—A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs and packaging and labeling materials.

Mother Liquor—The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It may be used for further processing.

Packaging Material—Any material intended to protect an intermediate or API during storage and transport.

Procedure—A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids—Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon, etc).

Process Control—See In-Process Control.

Production—All operations involved in the preparation of an API from receipt of materials through processing and packaging of the API.

Qualification—Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)—The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)—Checking or testing that specifications are met.

Quality Unit(s)—An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine—The status of materials isolated physically or by other effective means pending a decision on their subsequent approval or rejection.

Raw Material—A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reference Standard, Primary—A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity. This standard can be (1) obtained from an officially recognized source, (2) prepared by independent synthesis, (3) obtained from existing production material of high purity, or (4) prepared by further purification of existing production material.

Reference Standard, Secondary—A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing—Introducing an intermediate or API, including one that does not conform to standards or specifications, back into the process and repeating a crystallization step or other appropriate chemical or physical manipulation steps (e.g., distillation, filtration, chromatography, milling) that are part of the established manufacturing process. Continuation of a process step after an in-process control test has shown that the step is incomplete if considered to be part of the normal process, and not reprocessing.

Retest Date—The date when a material should be reexamined to ensure that it is still suitable for use.

Reworking—Subjecting an intermediate or API that does not conform to standards or specifications to one or more processing steps that are different from the established manufacturing process to obtain acceptable quality intermediate or API (e.g., recrystallizing with a different solvent).

Signature (signed)—See definition for signed

Signed (signature)—The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent—An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification—A list of tests, references to analytical procedures, and appropriate acceptance criteria that are numerical limits, ranges, or other criteria for the test described. It establishes the set of criteria to which a material should conform to be considered acceptable for its intended use. "Conformance to specification" means that the material, when tested according to the listed analytical procedures, will meet the listed acceptance criteria.

Validation—A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

Validation Protocol—A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected—The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical—The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

Validation of Analytical Procedures

I. INTRODUCTION

The objective of validation of an analytical procedure is to demonstrate that it is suitable for its intended purpose. A tabular summation of the characteristics applicable to identification, control of impurities, and assay procedures is included. Other analytical procedures may be considered in future additions to this document.

II. TYPES OF ANALYTICAL PROCEDURES TO BE VALIDATED

The four most common types of analytical procedures are as follows:

- Identification tests
- Quantitative tests for impurities' content
- Limit tests for the control of impurities
- Quantitative tests of the active moiety in samples of drug substance or drug product or other selected component(s) in the drug product

Although there are many other analytical procedures, such as dissolution testing for drug products or particle size determination for drug substance, these have not been addressed in the initial text on validation of analytical procedures. Validation of these additional analytical procedures is equally important to those listed herein and may be addressed in subsequent documents.

A brief description of the types of tests considered in this document is provided below.

- Identification tests are intended to ensure the identity of an analyte in a sample. This is normally achieved by comparison of a property of the sample (e.g., spectrum, chromatographic behavior, chemical reactivity, etc.) to that of a reference standard.
- Testing for impurities can be either a quantitative test or a limit test for the impurity in a sample. Either test is intended to accurately reflect the purity characteristics of the sample. Different validation characteristics are required for a quantitative test than for a limit test.
- Assay procedures are intended to measure the analyte present in a given sample. In the context of this document, the assay represents a quantitative measurement of the major component(s) in the drug substance. For the drug product, similar validation characteristics also apply when assaying for the active or other selected component(s). The same validation characteristics may also apply to assays associated with other analytical procedures (e.g., dissolution).

The objective of the analytical procedure should be clearly understood since this will govern the validation characteristics, which need to be evaluated. Typical validation characteristics which should be considered are listed below:

Accuracy
Precision
Repeatability
Intermediate Precision
Specificity
Detection Limit
Quantitation Limit
Linearity
Range

Each of these validation characteristics is defined in the attached Glossary. The table lists those validation characteristics regarded as the most important for the validation of different types of analytical procedures. This list should be considered typical for the analytical procedures cited but occasional exceptions should be dealt with on a case-by-case basis. It should be noted that robustness is not listed in the table but should be considered at an appropriate stage in the development of the analytical procedure.

Furthermore revalidation may be necessary in the following circumstances:

- changes in the synthesis of the drug substance,
- changes in the composition of the finished product, and
- changes in the analytical procedure.

The degree of revalidation required depends on the nature of the changes. Certain other changes may require validation as well.

Type of Analytical Procedure Characteristics	Identification	Testing for Impurities Quantitation Limit		Assay - Dissolution (Measurement only)	- Content/potency
Accuracy	–	+	–		+
Precision					
Repeatability	–	+	–	+	
Intermediate Precision	–	+[a]	–	+[a]	
Specificity[b]	+	+	+		+
Detection Limit	–	–[c]	+		–
Quantitation Limit	–	+	–		–
Linearity	–	+	–		+
Range	–	+	–		+

– signifies that this characteristic is not normally evaluated
+ signifies that this characteristic is normally evaluated
[a] In cases where reproducibility (see Glossary) has been performed, Intermediate Precision is not needed.
[b] Lack of specificity of one analytical procedure could be compensated by other supporting analytical procedure(s).
[c] May be needed in some cases.

GLOSSARY

Analytical Procedure—The analytical procedure refers to the way of performing the analysis. It should describe in detail the steps necessary to perform each analytical test. This may include but is not limited to the sample, the reference standard and the reagents preparations, use of the apparatus, generation of the calibration curve, use of the formulae for the calculation, etc.

Specificity—Specificity is the ability to assess unequivocally the analyte in the presence of components, which may be expected to be present. Typically, these might include impurities, degradants, matrix, etc.

Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedure(s).

This definition has the following implications:

Identification: to ensure the identity of an analyte.

Purity Tests: to ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte, that is, related substances test, heavy metals, residual solvents content, etc.

Assay (content or potency): to provide an exact result, which allows an accurate statement on the content or potency of the analyte in a sample.

Accuracy—The accuracy of an analytical procedure expresses the closeness of agreement between the value, which is accepted either as a conventional true value or an accepted reference value and the value found.

This is sometimes termed trueness.

Precision—The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision, and reproducibility.

Precision should be investigated using homogeneous, authentic samples. However, if it is not possible to obtain a homogeneous sample, it may be investigated using artificially prepared samples or a sample solution.

The precision of an analytical procedure is usually expressed as the variance, standard deviation, or coefficient of variation of a series of measurements.

1. **Repeatability—**Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision.
2. **Intermediate Precision—**Intermediate precision expresses within-laboratories variations: different days, different analysts, different equipment, etc.
3. **Reproducibility—**Reproducibility expresses the precision between laboratories (collaborative studies, usually applied to standardization of methodology).

Detection Limit—The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample, which can be detected but not necessarily quantitated as an exact value.

Quantitation Limit—The Quantitation Limit of an individual analytical procedure is the lowest amount of analyte in a sample, which can be quantitatively determined with suitable precision and accuracy. The Quantitation Limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

Linearity—The linearity of an analytical procedure is its ability (within a given range) to obtain test results, which are directly proportional to the concentration (amount) of analyte in the sample.

Range—The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy, and linearity.

Robustness—The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

Validation of Analytical Procedures: Methodology

I. INTRODUCTION

All relevant data collected during validation and formulae used for calculating validation characteristics should be submitted and discussed as appropriate.

Approaches other than those set forth in this guideline may be applicable and acceptable. It is the responsibility of the applicant to choose the validation procedure and protocol most suitable for their product. However, it is important to remember that the main objective of validation of an analytical procedure is to demonstrate that the procedure is suitable for its intended purpose. Because of their complex nature, analytical procedures for biological and biotechnological products in some cases may be approached differently than in this document.

Well-characterized reference materials, with documented purity, should be used throughout the validation study. The degree of purity necessary depends on the intended use.

In accordance with the parent document, and for the sake of clarity, this document considers the various validation characteristics in distinct sections. The arrangement of these sections reflects the process by which an analytical procedure may be developed and evaluated.

In practice, it is usually possible to design the experimental work such that the appropriate validation characteristics can be considered simultaneously to provide a sound, overall knowledge of the capabilities of the analytical procedure, for instance, specificity, linearity, range, accuracy, and precision.

II. SPECIFICITY

An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities, and the assay. The procedures used to demonstrate specificity will depend on the intended objective of the analytical procedure.

It is not always possible to demonstrate that an analytical procedure is specific for a particular analyte (complete discrimination). In this case, a combination of two or more analytical procedures is recommended to achieve the necessary level of discrimination.

A. Identification

Suitable identification tests should be able to discriminate between compounds of closely related structures, which are likely to be present. The discrimination of a procedure may be confirmed by obtaining positive results (perhaps by comparison with a known reference material) from samples containing the analyte, coupled with negative results from samples, which do not contain the analyte. In addition, the identification test may be applied to materials structurally similar to or closely related to the analyte to confirm that a positive response is not obtained. The choice of such potentially interfering materials should be based on sound scientific judgment with a consideration of the interferences that could occur.

B. Assay and Impurity Test(s)

For chromatographic procedures, representative chromatograms should be used to demonstrate specificity and individual components should be appropriately labeled. Similar considerations should be given to other separation techniques.

Critical separations in chromatography should be investigated at an appropriate level. For critical separations, specificity can be demonstrated by the resolution of the two components, which elute closest to each other.

In cases where a nonspecific assay is used, other supporting analytical procedures should be used to demonstrate overall specificity. For example, where a titration is adopted to assay the drug substance for release, the combination of the assay and a suitable test for impurities can be used.

The approach is similar for both assay and impurity tests.

1. Impurities Are Available

For the assay, this should involve demonstration of the discrimination of the analyte in the presence of impurities and/or excipients; practically, this can be done by spiking pure substances (drug substance or drug product) with appropriate levels of impurities and/or excipients and demonstrating that the assay result is unaffected by the presence of these materials (by comparison with the assay result obtained on unspiked samples).

For the impurity test, the discrimination may be established by spiking drug substance or drug product with appropriate levels of impurities and demonstrating the separation of these impurities individually and/or from other components in the sample matrix.

2. Impurities Are Not Available

If impurity or degradation product standards are unavailable, specificity may be demonstrated by comparing the test results of samples containing impurities or degradation products to a second well-characterized procedure, for example, pharmacopoeial method or other validated analytical procedure (independent procedure). As appropriate, this should include samples stored under relevant stress conditions: light, heat, humidity, acid/base hydrolysis, and oxidation.

- For the assay, the two results should be compared
- For the impurity tests, the impurity profiles should be compared

Peak purity tests may be useful to show that the analyte chromatographic peak is not attributable to more than one component (e.g., diode array, mass spectrometry).

III. LINEARITY

A linear relationship should be evaluated across the range (see section 3) of the analytical procedure. It may be demonstrated directly on the drug substance (by dilution of a standard stock solution) and/or separate weighings of synthetic mixtures of the drug product components, using the proposed procedure. The latter aspect can be studied during investigation of the range.

Linearity should be evaluated by visual inspection of a plot of signals as a function of analyte concentration or content. If there is a linear relationship, test results should be evaluated by appropriate statistical methods, for example, by calculation of a regression line by the method of least squares. In some cases, to obtain linearity between assays and sample concentrations, the test data may need to be subjected to a mathematical transformation prior to the regression analysis. Data from the regression line itself may be helpful to provide mathematical estimates of the degree of linearity.

The correlation coefficient, y-intercept, slope of the regression line, and residual sum of squares should be submitted. A plot of the data should be included. In addition, an analysis of the deviation of the actual data points from the regression line may also be helpful for evaluating linearity.

Some analytical procedures, such as immunoassays, do not demonstrate linearity after any transformation. In this case, the analytical response should be described by an appropriate function of the concentration (amount) of an analyte in a sample.

For the establishment of linearity, a minimum of five concentrations is recommended. Other approaches should be justified.

IV. RANGE

The specified range is normally derived from linearity studies and depends on the intended application of the procedure. It is established by confirming that the analytical procedure provides an acceptable degree of linearity, accuracy, and precision when applied to samples containing amounts of analyte within or at the extremes of the specified range of the analytical procedure.

The following minimum specified ranges should be considered:

- For the assay of a drug substance or a finished (drug) product: normally from 80% to 120% of the test concentration;
- For content uniformity, covering a minimum of 70% to 130% of the test concentration, unless a wider more appropriate range, based on the nature of the dosage form (e.g., metered dose inhalers), is justified;
- For dissolution testing: +/−20% over the specified range;

For example, if the specifications for a controlled released product cover a region from 20%, after 1 hour, up to 90%, after 24 hours, the validated range would be 0% to 110% of the label claim.

- For the determination of an impurity: from the reporting level of an impurity to 120% of the specification.
- For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the detection/quantitation limit should be commensurate with the level at which the impurities must be controlled.

  Note: For validation of impurity test procedures carried out during development, it may be necessary to consider the range around a suggested (probable) limit.
- If assay and purity are performed together as one test and only a 100% standard is used, linearity should cover the range from the reporting level of the impurities[1] to 120% of the assay specification.

V. ACCURACY

Accuracy should be established across the specified range of the analytical procedure.

A. Assay

1. Drug Substance

Several methods of determining accuracy are available:

(a) Application of an analytical procedure to an analyte of known purity (e.g. reference material)
(b) Comparison of the results of the proposed analytical procedure with those of a second well-characterized procedure, the accuracy of which is stated and/or defined (independent procedure, see Assay and Impurity Test(s))
(c) Accuracy may be inferred once precision, linearity and specificity have been established

2. Drug Product

Several methods for determining accuracy are available:

(a) Application of the analytical procedure to synthetic mixtures of the drug product components to which known quantities of the drug substance to be analysed have been added
(b) In cases where it is impossible to obtain samples of all drug product components, it may be acceptable either to add known quantities of the analyte to the drug product or to compare the results obtained from a second, well-characterized procedure, the accuracy of which is stated and/or defined [independent procedure, see Assay and Impurity Test(s)]
(c) Accuracy may be inferred once precision, linearity, and specificity have been established

B. Impurities (Quantitation)

Accuracy should be assessed on samples (drug substance/drug product) spiked with known amounts of impurities.

In cases where it is impossible to obtain samples of certain impurities and/or degradation products, it is considered acceptable to compare results obtained by an independent procedure [see Assay and Impurity Test(s)]. The response factor of the drug substance can be used.

It should be clear how the individual or total impurities are to be determined for example, weight/weight or area percent, in all cases with respect to the major analyte.

C. Recommended Data

Accuracy should be assessed using a minimum of nine determinations over a minimum of three concentration levels covering the specified range (e.g., 3 concentrations/3 replicates each of the total analytical procedure).

Accuracy should be reported as percent recovery by the assay of known added amount of analyte in the sample or as the difference between the mean and the accepted true value together with the confidence intervals.

VI. PRECISION

Validation of tests for assay and for quantitative determination of impurities includes an investigation of precision.

A. Repeatability

Repeatability should be assessed using:

(a) a minimum of nine determinations covering the specified range for the procedure (e.g., three concentrations/3 replicates each); or
(b) a minimum of six determinations at 100% of the test concentration.

B. Intermediate Precision

The extent to which intermediate precision should be established depends on the circumstances under which the procedure is intended to be used. The applicant should establish the effects of random events on the precision of the analytical procedure. Typical variations to be studied include days, analysts, equipment, etc. It is not considered necessary to study these effects individually. The use of an experimental design (matrix) is encouraged.

C. Reproducibility

Reproducibility is assessed by means of an interlaboratory trial. Reproducibility should be considered in case of the standardization of an analytical procedure, for instance, for inclusion of procedures in pharmacopoeias. These data are not part of the marketing authorization dossier.

D. Recommended Data

The standard deviation, relative standard deviation (coefficient of variation), and confidence interval should be reported for each type of precision investigated.

VII. DETECTION LIMIT

Several approaches for determining the detection limit are possible, depending on whether the procedure is a noninstrumental or instrumental. Approaches other than those listed below may be acceptable.

A. Based on Visual Evaluation

Visual evaluation may be used for noninstrumental methods but may also be used with instrumental methods.

The detection limit is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected.

B. Based on Signal-to-Noise

This approach can only be applied to analytical procedures, which exhibit baseline noise.

Determination of the signal-to-noise ratio is performed by comparing measured signals from samples with known low concentrations of analyte with those of blank samples and establishing the minimum concentration at which the analyte can be reliably detected. A signal-to-noise ratio between 3 or 2:1 is generally considered acceptable for estimating the detection limit.

C. Based on the Standard Deviation of the Response and the Slope

The detection limit (DL) may be expressed as:

$$DL = \frac{3.3\sigma}{S}$$

where,

σ = the standard deviation of the response
S = the slope of the calibration curve

The slope S may be estimated from the calibration curve of the analyte. The estimate of σ may be carried out in a variety of ways, for example:

1. Based on the Standard Deviation of the Blank

Measurement of the magnitude of analytical background response is performed by analyzing an appropriate number of blank samples and calculating the standard deviation of these responses.

2. Based on the Calibration Curve

A specific calibration curve should be studied using samples containing an analyte in the range of DL. The residual standard deviation of a regression line or the standard deviation of y-intercepts of regression lines may be used as the standard deviation.

D. Recommended Data

The detection limit and the method used for determining the detection limit should be presented. If DL is determined based on visual evaluation or based on signal to noise ratio, the presentation of the relevant chromatograms is considered acceptable for justification.

In cases where an estimated value for the detection limit is obtained by calculation or extrapolation, this estimate may subsequently be validated by the independent analysis of a suitable number of samples known to be near or prepared at the detection limit.

VIII. QUANTITATION LIMIT

Several approaches for determining the quantitation limit are possible, depending on whether the procedure is a noninstrumental or instrumental. Approaches other than those listed below may be acceptable.

A. Based on Visual Evaluation

Visual evaluation may be used for noninstrumental methods but may also be used with instrumental methods.

The quantitation limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be quantified with acceptable accuracy and precision.

B. Based on Signal-to-Noise Approach

This approach can only be applied to analytical procedures that exhibit baseline noise.

Determination of the signal-to-noise ratio is performed by comparing measured signals from samples with known low concentrations of analyte with those of blank samples and by establishing the minimum concentration at which the analyte can be reliably quantified. A typical signal-to-noise ratio is 10:1.

C. Based on the Standard Deviation of the Response and the Slope

The quantitation limit (*QL*) may be expressed as:

$$QL = \frac{10\sigma}{S}$$

where,

σ = the standard deviation of the response
S = the slope of the calibration curve

The slope S may be estimated from the calibration curve of the analyte. The estimate of σ may be carried out in a variety of ways for example:

1. Based on Standard Deviation of the Blank

Measurement of the magnitude of analytical background response is performed by analyzing an appropriate number of blank samples and calculating the standard deviation of these responses.

2. Based on the Calibration Curve

A specific calibration curve should be studied using samples, containing an analyte in the range of *QL*. The residual standard deviation of a regression line or the standard deviation of y-intercepts of regression lines may be used as the standard deviation.

D. Recommended Data

The quantitation limit and the method used for determining the quantitation limit should be presented.

The limit should be subsequently validated by the analysis of a suitable number of samples known to be near or prepared at the quantitation limit.

IX. ROBUSTNESS

The evaluation of robustness should be considered during the development phase and depends on the type of procedure under study. It should show the reliability of an analysis with respect to deliberate variations in method parameters.

If measurements are susceptible to variations in analytical conditions, the analytical conditions should be suitably controlled or a precautionary statement should be included in the procedure. One consequence of the evaluation of robustness should be that a series of system suitability parameters (e.g., resolution test) is established to ensure that the validity of the analytical procedure is maintained whenever used.

Examples of typical variations are:

- Stability of analytical solutions
- Extraction time

In the case of liquid chromatography, examples of typical variations are:

- Influence of variations of pH in a mobile phase
- Influence of variations in mobile phase composition
- Different columns (different lots and/or suppliers)
- Temperature
- Flow rate

In the case of gas chromatography, examples of typical variations are:

- Different columns (different lots and/or suppliers)
- Temperature
- Flow rate

X. SYSTEM SUITABILITY TESTING

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters to be established for a particular procedure depend on the type of procedure being validated. See Pharmacopoeias for additional information.

10

Bioequivalence Testing of Topical Drugs

For topical dermatologic drug products, PK measurements in blood, plasma, and/or urine are usually not feasible to document BE because topical dermatologic products generally do not produce measurable concentrations in extracutaneous biological fluids. The BE determination for these products is thus often based on PD or clinical studies. An additional approach is to document BE through reliance on measurement of the active moiety(ies) in the stratum corneum. This approach is termed dermatopharmacokinetics (DPK). Although measurement of the active moiety(ies) in blood or urine is not regarded as an acceptable measurement of BE for dermatologic drug products, it may be used to measure systemic exposure.

I. INACTIVE INGREDIENTS

During the investigational new drug (IND) process for an NDA, the safety of inactive ingredients in a topical drug product should be documented by specific studies or may be based on a prior history of successful use in the same amount administered via the same route of administration in an approved product. The requisite safety studies to establish the safety of a new excipient during the investigational new drug (IND) process should be discussed with appropriate review staff at the FDA. For an ANDA, the safety of inactive ingredients in an ANDA can be based on a prior history of successful use in an NDA or ANDA. If the inactive ingredients in an ANDA are not the same as the reference listed drug, the applicant should demonstrate to the agency that the changes(s) do not affect the safety and/or efficacy of the proposed drug product. In some instances, a comparative bioavailability study will satisfy this recommendation. If preclinical or clinical studies are needed to demonstrate the safety of inactive ingredients(s) in the generic drug product, the ANDA may not be approved. In this circumstance, the applicant may wish to resubmit their application as an NDA under the provisions of 505(b)(1) or (b)(2) of the act.

II. WAIVER OF BIOEQUIVALENCE

In accordance with 21 CFR 314.94(a)(9)(v), generally, the test (generic) product intended for topical use must contain the same inactive ingredients as the RLD. For all topical drug products intended for marketing under an abbreviated application, documentation of in vivo bioequivalence is required under 21 CFR 320.21(b). For a topical solution drug product, in vivo bioequivalence may be waived if the inactive ingredients in the product are qualitatively identical and quantitatively essentially the same compared to the listed drug. In this setting, quantitatively *essentially the same* means that the amount/concentration of the inactive ingredient(s) in the test product cannot differ by more than ±5% of the amount/concentration of the listed drug. Where a test solution differs qualitatively or quantitatively from the listed drug, in vivo BE may be waived, provided the sponsor submits evidence that the difference does not affect safety and/or efficacy of the product at the time a waiver is requested.

III. BIOEQUIVALENCE APPROACHES

Comparative clinical trials are generally difficult to perform, highly variable, and insensitive. For these reasons, other approaches, such as dermatopharmacokinetic (DPK) or pharmacodynamic (PD) may be used for BE determination.

A. Dermatopharmacokinetic Approaches

The DPK approach is comparable to a blood, plasma, urine PK approach applied to the stratum corneum. DPK encompasses drug concentration measurements with respect to time and provides information on drug uptake, apparent steady-state levels, and drug elimination from the stratum corneum based on a stratum corneum concentration–time curve.

When applied to diseased skin, topical drug products induce one or more therapeutic responses, where onset, duration, and magnitude depend on the relative efficiency of three sequential processes, namely, (1) the release of the drug from the dosage form, (2) penetration of the drug through the skin barrier, and (3) generation of the desired pharmacological effect. Because topical products deliver the drug directly to or near the intended site of action, measurement of the drug uptake into and drug elimination from the stratum corneum can provide a DPK means of assessing the BE of two topical drug products. Presumably, two formulations that produce comparable stratum corneum concentration–time curves may be BE, just as two oral formulations are judged BE if they produce comparable plasma concentration–time curves. Even though the target site for topical dermatologic drug products in some instances may not be the stratum corneum, the topical drug must still pass through the stratum corneum, except in instances of damage, to reach deeper sites of action. In certain instances, the stratum corneum itself is the site of action. For example, in fungal infections of the skin, fungi reside in the stratum corneum and therefore DPK measurement of an antifungal drug in the stratum corneum represents direct measurement of drug concentration at the site of action. In instances where the stratum corneum is disrupted or damaged, in vitro drug release may provide additional information toward the BE assessment. In this context, the drug release rate may reflect drug delivery directly to the dermal skin site without passage through the stratum corneum. For antiacne drug products, target sites are the hair follicles and sebaceous glands. In this setting, the drug diffuses through the stratum corneum, epidermis, and dermis to reach the site of action. The drug may also follow follicular pathways to reach the sites of action. The extent of follicular penetration depends on the particle size of the active ingredient if it is in the form of a suspension. Under these circumstances, the DPK

approach is still expected to be applicable because studies indicate a positive correlation between the stratum corneum and follicular concentrations. Although the exact mechanism of action for some dermatologic drugs is unclear, the DPK approach may still be useful as a measure of BE because it has been demonstrated that the stratum corneum functions as a reservoir, and stratum corneum concentration is a predictor of the amount of drug absorbed.

For reasons thus cited, DPK principles should be generally applicable to all topical dermatologic drug products including antifungal, antiviral, antiacne, antibiotic, corticosteroid, and vaginally applied drug products. The DPK approach can thus be the primary means to document BA/BE. Additional information, such as comparative in vitro release data and particle size distribution of the active ingredient between the RLD and the test product, may provide additional supportive information. Generally, BE determinations using DPK studies are performed in healthy subjects because skin where disease is present demonstrates high variability and changes over time. Use of healthy subjects is consistent with similar use in BE studies for oral drug products.

A DPK approach is not generally applicable when (1) a single application of the dermatologic preparation damages the stratum corneum, (2) for otic preparations except when the product is intended for otic inflammation of the skin, and (3) for ophthalmic preparations because the cornea is structurally different from the stratum corneum. The following three sections of the guidance provide general procedures for conducting a BA/BE study using DPK methodology.

1. Performance and Validation of the Skin Stripping Technique

DPK studies should include validation of both analytical methods and the technique of skin stripping. Since the DPK approach involves two components of validation (sampling and analytical method), overall DPK variability may be greater than with other methodologies. For analytical methods, levels of accuracy, precision, sensitivity, specificity, and reproducibility should be documented according to established procedures. Although the forearm, back, thigh, or other part of the body can be used for skin stripping studies, most studies are conducted on the forearm, for reasons of convenience. Care should be taken to avoid any damage with physical, mechanical, or chemical irritants (e.g., soaps, detergents, agents). Usual hydration and environmental conditions should be maintained. After washing prior to treatment, sufficient time, preferably 2 hours, should be allowed to normalize the skin surface. Detailed and workable standard operating procedures (SOPs) for area and amount of drug application, excess drug removal, and skin stripping methodology should be developed. The product's stability during the course of the study should be established. If the product is unstable, the rate and extent of degradation in situ over the period should be determined accurately so that a correction factor may be applied. Skin on both left and right arms of healthy subjects may be used to provide eight or more sites per arm. The size of the skin stripping area is important to allow collection of a sufficient drug in a sample to achieve adequate analytical detectability. Inter- and intra-arm variability should be assessed, and the treatment sites should be randomized appropriately. If a sponsor or applicant is using multiple investigators to conduct a single study, the reproducibility of skin stripping data between the investigators should be established. Either of the following approaches are recommended:

- A dose–response relationship between the drug concentration in the applied dosage form and the drug concentration in the stratum corneum should be established using the skin stripping method. A DPK dose–response relationship is analogous to a dose proportionality study performed with solid oral dosage forms. This type of study can be readily performed using three different strengths of the formulations. These can be marketed or specially manufactured products. Alternatively, a solution of the active drug representing three concentrations can be prepared for this purpose. Amount of drug in the stratum corneum at the end of a specified time interval, such as 3 hours, can provide a dose–response relationship.
- The skin stripping method should be capable of detecting differences of ±25% in the strength of a product. This can be determined by applying different concentrations (e.g., 75%, 100%, 125%) of a test dosage form such as a simple solution to the skin surface for a specified exposure time such as 3 hours, executing the skin stripping method, and performing the appropriate statistical tests comparing the strength applied to the measured drug concentration in the stratum corneum.

Using the reference product, the approximate minimum time required for drug to reach saturation level in the stratum corneum should be determined. This study establishes the time point at which the elimination phase of the study may be initiated.

The drug concentration–time profile may vary with the drug, the drug potency class, formulation, subject, sites of application, circadian rhythm, ambient temperature, and humidity. These factors should be considered and controlled as necessary.

Circadian rhythms may be present and may affect the measurement of skin stripping drug concentration if the drug is also an endogenous chemical (e.g., corticosteroid or retinoic acid). In such circumstances, the baseline concentration of the endogenous compound should be measured over time from sites where no drug product has been applied.

IV. SAMPLE PILOT STUDY

The reference drug product is randomly applied to eight sites on one forearm, with skin stripping performed at incremental times after application (e.g., 15, 30, 60, and 180 minutes) (Fig. 10.1). One site is used for each time point. Four additional sites at 180 minutes on the same arm should be assessed to provide a total of five replicates for the same time point. An additional site with no application of a drug product should be sampled as a control, yielding a total of nine sampling sites. The contralateral forearm may be used to assess dose–response and sensitivity relationships by applying at least three concentrations of the drug product or simple drug solution for 180 minutes in duplicates. Two additional applications of the reference drug product on the same arm should be tested for 180 minutes as well to provide additional information about inter- and intra-arm variability and reproducibility. A control site with no drug application should also be included for a total of nine sites on the contralateral arm. The pilot study should be carried out in at least six subjects. Stratum corneum samples are removed according to procedures described below and analyzed for drug concentration. Standard procedures should be followed in all elements of the study and should be carried through all subsequent studies.

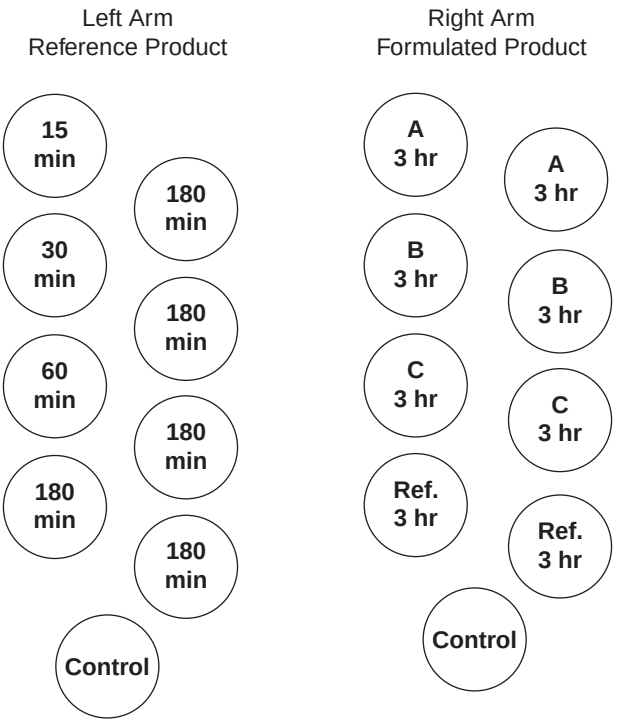


Figure 10.1 Schematic for drug application and removal sites for pilot study. Figures 10.1(A) to 10.1(C) represent three concentrations of the drug product or drug solution.

A. DPK Bioequivalence Study Protocol

1. Protocol and Subject Selection

Healthy volunteers with no history of previous skin disease or atopic dermatitis and with a healthy, homogeneous forearm (or other) skin areas sufficient to accommodate at least eight treatment and measurement sites (time points) should be recruited. The number of subjects to be entered may be obtained from power calculations using intra- and intersubject variability from the pilot study. Because skin stripping is highly sensitive to specific study site factors, care should be taken to perfecting the technique and enrolling a sufficient number of subjects. The following study design is based on a crossover study design, where the crossover occurs at the same time using both arms of a single subject. A crossover design in which subjects are studied on two different occasions may also be employed. If this design is employed, at least 28 days should be allowed to rejuvenate the harvested stratum corneum.

2. Application and Removal of Test and Reference Products

The treatment areas are marked using a template without disturbing or injuring the stratum corneum/skin. The size of the treatment area will depend on multiple factors including drug strength, analytical sensitivity, the extent of drug diffusion, and exposure time. The stratum corneum is highly sensitive to certain environmental factors. To avoid bias and to remain within the limits of experimental convenience and accuracy, the treatment sites and arms should be randomized. Uptake, steady-state, and elimination phases, as described in more detail below, may be randomized between the right and left arms in a subject. Exposure time points in each phase may be randomized among various sites on each arm. The test and reference products for a particular exposure time point may be applied on adjacent sites to minimize differences. Test and reference products should be applied concurrently on the same subjects according to a SOP that has been previously developed and validated. The premarked sites are treated with predetermined amounts of the products (e.g., 5 mg/sq cm) and covered with a nonocclusive guard. Occlusion is used only if recommended in product labeling. Removal of the drug product is performed according to SOPs at the designated time points, using multiple cotton swabs or Q-tips with care to avoid stratum corneum damage. In case of certain oily preparations such as ointments, washing the area with a mild soap may be needed before skin stripping. If washing is carried out, it should be part of an SOP.

3. Sites and Duration of Application

The BE study should include measurements of drug uptake into the stratum corneum and drug elimination from skin. Each of these elements is important to establish bioavailability and/or bioequivalence of two products, and each may be affected by the excipients present in the product. A minimum of eight sites should be employed to assess uptake/elimination from each product. The time to reach steady state in the stratum corneum should be used to determine timing of samples. For example, if the drug reaches steady state in 3 hours, 0.25, 0.5, 1, and 3 hours posttreatment may be selected to determine uptake and 4, 6, 8, and 24 hours may be used to assess elimination. A *zero* time point (control site away from test sites) on each subject should be selected to provide baseline data. If the test/reference drug products are studied on both forearms, randomly selected sites on one arm may be designated to measure drug uptake/steady state. Sites on the contralateral arm may then be designated to measure drug elimination. During drug uptake, both the excess drug removal and stratum corneum stripping times are the same so that the stratum corneum stripping immediately follows the removal of the excess drug. In the elimination phase, the excess drug is removed from the sites at the steady-state time point, and the stratum corneum is harvested at succeeding times over 24 hours to provide an estimate of an elimination phase (Fig. 10.2).

4. Collection of Sample

Skin stripping proceeds first with the removal of the first 1 to 2 layers of stratum corneum with two adhesive tapes strip/disc applications, using a commercially available product (e.g., D-Squame, Transpore). These first two tape strip(s) contain the generally unabsorbed, as opposed to penetrated or absorbed, drug and therefore should be analyzed separately from the rest of the tape strips. The remaining stratum corneum layers from each site are stripped at the designated time intervals. This is achieved by stripping the site with an additional 10 adhesive tape strips. All 10 tape strips obtained from a given time point are combined and extracted, with drug content determined using a validated analytical method. The values are generally expressed as amounts/area (e.g., ng/cm) to maintain uniformity in reported values. Data may be computed to obtain full drug concentration–time profiles, $C_{max\text{-}ss}$, $T_{max\text{-}ss}$, and AUCs for the test and reference products.

5. Procedure for Skin Stripping

The general test procedures in either the pilot study or the pivotal BA/BE study are summarized below.

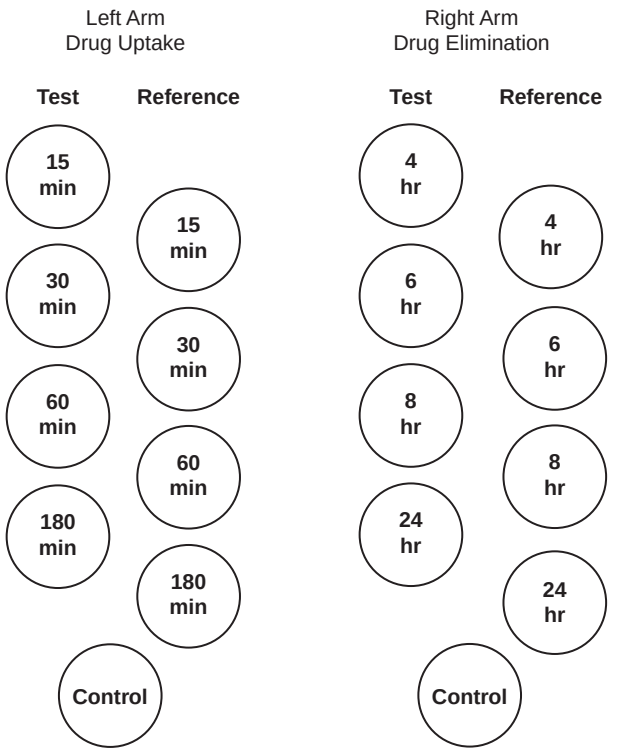


Figure 10.2 Schematic for drug uptake and drug elimination for bioequivalence study.

To assess drug uptake:

- Apply the test and/or reference drug products concurrently at multiple sites.
- After an appropriate interval, remove the excess drug from a specific site by wiping 3 times lightly with a tissue or cotton swab.
- Using information from the pilot study, determine the appropriate times of sample collection to assess drug uptake.
- Repeat the application of adhesive tape 2 times, using uniform pressure, discarding these first two tape strips.
- Continue stripping at the same site to collect ten more stratum corneum samples.
- Care should be taken to avoid contamination with other sites.
- Repeat the procedure for each site at other designated time points.
- Extract the drug from the combined ten skin strippings and determine the concentration using a validated analytical method.
- Express the results as amount of drug per square cm treatment area of the adhesive tape.

To assess drug elimination:

- Apply the test and reference drug product concurrently at multiple sites chosen based on the results of the pilot study. Allow sufficient exposure period to reach apparent steady-state level.
- Remove any excess drug from the skin surface as described previously, including the first two skin strippings.
- Collect skin stripping samples using ten successive tape strips at time intervals based on the pilot study and analyze them for drug content.

B. Metrics and Statistical Analyses

A plot of stratum corneum drug concentration versus a time profile should be constructed to yield stratum corneum metrics of C_{max}, T_{max}, and AUC. The two one-sided hypotheses at the $p = 0.05$ level of significance should be tested for AUC and C_{max} by constructing the 90% confidence interval (CI) for the ratio between the test and reference averages. Individual subject parameters, as well as summary statistics (average, standard deviation, coefficient of variation, 90% CI) should be reported. For the test product to be BE, the 90% CI for the ratio of means (population geometric means based on log-transformed data) of test and reference treatments should fall within 80% to 125% for AUC and 70% to 143% for C_{max}. Alternate approaches in the calculation of metrics and statistics are acceptable with justification.

V. PHARMACODYNAMIC APPROACHES

Sometimes topically applied dermatologic drug products produce direct/indirect PD responses that may be useful to measure BE. For example, topically applied corticosteroids produce a vasoconstrictor effect that results in skin blanching. This PD response has been correlated with corticosteroid potency and efficacy. Based on this PD response, FDA issued a guidance entitled *Topical Dermatological Corticosteroids: In Vivo Bioequivalence* (June, 1995). The guidance recommends that a pilot study be conducted to assess the dose-response characteristics of the corticosteroid followed by a formal study to assess/BE. Topically applied retinoid produces transepidermal water loss that may be used as a PD measure to assess BE.

A. In Vitro Release Approaches (Lower Strength)

Usually, only one strength of a topical dermatologic drug product is available although sometimes two or, rarely, three strengths may be marketed. When multiple strengths are available, a standard practice is to create lower strengths by altering the percentage of active ingredients without otherwise changing the formulation or its manufacturing process. Topical dermatologic drug products usually contain relatively small amounts of the active drug substance, usually $\leq$5% and frequently $\leq$1%. In this setting, changes in the active ingredient may have little impact on the overall formulation.

Safety and efficacy should be documented for all strengths of topical drug products in the NDA submissions. Using some of the approaches suggested in this guidance, BA may also be documented for the highest strength. For lower strengths, where documentation of BA is considered important, this guidance suggests that in vitro release may be performed. Similarly, for an ANDA, when bioequivalence has been documented for the highest strength, in vitro release may also be used to waive in vivo studies to assess bioequivalence between these lower strengths and the corresponding strengths of the RLD. If this approach suggests bioinequivalence, further studies may be important.

To support the BE of lower strengths in an ANDA, the following conditions are important.

- Formulations of the two strengths should differ only in the concentration of the active ingredient and equivalent amount of the diluent.
- No differences should exist in manufacturing process and equipment between the two strengths.

- For an ANDA, the RLD should be marketed at both higher and lower strengths.
- For an ANDA, the higher strength of the test product should be BE to the higher strength of RLD.

In vitro drug release rate studies should be measured under the same test conditions for all strengths of both the test and RLD products. The in vitro release rate should be compared between (1) the RLD at both the higher (RHS) and lower strengths (RLS), and (2) the test (generic) products at both higher (THS) and lower strengths (TLS). Using the in vitro release rate, the following ratios and comparisons should be made:

Release rate of RHS/Release rate of RLS $\approx$ Release rate of THS/Release rate of TLS

The ratio of the release rates of the two strengths of the test products should be about the same as the ratio of the release rate of reference products, that is:

(Release rate of RHS $\times$ Release rate of TLS)/Release rate of RLS $\times$Release rate of THS) ≈ 1

Using appropriate statistical methods, the standard BE interval (80–120) for a lower strength comparison of test and reference products should be used.

After approval, a sponsor may wish to develop an intermediate strength of a topical dermatologic drug product when two strengths have been approved and are in the marketplace. In this case, the in vitro release rate of the intermediate strength should fall between the in vitro release rates of the upper and lower strengths. Modifications of the approach described in this section of the guidance can thus be applied, providing all strengths differ only in the amount of active ingredient and do not differ in manufacturing processes and equipment.

B. In Vitro Release: Extension of the Methodology

Drug release from semisolid formulations is a property of the dosage form. Current scientific consensus is that in vitro release is an acceptable regulatory measure to signal inequivalence in the presence of certain formulation and manufacturing changes. With suitable validation, in vitro release may be used to assess batch-to-batch quality, replacing a series of tests that in the aggregate assess product quality and drug release (e.g., particle size determination, viscosity, and rheology). Because topical dosage forms are complex dosage forms, manufacturers should optimize the in vitro release test procedure for their product in a manner analogous to the use of in vitro dissolution to assess the quality of extended-release products from batch to batch. In addition, in vitro release might be used in a sponsor-specific comparability protocol to allow more extensive postapproval changes in formulation and/or manufacturing, provided that BE between two products representing the extremes of the formulation and manufacturing changes have been shown to be bioequivalent, using approaches recommended earlier in this document.

C. Systemic Exposure Studies

To ensure safety, and, when appropriate, comparable safety, information on systemic exposure is important for certain types of topical dermatologic drug products, such as retinoid and high-potency corticosteroids. The degree of systemic exposure for the majority of topical dermatologic drug products may be determined via standard in vivo blood, plasma, or urine PK techniques. For corticosteroids, an in vivo assessment of the HPA axis suppression test may provide the information. For other topical dermatologic drug products, such tests may not be needed.

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Good Manufacturing Requirements for Active Pharmaceutical Ingredients

I. INTRODUCTION

The U.S. FDA has recently updated a program in its Compliance Program Guidance Manual chapter on Drug Quality Assurance, entitled "Active Pharmaceutical Ingredient (API) Process Inspection" (Compliance Program). The program has been updated to address API compliance with the adulteration provisions of the Federal Food, Drug, and Cosmetic Act (the Act) in light of FDAs efforts as part of its "Pharmaceutical CGMPs for the 21st Century" initiative. Among other things, the revised program elaborates on the Agency's current risk-based, systems approach to inspections as it applies to the manufacture of APIs and incorporates an ICH-developed guidance document, ICH Q7A, to clarify appropriate good manufacturing practice requirements for APIs.

Active pharmaceutical ingredients, colloquially referred to as "APIs," are considered adulterated "if it is a drug and the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of . . . safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess." The Act does not distinguish between APIs and drug products regarding what constitutes adulteration or current good manufacturing practices (CGMPs). However, FDA has delineated the two. FDA has promulgated regulations establishing the CGMPs for finished pharmaceuticals, found in 21 CFR parts 210 and 211, but has not developed similar regulations specifically for APIs or drug components.

FDA has consistently maintained that the concepts provided for finished pharmaceutical CGMPs in parts 210 and 211 are valid and applicable "in concept" when considering API manufacturing. Among the several concepts described in the finished pharmaceutical CGMPs are the ideas of building quality into the drug by using suitable equipment and employing appropriate personnel, establishing and implementing adequate written procedures and controls to assure that the processes and controls used in manufacturing are valid, and ensuring drug stability throughout the product's intended use period.

Although the concepts are universal, as FDA contends, the processes used in the manufacture of APIs and drug products are not. In fact, the process characteristics of an API and a drug product are fundamentally different. API processing includes chemical and biological processing, including synthesis, fermentation, extraction, and purification, while drug product processing includes physical processing, such as granulating, dissolving, mixing, and compressing. Because of this difference, API and drug product processing employ distinct facilities, equipment, and processes. This process distinction results in differences in process water quality, in process controls, process validation, reprocessing and rework, and recovery of materials and solvents. To help illuminate what constitutes CGMPs for APIs, FDA has adopted as part of the Compliance Program an internationally harmonized guidance, "ICH Q7A, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients," which was developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and which specifically addresses the distinctive attributes of API processes.

As FDA reminds in the Compliance Program, the guidance represents its current thinking on CGMPs for APIs. Moreover, the Compliance Program adopts the ICH Q7A definition of "active pharmaceutical ingredient," which is defined under the guidance as "any substance or mixture of substances intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient in the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body." The adoption and incorporation of ICH Q7A into the Compliance Program reaffirms FDAs abandonment of its March 1998 Draft Guidance to Industry on "Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients," even though the document has not been officially withdrawn. Thus, ICH Q7A is essential to the Compliance Program; not only does it establish the definition FDA applies to determine what constitutes an API, but it also serves as the guidelines to FDA for inspecting the processes of API manufacturers. Nevertheless, even given ICH Q7As importance to the Compliance Program, FDA openly acknowledges there are approaches not considered in ICH Q7A that may meet the CGMP requirements for API manufacture and that such approaches may be used if they satisfy the underlying statutory requirement. This position reflects FDAs current "science-based" policies.

II. FDAs RISK-BASED, SYSTEMS APPROACH TO API INSPECTIONS

FDA maintains the goal of conducting inspections of API firms once every 2 years. In addition, the Center for Drug Evaluation and Research supplements this biennial target by providing additional API firms for inspection pursuant to Agency performance goals. FDA applies a risk-based strategy in inspecting these API manufacturers. This means that the frequency and depth of coverage of inspections is expected to reflect the relative risks associated with a firm's operations, including elements such as the firm's compliance history, the types of technology employed by the firm, and the intended use of the finished API. The risk-based approach allows the agency to adjust the regulatory scrutiny in a given circumstance to a level proportionate to the public health risks involved, to apply a uniform approach to the regulatory inspection process, and to place resources into the most useful and needed inspections.

The Compliance Program defines FDAs systems-based approach for the conduct of API inspections, which has been customized to evaluate API processes rather than drug product processes. Inspections of API facilities include an audit of two or more "systems," which are described generally by FDA as:

Quality System: The Quality System assures overall compliance with CGMPs and a company's internal procedures and specification.

Facilities and Equipment System: The Facilities and Equipment System comprises the physical environment and resources used to produce APIs.

Materials System: The Materials System includes the mechanisms by which starting materials, intermediates, and containers are controlled, including validation of computerized control processes, storage, and distribution controls.

Production System: The Production System is the scheme for controlling the manufacture of APIs; this includes in-process sampling/testing and process validation.

Packaging and Labeling System: The Packaging and Labeling System consists of elements that control the packaging and labeling of intermediates and APIs.

Laboratory Control System: The Laboratory Control System is the system used to direct laboratory procedures, testing, analytical methods development, and methods validation or verification, as well as the stability program.

These six areas of measures and activities form the basis of FDAs general regulatory inspection scheme.

As noted, every inspection of an API facility conducted by FDA includes a review of the Quality System. FDA will also apply its risk-based approach and select one or more additional systems for review. By reviewing at least two of the six systems, FDA believes it can adequately assess the overall "health" of the manufacturing practices utilized by the firm and forms an opinion of overall CGMP compliance based solely on the systems reviewed. FDA considers the inspection of the Quality System and the other selected systems to be applicable to each API product using the system and encourages inspectors to select a sufficient number and type of APIs to adequately review the system's coverage. The selected APIs are intended and expected to be representative of the firm's overall CGMP capabilities.

The Quality System

During each inspection, FDA will scrutinize an API manufacturer's Quality System, an assessment FDA views as having two phases. First, the inspector will evaluate whether the Quality Unit has fulfilled its responsibility to review and approve all procedures related to production, quality assurance, and quality controls and whether the procedures are adequate to fulfill their stated purpose, including associated record-keeping systems. Second, the inspector will assess the data collected pursuant to these specified procedures to identify quality problems. The Quality System evaluation may trigger a review of other major systems that were not otherwise slated for inspection.

Under the Compliance Program, an inspector is instructed to review and assess specified written and approved procedures and corresponding documentation resulting from implementation of the specified procedures that characterize an API manufacturer's Quality System. These include procedures and data regarding:

- the adequacy of staffing, as well as the training and qualification of employees in quality control functions;
- the conduct of periodic quality reviews and complaint reviews;
- any discrepancy and failure investigations related to manufacturing and testing;
- batches manufactured since last inspection (to appraise any rejections or conversions);
- change control;
- returns and salvages;
- rejects;
- reprocessing/reworking events;
- recalls;
- the system for raw material release;
- stability failures; and
- the status of validation activities.

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FDA Active Pharmaceutical Ingredient Manufacturing Facility Inspection

PART I—BACKGROUND

General

APIs are subject to the adulteration provisions of section 501(a)(2)(B) of the act, which requires all drugs to be manufactured in conformance with cGMP. No distinction is made between an API and a finished pharmaceutical in the act and the failure of either to comply with cGMP constitutes a violation of the act. FDA has not promulgated cGMP regulations specifically for APIs or drug components (as we have for finished pharmaceuticals). Thus, the use of "cGMP" in this document refers to the requirements of the act rather than the requirements of 21CFR Parts 210 and 211 regulations for finished pharmaceuticals.

FDA has long recognized that the cGMP requirements in the good manufacturing practice regulations for finished pharmaceuticals (21 CFR Parts 210 and 211) are valid and applicable in concept to active pharmaceutical ingredient (API) manufacturing. These concepts include, among others, building quality into the drug by using suitable equipment and employing appropriately qualified and trained personnel, establishing adequate written procedures and controls designed to assure manufacturing processes and controls are valid, establishing a system of in-process material and final drug tests, and ensuring stability of drugs for their intended period of use. In 2001, FDA adopted an internationally harmonized guidance to industry on API cGMPs in conjunction with regulatory partners in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This guidance is ICH Q7A, *Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*. ICH Q7A represents the FDA's current thinking on cGMPs for APIs. Thus, API and related manufacturing and testing facilities that follow this guidance generally will be considered to comply with the statutory cGMP requirement. However, alternate approaches may be used if such approaches satisfy the requirements of section 501(a)(2)(B) of the act as long as the approach ensure that the API meets its purported or represented purity, identity, and quality characteristics.

The term "active pharmaceutical ingredient" (API) is used in this program consistent with the meaning of this term as defined in ICH Q7A. An active pharmaceutical ingredient is defined in ICH Q7A as "any substance or mixture of substances intended to be used in the manufacture of a drug product and that, when used in the production of a drug, becomes an active ingredient in the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease or to affect the structure and function of the body." Currently, other terms are also used by FDA and industry to mean an API. "Drug substance" and "bulk pharmaceutical chemical" (BPC) are the terms commonly used to mean API and, for BPC, inactive ingredients. The use of these terms to describe active ingredients may be considered equivalent to the term used here, API.

FDA expects API manufacturers to apply cGMPs to the API process beginning with the use of starting materials, and to validate critical process steps that impact the quality and purity of the final API. Controls over material quality are expected to increase as the process approaches the final API. The level of control needed is highly dependent on the manufacturing process and increases throughout the process as it proceeds from early intermediate steps to final isolation and purification steps. The appropriate level of control depends on the risk or criticality associated with each specific process step.

ICH Q7A contains general guidance to industry on the extent and application of cGMP for manufacturing APIs under an appropriate system for managing quality. It is also intended to help ensure that APIs meet the quality and purity characteristics that they purport or are represented to possess. ICH Q7A is to be used as a guideline for inspecting API manufacturers and related facilities. If an investigator believes that a particular practice conforming to this guidance is believed to be deficient, the investigator or district should consult with CDER DMPQ before making an observation that is in conflict with ICH Q7A. A firm may also use alternate approaches to those described in ICH Q7A.

API manufacturers must register and APIs in commercial distribution must be listed under section 510(g) of the act unless exempted under 21 CFR 207.10. Foreign drug manufacturers are also required to register and list all drugs imported or offered for import into the United States. Refer to 21 CFR 207.40 for additional information on establishment registration and drug listing requirements for foreign drug facilities.

The inspection guidance in this program is structured for the efficient use of resources planned for routine surveillance coverage of API manufacturing facilities, recognizing that in-depth coverage of all systems and all processes is not feasible for all firms on a biennial basis. It also provides for follow-up compliance coverage as needed.

Scope of APIs Covered by This Program

An API process is a related series of operations which result in the preparation of an active pharmaceutical ingredient. Major operations or steps in an API process may include multistep chemical synthesis and fermentation, purification, crystallization, drying, milling, packing, labeling, and testing.

Some drugs processed similarly to an API may in fact be bulk finished product and subject to the requirements of 21 CFR Parts 210 and 211. If the drug material will not undergo further processing or compounding after its synthesis/fermentation/extraction but is merely repackaged into market containers, it is a bulk finished product. However, investigators should use this program as guidance when covering the synthesis/fermentation processes that result in such APIs rather than the program for dosage forms (CP 7356.002).

This program does not cover all vaccines, whole cells, whole blood and plasma, blood and plasma derivatives

(plasma fractionation), and gene therapy APIs as these drugs are regulated under the jurisdiction of the Center for Biologics Evaluation and Research.

The following APIs are to be inspected using CP7256.002M, Inspections of Licensed Biological Therapeutic Drug Products:

- Biotechnology-derived APIs, including those expressed from mammalian or bacterial cell cultures
- Polypeptides

Neither this Compliance Program nor ICH Q7A will provide guidance on the sterilization and aseptic processing of sterile APIs (see Q7A section 1.3). Investigators are to use the finished product regulations (21 CFR 210 and 211) as guidance and follow CP 7356.002A, *Sterile Drug Process Inspections*, when inspecting the sterile processing of APIs labeled as sterile. Investigators are also to use FDA guidance on aseptic processing, *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*, 2004, in evaluating aseptic processing conditions for sterile APIs.

PART II—IMPLEMENTATION

Objective

The primary objective of this compliance program is to provide comprehensive cGMP inspectional coverage of the domestic and foreign API industry in all profile classes (i.e., types of API manufacturing processes) to determine whether a manufacturer is operating in a state of control. An API manufacturer is considered to be operating in a state of control when it employs conditions and practices that assure compliance with the intent of section 501(a)(2)(B) of the act. A firm in a state of control produces APIs for which there is an adequate level of assurance of quality, identity, and purity.

A firm is not in a sufficient state of control if any one system, as defined in this program, is found to be significantly noncompliant with cGMPs, such that the quality, identity, and purity of the API resulting from that system cannot be adequately assured. Documented cGMP deficiencies provide the evidence for concluding that a system is not operating in a state of control. See part V, *Regulatory/Administrative Strategy*, for a discussion of compliance actions based on inspection findings demonstrating that a system(s) is not in a state of control.

Profile classes generalize inspection coverage from a small number of specific APIs to all APIs in that class. This program establishes a systems approach to further generalize inspection coverage from a small number of profile classes to an overall evaluation of the firm. This allows for preapproval program inspections to focus on the specific issues related to a given application and improves the review process by providing timely and efficient support for application decisions.

Inspection of API manufacturers should be conducted and reported using the system definitions and organization in this compliance program. Focusing on systems, rather than just profile classes, will increase efficiency in conducting inspections because the systems are often applicable to multiple profile classes. An inspection under this program is profileable and will result in a determination of acceptability/nonacceptability for all API profile classes. Inspection coverage should be representative of all API profile classes manufactured by the firm. All other profile classes should be covered under the main program CP 7356.002, or related program circular, as appropriate.

Program Management Instructions

The Field will conduct API manufacturing inspections and maintain profiles or other monitoring systems with the goal that each API firm will receive biennial inspectional coverage. CDER will also identify firms for inspection coverage under this program to fulfill CDER and agency annual performance goals and as part of an initiative to ensure risk-based prioritization of inspection coverage.

Unless specifically directed by CDER, the District Office is responsible for determining the frequency and depth of coverage given to each API firm consistent with this compliance program's instructions. cGMP inspectional coverage under this program shall be sufficient to assess the state of compliance for each firm.

An inspection under this program is defined as audit coverage of two or more systems (the "systems" are defined below in this section and are consistent with the main program, 7356.002), with mandatory coverage of the Quality System. Inspecting at least two systems (i.e., the Quality System and one other system) will provide the basis for an overall cGMP decision.

Coverage of a system should be sufficiently detailed, with specific examples selected, so that the system inspection outcome reflects the state of control in that system for every profile class. If a particular representative system is adequate, it should be adequate for all profile classes manufactured by the firm.

If an API selected for inspection coverage is associated with a unique processing or control function in a system not chosen for coverage, you may cover the unique function for that API. In doing so, you need not give full coverage to that system. For example, if an API chosen for coverage uses high purity water alone in its manufacture, you may inspect the water purification system without having to give full inspection coverage of the Materials System.

In some circumstances, it may not be possible to generalize certain deficiencies in a system to all API profile classes. If so, the unaffected profile classes may be considered acceptable if found otherwise acceptable.

Selecting unique functions within a system will be at the discretion of the investigator. Any given inspection need not cover every system.

Complete inspection of one system may necessitate further follow-up of some aspects of another system to fully document the findings. However, this coverage does not constitute nor require complete coverage of the other system.

A general scheme of systems for auditing the manufacture of API consists of the following:

1. *Quality System* assures overall compliance with cGMPs and internal procedures and specifications.
2. *Facilities and Equipment System* includes activities which provide an appropriate physical environment and resources used in the production of APIs.
3. *Materials System* includes measures and activities to control starting materials, intermediates, and containers. It includes validation of computerized and inventory control processes, storage, and distribution controls.
4. *Production System* includes measures and activities to control the manufacture of APIs, including in-process sampling and testing, and process validation.
5. *Packaging and Labeling System* includes measures and activities that control the packaging and labeling of intermediates and APIs.
6. *Laboratory Control System* includes measures and activities related to laboratory procedures, testing, analytical

methods development and methods validation or verification, and the stability program.

Detailed inspection coverage guidance under these systems is given in Appendix A of this program.

Inspection Planning

This program is intended to provide for a risk-based inspection strategy. Inspection depth should therefore reflect appropriate risks associated with a particular firm's operations, such as the firm's compliance history, the technology employed, the labeled and purported characteristics, and the intended use in the finished product, if known, of the APIs.

When a system is inspected, the inspection of that system may be considered applicable to all API products which use it. Investigators should select an adequate number and type of APIs to accomplish coverage of the system. APIs selected for coverage should be representative of the firm's overall abilities in manufacturing within cGMPs. (A profile classification scheme is used to categorize APIs by the nature of their processing, as described below.)

Profile class codes or APIs selected for coverage are to be representative of all APIs processed at the firm being inspected. Profile class codes may also be grouped by similarity, such that coverage of one profile class is sufficient to demonstrate cGMP conditions for another profile class. For example, inspecting a CSS API could amount to surrogate coverage of CSN. Similarly, inspecting a CBI could amount to surrogate coverage of other profile classes, such as CFN, CFS, and perhaps CEX.

The public health significance of certain cGMP deviations may be lower when the API is intended for a dosage form that has no dosage limitation, such as in products like calamine lotion or some OTC-medicated shampoos. Such APIs should be given inspection coverage of reduced depth and intensity.

Profile Classes

The inspection findings will be used as the basis for updating all profile classes in the profile screen of the FACTS EIR coversheet that is used to record profile/class determinations. *Normally, an inspection under this system approach will result in all profile classes being updated.* Effective with this program circular is a list of profile class codes that are used to report the processes covered during API inspections. These are as follows:

Profile Class	Full Description
CSN	Non-sterile API by chemical synthesis
CSS	Sterile API by chemical synthesis
CFN	Non-sterile API by fermentation
CFS	Sterile API by fermentation
CEX	Plant/animal extraction API
CTL	Control testing laboratory
CTX	Testing laboratory plus manufacturer
CRU	Crude bulk not elsewhere classified (CRU of bulk intermediates, and contract micronizers)

Types of Inspections

There are two basic types of inspections: surveillance and compliance. Surveillance inspections are conducted on a routine basis to satisfy FDA's responsibilities to inspect drug manufacturing facilities. Compliance inspections are conducted in response to violative surveillance inspections and when a need arises to inspect a facility for-cause.

This program follows the approach in the main compliance program, 7356.002. There are two alternate approaches to inspect a facility to satisfy FDA inspection obligations; these are termed "Full Inspection" and "Abbreviated Inspection." These are described in part III, *Inspectional*, of this program.

PART III—INSPECTIONAL

Inspections of API manufacturers, whether foreign or domestic, should be conducted by experienced investigators with education and/or training particularly in fermentation (see also 7356.002M for additional inspection guidance) and chemical synthesis manufacturing methods. Use of chemists and/or microbiologists during API inspections is recommended, particularly for evaluating laboratory operations (e.g., analytical methods evaluation, analytical data, laboratory procedures and instrumentation), analytical review of methods used to establish impurity profiles, fermentation manufacturing processes, and complex multistep chemical synthesis processes.

Investigators conducting API inspections must understand the basic differences between the processes used for the production of APIs and those used for finished dosage forms. APIs are usually produced by chemical synthesis or by cell culture and extraction. Thus, the production of APIs typically involves significant changes of starting materials or intermediates by various chemical, physical, and biological processing steps. The ultimate objective in API processing generally is to achieve a pure compound of certain identity, whereas the ultimate objective of finished dosage form manufacturing generally is to achieve the uniform distribution of an API among many dosing units designed to deliver a precise amount of API to a specific area of the body.

Since manufacturers of APIs are often referenced in many drug applications, each inspection should cover representative APIs when covering the systems selected (e.g., if inspecting the Production System for a site making an API by fermentation and another by synthesis, the inspection should include physical inspection and audit a sampling of records for both types of processing). This strategy, together with the classification of all profile classes upon completion of the inspection, will maximize the use of agency resources and avoid repeated visits to the same manufacturing site to cover different API profile classes referenced in subsequent applications. Any inspection of an API manufacturer should be recorded as a cGMP qualifying inspection.

Inspections should cover any specific APIs referenced in the assignment and any other representative APIs not inspected in the last 2 years. For foreign API firms, investigators should cover only APIs intended to be marketed or already marketed in the United States.

APIs selected for coverage should include those that are referenced in drug applications, are therapeutically significant, are intended for use in parenteral drug products, are difficult to manufacture, or are documented as having past compliance problems. However, this does not preclude the selection of less therapeutically significant APIs to evaluate specific APIs (or profile classes) not previously given in-depth coverage at the facility.

Investigators conducting API inspections should understand the general inspection strategy set forth in this program. Recognizing that API firms vary greatly in size, diversity of operations, and quality assurance systems,

investigators should carefully plan their inspectional strategy at each firm. Further guidance on preparing an inspection strategy appears later.

Investigators should also review the firm's rationale for the point at which cGMPs begin, which is expected to vary by type of process (e.g., synthetic, fermentation, extraction, purification).

For an API inspection that is initiated by a preapproval assignment, CP 7346.832, Pre-Approval Inspections/Investigations, inspection time should be reported under the appropriate program assignment codes referenced in both compliance programs based on the actual time spent in each program.

Inspection Approaches

This program provides two surveillance inspectional options: Full Inspection Option and Abbreviated Inspection Option. Either option may satisfy the biennial inspection requirement.

Full Inspection Option

The full inspection option is a surveillance or compliance inspection which is meant to provide a broad and in-depth evaluation of the firm's conformity to cGMPs. The full inspection option is an inspection of at least four of the six systems as listed in part II and Appendix A of this program, one of which must be the Quality System.

A Full Inspection Is Appropriate

a. For an initial FDA inspection of a facility, or after a significant change in management or organizational procedures, such as might occur after a change in ownership.
b. For a firm with a history of noncompliance or a recidivist firm whose ability to comply is short-lived. To determine if the firm meets this criterion, the District should use all information at its disposal, such as current and past inspection findings, results of sample analyses, complaints, recalls, and compliance actions.
c. To evaluate if important changes have occurred in the firm's state of control by comparing current operations against the EIR for the previous Full Inspection (e.g., by conducting a Full Inspection at every fourth inspection cycle.) In addition to changes in management or ownership, the following types of changes are typical of those that warrant the full inspection option:
   i. New potential for cross-contamination arising through changes in processing or type of APIs using that equipment.
   ii. Use of new technology requiring new expertise, significant equipment changes and/or additions, or new facilities.
d. When District management or CDER specifically requests this option.
e. To follow up on a Warning Letter or other regulatory action.

Abbreviated Inspection Option

The abbreviated inspection option is a surveillance or compliance inspection which is meant to provide an efficient update evaluation of the firm's conformity to cGMPs. A satisfactory Abbreviated Inspection will provide documentation for continuing a firm in an acceptable cGMP compliance status. The abbreviated inspection option is an inspection audit of at least two systems but not more than three systems, one of which must be the Quality System. During the course of an Abbreviated Inspection, verification of Quality System activities may require limited coverage in other systems.

An Abbreviated Inspection is appropriate when the full inspection option is not warranted, including the following:

a. To maintain surveillance over a historically compliant firm's activities and to provide input to the firm on maintaining and improving the cGMP level of assurance of quality of its APIs.
b. When an intended Full Inspection finds objectionable conditions as listed in part V of this program in one or more systems (a minimum of two systems must be completed) and District management and, as necessary, CDER Office of Compliance, concurs with reducing inspection coverage in order to expedite the issuance of a Warning Letter to correct violations.

Compliance Inspections

Compliance inspections are inspections done "for-cause" and to evaluate or verify corrective actions after a regulatory action has been taken. The coverage given in compliance inspections must be related to the areas found deficient and subjected to corrective actions.

In addition, coverage must be given to other systems because a determination must be made on the overall compliance status of the firm after the corrective actions are taken. The firm is expected to address all of its operations in its corrective action plan after a previously violative inspection, not just the deficiencies noted in the FDA-483. The full inspection option should be used for a compliance inspection, especially if the abbreviated inspection option was used during the violative inspection.

Compliance inspections include "For-Cause Inspections." For-Cause Inspections are for the purpose of investigating a specific problem that has come to the attention of the agency and may not result in the coverage of systems as described in this program. The problem may be identified by a complaint, recall, or other indicator of defective API or poorly controlled process. Coverage of these problems may be assigned under other compliance programs or PACs; however, expansion of the coverage to a cGMP inspection is to be reported under this program. For-Cause Inspections may be assigned under this program as the need arises.

Selecting Systems for Coverage

A complete description of each system and the areas for coverage are in Appendix A of this program. The selection of the system(s) for coverage and the relative depth or intensity of audit coverage should take into consideration the relative significance of a particular system for the firm's specific operating conditions, history of previous coverage, and history of cGMP compliance. It is expected that a Full Inspection will not be conducted every two years at most firms. Districts should select different systems for inspection coverage as a cycle of Abbreviated Inspections is carried out to build comprehensive information on the firm's total manufacturing activities over time.

Preparing the Inspection Strategy

This guidance is in addition to that given in the *Investigations Operations Manual*.

1. Select two or more, as appropriate, systems for inspection coverage as guided by this program (see Inspection Approaches above). Appendix A contains a detailed description of the inspection coverage to be given each system when selected for inspection.
2. Select significant APIs for inspection coverage, if not specified in the assignment. Significant APIs are those which

use all the systems in the firm very broadly and/or use special manufacturing features, e.g., complex chemical synthesis, highly sensitizing material, material of an infectious nature, or a new chemical entity made under an approved drug application. Review the firm's FACTS listing, Drug Master Files (DMF), or A/NDA files.

3. If a CDER product or cGMP/regulatory reviewer (compliance officer) is assigned to participate as a member of the inspection team, the lead investigator is to brief them on the intended inspection strategy and explain their supporting role and responsibilities for the inspection. The lead investigator should consult the reviewer on any specific A/NDA Chemistry, Manufacturing and Controls issues (whether premarket or postmarket) to be covered during the inspection.
4. Review the impurity profile for each API process to be covered during the inspection and compare these to the impurity profiles submitted in the application or DMF, if filed. (Investigators and Chemists should be particularly familiar with USP <1086> Impurities in Official Articles.) If the impurity profile has not been filed to CDER, review the guidance on establishing impurity profiles in ICH Q3A and Q3C.
5. Review any compendia monographs for the APIs to be inspected to verify conformity, as appropriate.
6. Before or during the inspection, determine if the firm has made process changes by comparing current operations against the EIR for the previous inspection. Also compare the current operations with those filed in the DMF or the drug application to determine whether the firm is complying with commitments made to the agency. (See also CP 7346.832 for conducting a preapproval inspection of an API.) The following changes are typical of those that would warrant extensive coverage during the inspection:
   a. New potential for cross-contamination arising through changes in API processes or product-type lines, to include processing numerous APIs of varying toxicity in common equipment and/or facilities.
   b. Use of new technology requiring new expertise, significantly new equipment or new facilities.
   c. Changes in starting materials, intermediates, equipment, facilities, support systems, processing steps, packaging materials, or computer software, particularly those that are not referenced in the DMF or application.
7. For foreign firms, Division of Field Investigations (DFI) will assist investigators in obtaining file information from the appropriate CDER reviewing division or compliance unit. Investigators may also request background information about the site assigned for inspection directly from the U.S. Agent before the initiation of the inspection.

Special Inspection Reporting Instructions:

Investigators should describe in the EIR their inspection coverage and findings in sufficient detail for further agency evaluation of the firm's state of control and conformance to cGMPs. ICH Q7A may be used as a guideline in describing coverage and any findings and deficiencies observed. However, do not reference specific ICH Q7A sections in the FDA 483 observations or in the EIR. The FDA 483, if issued, is to be organized into sections for each of the systems covered. In addition to the *Investigations Operations Manual* format and information reporting requirements, all EIRs of API manufacturers must include

1. a list of APIs manufactured (or categories of drugs, if many) along with the general manufacturing process for each (e.g., chemical synthesis, fermentation, extraction of botanical material);
2. for foreign API manufacturers, the names, titles, complete mailing address, telephone and fax number of the firm's U.S. Agent;
3. for foreign API manufacturers, a report of all APIs imported into the United States in the last two years, their consignees, and an estimate of the frequency and quantity of shipments to these consignees;
4. a description of each of the systems selected for coverage, (i.e., areas, processes, and operations), what was covered, who was interviewed, and what manufacturing activities were taking place during the inspection;
5. an explanation of the choice of APIs selected for coverage; and
6. any significant changes to a firm's packaging, labeling, product line, or processes, particularly those changes not properly filed, submitted, or reported in a DMF or A/NDA.

Special Instructions for Foreign Drug Inspections

The DFI schedules foreign inspections, makes travel arrangements for inspection teams, and resolves logistical problems. CDER's Office of Compliance, Foreign Inspection Team (FIT), receives and reviews all foreign establishment inspection reports, receives and reviews all foreign firms' responses to an FDA 483, and handles all correspondence regarding inspection outcomes with foreign firms. CDER/FIT maintains the complete file for each foreign drug facility.

Investigators should instruct management at foreign firms to submit their original written response to an FDA 483 directly to CDER's Office of Compliance, with a copy to the investigator. The original response with appropriate documentation should be submitted to the following address:

Food and Drug Administration
Foreign Inspection Team, HFD-325
Division of Manufacturing and Product Quality
Center for Drug Evaluation and Research
11919 Rockville Pike
Rockville, Maryland 20852–2784
USA

Investigators and analysts are to submit their written comments to a foreign firm's response to their issued FDA 483 directly to CDER's FIT as soon as possible. After appropriate district office review and endorsement, all foreign establishment inspection reports will be promptly forwarded to FIT for review and final classification.

FIT will draft and coordinate the issuance of Warning Letters, Untitled Letters, and other correspondence to foreign firms. FIT will also recommend automatic detention of foreign firms/APIs, make recommendations to review units, and request follow-up inspections, as appropriate.

PART IV—ANALYTICAL

API samples collected by the investigator for the purpose of evaluating quality are to be submitted to the appropriate servicing laboratory. A list of each analyzing laboratory for API testing is maintained in Compliance Program Guidance 7356.002 and 7346.832. However, it should be noted that physical API samples are not required to support regulatory or administrative action against a violative firm or drug.

Forensic Chemistry Center (FCC) will request profile (also called "forensic" and "fingerprint") samples of both foreign and domestic source APIs directly from the manufacturer. Investigators are to collect API samples for profile analysis only upon specific request for collection from FCC. Such requests will be made through DFI. If an investigator is instructed to collect a profile sample, FCC will provide specific instructions as to method and amount of collection and shipping. FCC contact information is in part VI, *Program Contacts*.

Prior to each foreign API site inspection, DFI will provide FCC with the inspection dates, the investigator's name, firm's name, address, telephone number, fax number, FEI number, any related product and application numbers, and the name of the contact person. FCC will then directly request a sample from the firm as needed. FCC may contact the investigator to request their collection of any specific information. The inspection dates will provide FCC information so they can access FACTS to obtain the EIR coversheet.

FCC is responsible for API profile sample collection and analysis and will provide periodic reports of such analysis and assist CDER in evaluating this program's effectiveness.

PART V—REGULATORY/ADMINISTRATIVE STRATEGY

An inspection report that documents that one or more systems is out of control should be classified OAI. Districts may recommend the issuance of a Warning Letter in accordance with the RPM. Normally, the issuance of a Warning Letter or the taking of other regulatory or administrative action should result in a classification of all profile classes as unacceptable. A CDER disapproval of a recommendation for Warning Letter or other regulatory action should result in a classification of all profile classes as acceptable.

A Warning Letter with a cGMP charge [i.e., 501(a)(2)(B) adulteration] involving a domestic API manufacturer requires CDER review and concurrence before issuance. See and follow FDA *Regulatory Procedures Manual* procedures for clearing Warning Letters and Untitled Letters.

A recommendation for regulatory action for API cGMP deficiencies is to cite the statute [501(a)(2)(B) or United States Code, 21 USC 351(a)(2)(B)] and not the finished pharmaceutical regulations at 21CFR 210 and 211. A recommendation should also not cite to ICH Q7A, but may use ICH Q7A as a guideline in describing the deficiencies observed. Any regulatory action based upon cGMP noncompliance for APIs should demonstrate how the observed deviations could or did result in actual or potential defects or risk to contamination. In evaluating whether to recommend regulatory or administrative action, consider the critical attributes of the API, its therapeutic significance, and its intended use in finished drug product manufacturing.

Evidence that supports a significant deficiency or pattern of deficiencies within a system may demonstrate the failure of a system. A failure of a system puts all drugs at risk and is to be promptly corrected. The following lists the deficiencies that should result in a recommendation for regulatory action to CDER; other deficiencies may also warrant regulatory action:

1. Contamination of APIs with filth, objectionable microorganisms, toxic chemicals, or significant amounts of other types of chemicals, or a reasonable potential for such contamination because of a finding of a demonstrated route of contamination. (Facilities and Equipment System; Production System)
2. Failure to show that API batches conform to established specifications, such as NDA, USP, customer specifications, and label claims. See also Compliance Policy Guide (CPG) 7132.05. (Quality System)
3. Failure to comply with commitments in drug applications, including DMFs, which should be accurate and current with respect to all required information, such as manufacturing process, impurity profiles (if filed), and other specifications or procedures associated with the manufacture of the API. (Quality System)
4. Distribution of an API that does not conform to established specifications. (Quality System)
5. Deliberate blending of API batches to dilute or hide filth or other noxious contaminants, or blending to disguise a critical quality defect in an attempt to obtain a batch that meets its specifications. (Production System)
6. Failure to demonstrate that water, including validation of the process water purification system, and any other solvents used in the final step of the API process are chemically and microbiologically suitable for their intended use and does not adversely alter the quality of the API. (Materials System)
7. Lack of adequate validation of critical steps in the API process, particularly concerning final separation and purification of the API, or when there is evidence that an API process is not adequately controlled. Lack of adequate control may be indicated by repeated batch failures or wide variation in final yields as compared to process average over time. See also the revised CPG 7132c.08, *Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval*. (Quality System; Production System)
8. Implementation of retrospective process validation for an existing API process when the process has changed significantly, when the firm lacks impurity profile data, or when there is evidence of repeated batch failures due to process variability. (Quality System; Production System)
9. Failure to establish an impurity profile for each API process. FDA expects manufactures to establish complete impurity profiles for each API as part of the process validation effort. This includes collecting data on (1) actual and potential organic impurities that may arise during synthesis, purification, and storage of the API; (2) inorganic impurities that may derive from the API process; and (3) organic and inorganic solvents used during the manufacturing process that are known to carry over to the API. Impurity profile testing of each batch or after a specified number of batches may detect new impurities that may appear because of a deliberate or nondeliberate change in the API manufacturing process. (Laboratory Control System)
10. Failure to show that a reprocessed batch complies with all established standards, specifications, and characteristics. (Quality System; Laboratory Control System)
11. Failure to test for residues of organic/inorganic solvents used during manufacturing that may carryover to the API using analytical procedures with appropriate levels of sensitivity. (Laboratory Control System)
12. Failure to have a formal process change control system in place to evaluate changes in starting materials, facilities, support systems, equipment, processing steps, and packaging materials that may affect the quality of APIs. (All systems)
13. Failure to maintain batch and quality control records. (Quality System)

14. Incomplete stability studies to establish API stability for the intended period of use, and/or failure to conduct forced degradation studies on APIs to isolate, identify, and quantify potential degradants that may arise during storage. (Laboratory Control System)
15. Use of laboratory test methods that are inadequate or have not been validated; or, the use of an inadequately qualified or untraceable reference standard. (Laboratory Control System)
16. Packaging and labeling in such a way that introduces a significant risk of mislabeling. (Packaging and Labeling System)

PART VI—REFERENCES, ATTACHMENTS, AND PROGRAM CONTACTS

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PART VII—CENTER RESPONSIBILITIES

Center responsibilities are as described in Drug Manufacturing Inspections Compliance Program Guidance 7356.002 and Pre-Approval Inspection/Investigations Compliance Program Guidance 7346.832.

Appendix A: Description of Each System and Areas of Coverage

QUALITY SYSTEM

Assessment of the Quality System has two phases. The first phase is to evaluate whether the Quality Unit has fulfilled the responsibility to review and approve all procedures related to production, quality control, and quality assurance and assure the procedures are adequate for their intended use. This also includes the associated recordkeeping systems. The second phase is to assess the data collected to identify quality problems and may link to other major systems for inspectional coverage.

For each of the following bulleted items, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final APIs only but may also include starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. All areas under this system should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Adequacy of staffing to ensure fulfillment of quality unit duties.
- Periodic quality reviews as described in ICH Q7A section 2.5, *Product Quality Review*; inspection audit coverage should include API types that are representative of manufacturing at this site; inspection audit should also examine some batch and data records associated with each API quality review to verify that firm's review was sufficiently complete; and audit should confirm that firm has identified any trends and has corrected or mitigated sources of unacceptable variation.
- Complaint reviews (quality and medical): documented, evaluated, and investigated in a timely manner, and also these include corrective action where appropriate. Determine whether pattern of complaints and records of internal rejection or reprocessing/reworking of API batches warrant expanding the inspection.
- Discrepancy and failure investigations related to manufacturing and testing: documented, evaluated, critical deviations investigated in a timely manner and expanded to include any related APIs and material, and also these include corrective action where appropriate.
- Change Control (including "process improvements"): documented, evaluated, approved, and need for revalidation assessed.
- Returns/Salvages: assessment, investigation expanded where warranted, and final disposition.
- Rejects: investigation expanded where warranted and corrective action where appropriate.
- System to release raw materials.
- Batches manufactured since last inspection to evaluate any rejections or conversions (i.e., from drug to nondrug use) due to processing problems.
- Reprocessing and/or reworking events are properly approved and evaluated for impact on material quality.
- Recalls (including any attempt to recover distributed API not meeting its specifications or purported quality), determine cause, and corrective actions taken.
- Stability Failures: investigation expanded where warranted and disposition. Determine if stability data supports API retest or expiry dates and storage conditions.
- Validation: status of validation/revalidation activities (e.g., computer, manufacturing process, laboratory methods), such as reviews and approvals of validation protocols and reports.
- Training/qualification of employees in quality control unit functions.

ICH Q7A references for Quality System are as follows:

- Section 2, Quality Management
- Section 13, *Change Control*
- Section 14, Rejection and Reuse of Materials

- Section 15, Complaints and Recalls
- Section 16, Contract Manufacturers (including laboratories)

FACILITIES AND EQUIPMENT SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

1. Facilities
   - Cleaning and maintenance.
   - Facility layout, flow of materials and personnel for prevention of cross-contamination, including from processing of nondrug materials.
   - Dedicated areas or containment controls for highly sensitizing materials (e.g., penicillin, β-lactams, steroids, hormones, and cytotoxics).
   - Utilities such as steam, gas, compressed air, heating, ventilation, and air-conditioning should be qualified and appropriately monitored (*note*: this system includes only those utilities whose output is not intended to be incorporated into the API, such as water used in cooling-/heating-jacketed vessels).
   - Lighting, sewage and refuse disposal, washing, and toilet facilities.
   - Control system for implementing changes in the building.
   - Sanitation of the building including use of rodenticides, fungicides, insecticides, cleaning, and sanitizing agents.
   - Training and qualification of personnel.
2. Process Equipment
   - Equipment installation, operational, performance qualification where appropriate.
   - Appropriate design, adequate size, and suitably located for its intended use.
   - Equipment surfaces should not be reactive, additive, or absorptive of materials under process so as to alter their quality.
   - Equipment (e.g., reactors, storage containers) and permanently installed processing lines should be appropriately identified.
   - Substances associated with the operation of equipment (e.g., lubricants, heating fluids, or coolants) should not come into contact with starting materials, intermediates, final APIs, and containers.
   - Cleaning procedures and cleaning validation and sanitization studies should be reviewed to verify that residues, microbial, and, when appropriate, endotoxin contamination are removed to below scientifically appropriate levels.
   - Calibrations using standards traceable to certified standards, preferably NIST, USP, or counterpart, recognized national government standard-setting authority.
   - Equipment qualification, calibration, and maintenance, including computer qualification/validation and security.
   - Control system for implementing changes in the equipment.
   - Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).
   - Training and qualification of personnel.

ICH Q7A references for Facilities and Equipment System are as follows:

- Section 4, Buildings and Facilities
- Section 5, Process Equipment
- Section 6, Documentation and Records

MATERIALS SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API only but may also incorporate starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Identification of starting materials and containers.
- Storage conditions.
- Holding of all material and APIs, including reprocessed material, under quarantine until tested or examined and released.
- Representative samples are collected, tested, or examined using appropriate means and against appropriate specifications.
- A system for evaluating the suppliers of critical materials.
- Rejection of any starting material, intermediate, or container not meeting acceptance requirement.
- Appropriate retesting/reexamination of starting materials, intermediates, or containers.
- First-in/first-out use of materials and containers.
- Quarantine and timely disposition of rejected materials.
- Suitability of process water used in the manufacture of API, including as appropriate the water system design, maintenance, validation, and operation.
- Suitability of process gas used in the manufacture of API (e.g., gas use to sparge a reactor), including as appropriate the gas system design, maintenance, validation, and operation.
- Containers and closures should not be additive, reactive, or absorptive.
- Control system for implementing changes.
- Qualification/validation and security of computerized or automated process.
- Finished API distribution records by batch.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).

ICH Q7A references for Materials System are as follows:

- Section 7, Materials Management
- Section 10, Storage and Distribution

- Section 4.3, *Water*
- Section 6, Documentation and Records

PRODUCTION SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API only but may also incorporate starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Establishment, adherence, and documented performance of approved manufacturing procedures.
- Control system for implementing changes to process.
- Controls over critical activities and operations.
- Documentation and investigation of critical deviations.
- Actual yields compared with expected yields at designated steps.
- Where appropriate established time limits for completion of phases of production.
- Appropriate identification of major equipment used in production of intermediates and API.
- Justification and consistency of intermediate specifications and API specification.
- Implementation and documentation of process controls, testing, and examinations (e.g., pH, temperature, purity, actual yields, clarity).
- In-process sampling should be conducted using procedures designed to prevent contamination of the sampled material.
- Recovery (e.g., from mother liquor or filtrates) of reactants; approved procedures and recovered materials meet specifications suitable for their intended use.
- Solvents can be recovered and reused in the same processes or in different processes provided that solvents meet appropriate standards before reuse or commingling.
- API micronization on multiuse equipment and the precautions taken by the firm to prevent or minimize the potential for cross-contamination.
- Process validation, including validation and security of computerized or automated process.
- Master batch production and control records.
- Batch production and control records.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).

ICH Q7A references for Production System are as follows:

- Section 6, Documentation and Records
- Section 8, Production and In-Process Controls
- Section 12, *Validation*
- Section 18, Specific Guidance for APIs Manufactured by Cell Culture/Fermentation

See also 7356.0002M for additional inspection guidance on fermentation, extraction, and purification processes.

PACKAGING AND LABELING SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API only but may also incorporate starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Acceptance operations for packaging and labeling materials.
- Control system for implementing changes in packaging and labeling operations.
- Adequate storage for labels and labeling, both approved and returned after issued.
- Control of labels which are similar in size, shape, and color for different APIs.
- Adequate packaging records that will include specimens of all labels used.
- Control of issuance of labeling, examination of issued labels, and reconciliation of used labels.
- Examination of the labeled finished APIs.
- Adequate inspection (proofing) of incoming labeling.
- Use of lot numbers, destruction of excess labeling bearing lot/control numbers.
- Adequate separation and controls when labeling more than one batch at a time.
- Adequate expiration or retest dates on the label.
- Validation of packaging and labeling operations including validation and security of computerized process.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).

ICH Q7A references for Packaging and Labeling System are as follows:

- Section 9, Packaging and Identification Labeling of APIs and Intermediates
- Section 17, *Agents, Brokers, Traders, Distributors, Repackers, and Relabellers* (applies to the handling of APIs after original site of manufacture and before receipt by the dosage manufacturer)

LABORATORY CONTROL SYSTEM

For each of the following, the firm should have written and approved procedures and documentation resulting therefrom. The firm's adherence to written procedures should be verified through observation whenever possible. These areas are not limited to the final API only but may also incorporate starting materials and intermediates. These areas may indicate deficiencies not only in this system but also in other systems that would warrant expansion of coverage. When this system is selected for coverage in addition to the Quality System, all areas listed below should be covered; however, the actual depth of coverage may vary from the planned inspection strategy depending upon inspectional findings.

- Training/qualification of personnel.
- Adequacy of staffing for laboratory operations.
- Adequacy of equipment and facility for intended use.
- Calibration and maintenance programs for analytical instruments and equipment.
- Validation and security of computerized or automated processes.
- Reference standards: source, purity and assay, and tests to establish equivalency to current official reference standards as appropriate.
- System suitability checks on chromatographic systems.
- Specifications, standards, and representative sampling plans.
- Validation/verification of analytical methods.
- Required testing is performed on the correct samples and by the approved or filed methods or equivalent methods.
- Documentation of any discrepancy (a critical discrepancy investigation is covered under the Quality System).
- Complete analytical records from all tests and summaries of results.
- Quality and retention of raw data (e.g., chromatograms and spectra).
- Correlation of result summaries to raw data; presence and disposition of unused data.
- Adherence to an adequate out of specification procedure, which includes timely completion of the investigation.
- Test methods for establishing a complete impurity profile for each API process (*note*: impurity profiles are often process related).
- Adequate reserve samples; documentation of reserve samples' examination.
- Stability testing program, including demonstration of stability indicating capability of the test methods.

ICH Q7A references for Laboratory System are as follows:

- Section 11, Laboratory Controls
- Section 6, Documentation and Records
- Section 12, *Validation*

ICH Q7A Sections 3, *Personnel*, and 6, *Documentation and Records*, apply to all systems. Section 19, *APIs for Use in Clinical Trials*, applies to APIs intended for the production of dosages solely for use in a clinical trial.

The organization and personnel, including appropriate qualifications and training, employed in any given system, will be evaluated as part of that system's operation. Production, control, or distribution records are required to maintain cGMPs and those selected for review should be included for inspection audit within the context of each of the above systems. Inspection of contract companies should be within the system for which the intermediate or API, or service is contracted and also include evaluation of their Quality System.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (or Drug Substance)—Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Air lock—An enclosed space with two or more doors, which is interposed between two or more rooms, for example, of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An air lock is designed for use either by people or for goods and/or equipment.

API—Active Pharmaceutical Ingredient.

API Starting Material—A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

Authorized Person—The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested, and approved for release in compliance with the laws and regulations in force in that country.

Batch (or Lot)—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Batch Number (or Lot Number)—A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, and so forth.

Batch Records—All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bioburden—The level and type (e.g., objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates, or APIs. Bioburden should not be considered contamination unless the

levels have been exceeded or defined objectionable organisms have been detected.

Bulk Product—Any product that has completed all processing stages up to, but not including, final packaging.

Calibration—The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

CDER—Center for Drug Evaluation and Research, FDA.

Clean Area—An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Computer System—A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions. A process or operation integrated with a computer system.

Consignment (or Delivery)—The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Contamination—The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or onto a raw material, intermediate, or API during production, sampling, packaging or repackaging, storage, or transport.

Contract Manufacturer—A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical—Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Critical Operation—An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Cross-Contamination—Contamination of a material or product with another material or product. Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Deviation—Departure from an approved instruction or established standard.

DMPQ—Division of Manufacturing and Product Quality, FDA.

Drug (Medicinal) Product—The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance—See Active Pharmaceutical Ingredient

EES—Establishment Evaluation System.

EIR—Establishment Inspection Report.

Expiry Date (or Expiration Date)—The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

FCC—Forensic Chemistry Center.

FEI—Federal Employment Identification.

Fnished Product—A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.

Impurity—Any component present in the intermediate or API that is not the desired entity.

Impurity Profile—A description of the identified and unidentified impurities present in an API.

In-Process Control—Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate—A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Large-Volume Parenterals—Sterile solutions intended for parenteral application with a volume of 100 mL or more in one container of the finished dosage form.

Lot—See Batch

Lot Number—see Batch Number

Manufacturer—A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of pharmaceuticals.

Marketing Authorization (Product License, Registration Certificate)—A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling, and shelf life.

Master Formula—A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master Record—A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Material—A general term used to denote raw materials (starting materials, reagents, and solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother Liquor—The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It may be used for further processing.

OAI—Office Action Indicated.

Packaging—All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under

aseptic conditions or a product intended to be terminally sterilized would not normally be regarded as part of packaging.

Packaging Material—Any material intended to protect an intermediate or API during storage and transport. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

PACS—Picture archiving and communication systems.

Pharmaceutical Product—Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Procedure—A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids—Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon).

Process Control—See In-Process Control

Production—All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labeling and relabeling, to completion of the finished product.

Qualification—Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)—The sum total of the organized arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)—Checking or testing that specifications are met.

Quality Unit(s)—An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine—The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Raw Material—A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reconciliation—A comparison between the theoretical quantity and the actual quantity.

Recovery—The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

Reference Standard, Primary—A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity.

Reference Standard, Secondary—A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing—Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate), or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and preapproved as part of the marketing authorization.

Retest Date—The date when a material should be reexamined to ensure that it is still suitable for use.

Reworking—Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not preapproved as part of the marketing authorization.

Self-Contained Area—Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well-established procedures, controls, and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

Signature (Signed)—See definition for signed

Signed (Signature)—The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent—An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification—A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Standard Operating Procedure (SOP)—An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g., equipment operation, maintenance, and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting Material—Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Validation—A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity, or system actually leads to the expected results (see also qualification).

Validation Protocol—A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing

process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected—The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical—The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

13

Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances

I. INTRODUCTION

A. Objective of the Guideline

This guideline is intended to assist to the extent possible, in the establishment of a single set of global specifications for new drug substances and new drug products. It provides guidance on the setting and justification of acceptance criteria and the selection of test procedures for new drug substances of synthetic chemical origin, and new drug products produced from them, which have not been registered previously in the United States, the European Union, or Japan.

B. Background

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Specifications are one part of a total control strategy for the drug substance and drug product designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, upon which specifications are based, and adherence to Good Manufacturing Practices; for example, suitable facilities, a validated manufacturing process, validated test procedure, raw material testing, in-process testing, stability testing, etc.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization, and should focus on those characteristics found to be useful in ensuring the safety and efficacy of the drug substance and drug product.

C. Scope of the Guideline

The quality of drug substances and drug products is determined by their design, development, in-process controls, GMP controls, and process validation, and by specifications applied to them throughout development and manufacture. This guideline addresses specifications, that is, those tests, procedures, and acceptance criteria which play a major role in assuring the quality of the new drug substance and new drug product at release and during shelf life. Specifications are an important component of quality assurance, but are not its only component. All of the considerations listed above are necessary to ensure consistent production of drug substances and drug products of high quality.

This guideline addresses only the marketing approval of new drug products (including combination products) and, where applicable, new drug substances; it does not address drug substances or drug products during the clinical research stages of drug development. This guideline may be applicable to synthetic and semisynthetic antibiotics and synthetic peptides of low-molecular-weight; however, it is not sufficient to adequately describe specifications of higher molecular weight peptides and polypeptides, and biotechnological/biological products. The ICH Guideline Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products addresses guideline specifications, tests, and procedures for biotechnological/biological products. Radiopharmaceuticals, products of fermentation, oligonucleotides, herbal products, and crude products of animal or plant origin are similarly not covered.

Guidance is provided with regard to acceptance criteria, which should be established for all new drug substances and new drug products, that is, universal acceptance criteria, and those that are considered specific to individual drug substances and/or dosage forms. This guideline should not be considered all encompassing. New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when justified.

Dosage forms addressed in this guideline include solid oral dosage forms, liquid oral dosage forms, and parenterals (small and large volume). This is not meant to be an all-inclusive list, or to limit the number of dosage forms to which this guideline applies. The dosage forms presented serve as models, which may be applicable to other dosage forms, which have not been discussed. The extended application of the concepts in this guideline to other dosage forms, for example, to inhalation dosage forms (powders, solutions, etc.), to topical formulations (creams, ointments, gels), and to transdermal systems, is encouraged.

II. GENERAL CONCEPTS

The following concepts are important in the development and setting of harmonized specifications. They are not universally applicable, but each should be considered in particular circumstances. This guideline presents a brief definition of each concept and an indication of the circumstances under which it may be applicable. Generally, proposals to implement these concepts should be justified by the applicant and approved by the appropriate regulatory authority before being put into effect.

A. Periodic or Skip Testing

Periodic or skip testing is the performance of specified tests at release on preselected batches and/or at predetermined

intervals, rather than on a batch-to-batch basis with the understanding that those batches not being tested still must meet all acceptance criteria established for that product. This represents a less than full schedule of testing and should therefore be justified and presented to and approved by the regulatory authority prior to implementation. This concept may be applicable to, for example, residual solvents and microbiological testing, for solid oral dosage forms. It is recognized that only limited data may be available at the time of submission of an application (see section 2.5). This concept should therefore generally be implemented postapproval. When tested, any failure to meet acceptance criteria established for the periodic test should be handled by proper notification of the appropriate regulatory authority(ies). If these data demonstrate a need to restore routine testing, then batch-by-batch release testing should be reinstated.

B. Release vs. Shelf life Acceptance Criteria

The concept of different acceptance criteria for release versus shelf life specifications applies to drug products only; it pertains to the establishment of more restrictive criteria for the release of a drug product than are applied to the shelf life. Examples where this may be applicable include assay and impurity (degradation product) levels. In Japan and the United States, this concept may only be applicable to in-house criteria, and not to the regulatory release criteria. Thus, in these regions, the regulatory acceptance criteria are the same from release throughout shelf life; however, an applicant may choose to have tighter in-house limits at the time of release to provide increased assurance to the applicant that the product will remain within the regulatory acceptance criterion throughout its shelf life. In the European Union, there is a regulatory requirement for distinct specifications for release and for shelf life where different.

C. In-process Tests

In-process tests, as presented in this guideline, are tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release.

In-process tests, which are only used for the purpose of adjusting process parameters within an operating range, for example, hardness and friability of tablet cores which will be coated and individual tablet weights, are not included in the specification.

Certain tests conducted during the manufacturing process, where the acceptance criterion is identical to or tighter than the release requirement, (e.g., pH of a solution) may be sufficient to satisfy specification requirements when the test is included in the specification. However, this approach should be validated to show that test results or product performance characteristics do not change from the in-process stage to finished product.

D. Design and Development Considerations

The experience and data accumulated during the development of a new drug substance or product should form the basis for the setting of specifications. It may be possible to propose excluding or replacing certain tests on this basis. Some examples are:

- microbiological testing for drug substances and solid dosage forms which have been shown during development not to support microbial viability or growth (see Decision Trees 6 and 8);
- extractables from product containers where it has been reproducibly shown that either no extractables are found in the drug product or the levels meet accepted standards for safety;
- particle size testing may fall into this category, may be performed as an in-process test, or may be performed as a release test, depending on its relevance to product performance; and
- dissolution testing for immediate release solid oral drug products made from highly water soluble drug substances may be replaced by disintegration testing, if these products have been demonstrated during development to have consistently rapid drug-release characteristics [see Decision Trees 7(1) through 7(2)].

E. Limited Data Available at Filing

It is recognized that only a limited amount of data may be available at the time of filing, which can influence the process of setting acceptance criteria. As a result, it may be necessary to propose revised acceptance criteria as additional experience is gained with the manufacture of a particular drug substance or drug product (e.g., acceptance limits for a specific impurity). The basis for the acceptance criteria at the time of filing should necessarily focus on safety and efficacy.

When only limited data are available, the initially approved tests and acceptance criteria should be reviewed as more information is collected, with a view towards possible modification. This could involve loosening, as well as tightening, acceptance criteria as appropriate.

F. Parametric Release

Parametric release can be used as an operational alternative to routine release testing for the drug product in certain cases when approved by the regulatory authority. Sterility testing for terminally sterilized drug products is one example. In this case, the release of each batch is based on satisfactory results from monitoring specific parameters, for example, temperature, pressure, and time during the terminal sterilization phase(s) of drug product manufacturing. These parameters can generally be more accurately controlled and measured, so that they are more reliable in predicting sterility assurance than is end-product sterility testing. Appropriate laboratory tests (e.g., chemical or physical indicator) may be included in the parametric release program. It is important to note that the sterilization process should be adequately validated before parametric release is proposed and maintenance of a validated state should be demonstrated by revalidation at established intervals. When parametric release is performed, the attribute which is indirectly controlled (e.g., sterility), together with a reference to the associated test procedure, still should be included in the specifications.

G. Alternative Procedures

Alternative procedures are those, which may be used to measure an attribute when such procedures control the quality of the drug substance or drug product to an extent that is comparable or superior to the official procedure. Example: for tablets that have been shown not to degrade during manufacture, it may be permissible to use a spectrophotometric procedure for release as opposed to the official procedure, which is chromatographic. However, the chromatographic procedure should still be used to demonstrate compliance with the acceptance criteria during the shelf life of the product.

H. Pharmacopoeial Tests and Acceptance Criteria

References to certain procedures are found in pharmacopoeias in each region. Wherever they are appropriate, pharmacopoeial procedures should be utilized. Whereas differences in pharmacopoeial procedures and/or acceptance criteria have existed among the regions, a harmonized specification is possible only if the procedures and acceptance criteria defined are acceptable to regulatory authorities in all regions.

The full utility of this guideline is dependent on the successful completion of harmonization of pharmacopoeial procedures for several attributes commonly considered in the specification for new drug substances or new drug products. The Pharmacopoeial Discussion Group (PDG) of the European Pharmacopoeia, the Japanese Pharmacopoeia, and the United States Pharmacopeia has expressed a commitment to achieving harmonization of the procedures in a timely fashion.

Where harmonization has been achieved, an appropriate reference to the harmonized procedure and acceptance criteria is considered acceptable for a specification in all three regions. For example, after harmonization sterility data generated using the JP procedure, as well as the JP procedure itself and its acceptance criteria, are considered acceptable for registration in all three regions. To signify the harmonized status of these procedures, the pharmacopoeias have agreed to include a statement in their respective texts, which indicates that the procedures and acceptance criteria from all three pharmacopoeias are considered equivalent and are, therefore, interchangeable.

Since the overall value of this guideline is linked to the extent of harmonization of the analytical procedures and acceptance criteria of the pharmacopoeias, it is agreed by the members of the Q6A expert working group that none of the three pharmacopoeias should change a harmonized monograph unilaterally. According to the PDG procedure for the revision of harmonized monographs and chapters, "no pharmacopoeia shall revise unilaterally any monograph or chapter after sign-off or after publication."

I. Evolving Technologies

New analytical technologies, and modifications to existing technology, are continually being developed. Such technologies should be used when they are considered to offer additional assurance of quality, or are otherwise justified.

J. Impact of Drug Substance on Drug Product Specifications

In general, it should not be necessary to test the drug product for quality attributes uniquely associated with the drug substance. For example, it is normally not considered necessary to test the drug product for synthesis impurities, which are controlled in the drug substance and are not degradation products. Refer to the ICH Guideline Impurities in New Drug Products for detailed information.

K. Reference Standard

A reference standard, or reference material, is a substance prepared for use as the standard in an assay, identification, or purity test. It should have a quality appropriate to its use. It is often characterized and evaluated for its intended purpose by additional procedures other than those used in routine testing. For new drug substance reference standards intended for use in assays, the impurities should be adequately identified and/or controlled, and purity should be measured by a quantitative procedure.

III. GUIDELINES

A. Specifications: Definition and Justification

1. Definition of Specifications

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a new drug substance or new drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

It is possible that, in addition to release tests, a specification may list in-process tests as defined in 2.3, periodic (skip) tests, and other tests, which are not always conducted on a batch-by-batch basis. In such cases, the applicant should specify which tests are routinely conducted batch-by-batch, and which tests are not, with an indication and justification of the actual testing frequency. In this situation, the drug substance and/or drug product should meet the acceptance criteria if tested.

It should be noted that changes in the specification after approval of the application may need prior approval by the regulatory authority.

2. Justification of Specifications

When a specification is first proposed, justification should be presented for each procedure and each acceptance criterion included. The justification should refer to relevant development data, pharmacopoeial standards, test data for drug substances and drug products used in toxicology and clinical studies, and results from accelerated and long-term stability studies, as appropriate. Additionally, a reasonable range of expected analytical and manufacturing variability should be considered. It is important to consider all of this information.

Approaches other than those set forth in this guideline may be applicable and acceptable. The applicant should justify alternative approaches. Such justification should be based on data derived from the new drug substance synthesis and/or the new drug product manufacturing process. This justification may consider theoretical tolerances for a given procedure or acceptance criterion, but the actual results obtained should form the primary basis for whatever approach is taken.

Test results from stability and scale-up/validation batches, with emphasis on the primary stability batches, should be considered in setting and justifying specifications. If multiple manufacturing sites are planned, it may be valuable to consider data from these sites in establishing the initial tests and acceptance criteria. This is particularly true when there is limited initial experience with the manufacture of the drug substance or drug product at any particular site. If data from a single representative manufacturing site are used in setting tests and acceptance criteria, product manufactured at all sites should still comply with these criteria.

Presentation of test results in graphic format may be helpful in justifying individual acceptance criteria, particularly for assay values and impurity levels. Data from development work should be included in such a presentation, along with stability data available for new drug substance or new drug product batches manufactured by the proposed commercial processes. Justification for proposing exclusion of a

test from the specification should be based on development data and on process validation data (where appropriate).

B. Universal Tests/Criteria

Implementation of the recommendations in the following section should take into account the ICH Guidelines "Text on Validation of Analytical Procedures" and "Validation of Analytical Procedures: Methodology".

1. New Drug Substances

The following tests and acceptance criteria are considered generally applicable to all new drug substances.

(a) *Description*: A qualitative statement about the state (e.g., solid, liquid) and color of the new drug substance. If any of these characteristics change during storage, this change should be investigated and appropriate action taken.

(b) *Identification:* Identification testing should optimally be able to discriminate between compounds of closely related structure which are likely to be present. Identification tests should be specific for the new drug substance, for example, infrared spectroscopy. Identification solely by a single chromatographic retention time, for example, is not regarded as being specific. However, the use of two chromatographic procedures, where the separation is based on different principles or a combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS is generally acceptable. If the new drug substance is a salt, identification testing should be specific for the individual ions. An identification test that is specific for the salt itself should suffice.

New drug substances, which are optically active may also need specific identification testing or performance of a chiral assay. Please refer to 3.3.1.d) in this guideline for further discussion of this topic.

(c) *Assay:* A specific, stability-indicating procedure should be included to determine the content of the new drug substance. In many cases, it is possible to employ the same procedure (e.g., HPLC) for both assay of the new drug substance and quantitation of impurities.

In cases where use of a nonspecific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where titration is adopted to assay the drug substance, the combination of the assay and a suitable test for impurities should be used.

(d) *Impurities:* Organic and inorganic impurities and residual solvents are included in this category. Refer to the ICH Guidelines Impurities in New Drug Substances and Residual Solvents in Pharmaceuticals for detailed information.

Decision tree 1 addresses the extrapolation of meaningful limits on impurities from the body of data generated during development. At the time of filing, it is unlikely that sufficient data will be available to assess process consistency. Therefore, it is considered inappropriate to establish acceptance criteria, which tightly encompass the batch data at the time of filing. (see section 2.5)

2. New Drug Products

The following tests and acceptance criteria are considered generally applicable to all new drug products:

(a) *Description:* A qualitative description of the dosage form should be provided (e.g., size, shape, and color). If any of these characteristics change during manufacture or storage, this change should be investigated and appropriate action taken. The acceptance criteria should include the final acceptable appearance. If color changes during storage, a quantitative procedure may be appropriate.

(b) *Identification:* Identification testing should establish the identity of the new drug substance(s) in the new drug product and should be able to discriminate between compounds of closely related structure which are likely to be present. Identity tests should be specific for the new drug substance, for example, infrared spectroscopy. Identification solely by a single chromatographic retention time, for example, is not regarded as being specific. However, the use of two chromatographic procedures, where the separation is based on different principles, or combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS, is generally acceptable.

(c) *Assay:* A specific, stability-indicating assay to determine strength (content) should be included for all new drug products. In many cases, it is possible to employ the same procedure (e.g., HPLC) for both assay of the new drug substance and quantitation of impurities. Results of content uniformity testing for new drug products can be used for quantitation of drug product strength, if the methods used for content uniformity are also appropriate as assays.

In cases where use of a nonspecific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where titration is adopted to assay the drug substance for release, the combination of the assay and a suitable test for impurities can be used. A specific procedure should be used when there is evidence of excipient interference with the nonspecific assay.

(d) *Impurities:* Organic and inorganic impurities (degradation products) and residual solvents are included in this category. Refer to the ICH Guidelines Impurities in New Drug Products and Residual Solvents for detailed information.

Organic impurities arising from degradation of the new drug substance and impurities that arise during the manufacturing process for the drug product should be monitored in the new drug product. Acceptance limits should be stated for individual specified degradation products, which may include both identified and unidentified degradation products as appropriate, and total degradation products. Process impurities from the new drug substance synthesis are normally controlled during drug substance testing, and therefore are not included in the total impurities limit. However, when a synthesis impurity is also a degradation product, its level should be monitored and included in the total degradation product limit. When it has been conclusively demonstrated via appropriate analytical methodology, that the drug substance does not degrade in the specific formulation, and under the specific storage conditions proposed in the new drug application, degradation product testing may be reduced or eliminated upon approval by the regulatory authorities.

Decision tree 2 addresses the extrapolation of meaningful limits on degradation products from the body of data generated during development. At the time of filing, it is unlikely that sufficient data will be available to assess process consistency. Therefore, it is considered inappropriate to establish acceptance criteria, which tightly encompass the batch data at the time of filing. (see section 2.5)

C. Specific Tests/Criteria

In addition to the universal tests listed above, the following tests may be considered on a case by case basis for drug substances and/or drug products. Individual tests/criteria should be included in the specification when the tests have an impact on the quality of the drug substance and drug product for batch control. Tests other than those listed below may be needed in particular situations or as new information becomes available.

1. New Drug Substances

(a) *Physicochemical properties:* These are properties such as pH of an aqueous solution, melting point/range, and refractive index. The procedures used for the measurement of these properties are usually unique and do not need much elaboration, for example, capillary melting point, Abbé refractometry. The tests performed in this category should be determined by the physical nature of the new drug substance and by its intended use.

(b) *Particle size:* For some new drug substances intended for use in solid or suspension drug products, particle size can have a significant effect on dissolution rates, bioavailability, and/or stability. In such instances, testing for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided.

Decision tree 3 provides additional guidance on when particle size testing should be considered.

(c) *Polymorphic forms:* Some new drug substances exist in different crystalline forms, which differ in their physical properties. Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Differences in these forms could, in some cases, affect the quality or performance of the new drug products. In cases where differences exist which have been shown to affect drug product performance, bioavailability, or stability, then the appropriate solid state should be specified.

Physicochemical measurements and techniques are commonly used to determine whether multiple forms exist. Examples of these procedures are: melting point (including hot-stage microscopy), solid state IR, X-ray powder diffraction, thermal analysis procedures (such as DSC, TGA, and DTA), Raman spectroscopy, optical microscopy, and solid-state NMR.

Decision trees 4(1) through 4(3) provide additional guidance on when, and how, polymorphic forms should be monitored and controlled.

Note: These decision trees should be followed sequentially. Trees 1 and 2 consider whether polymorphism is exhibited by the drug substance, and whether the different polymorphic forms can affect performance of the drug product. Tree 3 should only be applied when polymorphism has been demonstrated for the drug substance, and shown to affect these properties. Tree 3 considers the potential for change in polymorphic forms in the drug product, and whether such a change has any effect on product performance.

It is generally technically very difficult to measure polymorphic changes in drug products. A surrogate test (e.g., dissolution) [see Decision tree 4(3)] can generally be used to monitor product performance, and polymorph content should only be used as a test and acceptance criterion of last resort.

(d) *Tests for chiral new drug substances:* Where a new drug substance is predominantly one enantiomer, the opposite enantiomer is excluded from the qualification and identification thresholds given in the ICH Guidelines on Impurities in New Drug Substances and Impurities in New Drug Products because of practical difficulties in quantifying it at those levels. However, that impurity in the chiral new drug substance and the resulting new drug product(s) should otherwise be treated according to the principles established in those guidelines.

Decision tree 5 summarizes when and if chiral identity tests, impurity tests, and assays may be needed for both new drug substances and new drug products, according to the following concepts:

Drug substance: Impurities. For chiral drug substances, which are developed as a single enantiomer, control of the other enantiomer should be considered in the same manner as for other impurities. However, technical limitations may preclude the same limits of quantification or qualification from being applied. Assurance of control also could be given by appropriate testing of a starting material or intermediate, with suitable justification.

Assay. An enantioselective determination of the drug substance should be part of the specification. It is considered acceptable for this to be achieved either through use of a chiral assay procedure or by the combination of an achiral assay together with appropriate methods of controlling the enantiomeric impurity.

Identity. For a drug substance developed as a single enantiomer, the identity test(s) should be capable of distinguishing both enantiomers and the racemic mixture. For a racemic drug substance, there are generally two situations where a stereospecific identity test is appropriate for release/acceptance testing: (1) where there is a significant possibility that the enantiomer might be substituted for the racemate, or (2) when there is evidence that preferential crystallization may lead to unintentional production of a nonracemic mixture.

Drug product: Degradation products. Control of the other enantiomer in a drug product is considered necessary unless racemization has been shown to be insignificant during manufacture of the dosage form, and on storage.

Assay: An achiral assay may be sufficient where racemization has been shown to be insignificant during manufacture of the dosage form, and on storage. Otherwise a chiral assay should be used, or alternatively, the combination of an achiral assay plus a validated procedure to control the presence of the opposite enantiomer may be used.

Identity: A stereospecific identity test is not generally needed in the drug product release specification. When racemization is insignificant during manufacture of the dosage form, and on storage, stereospecific identity testing is more appropriately addressed as part of the drug substance specification. When racemization in the dosage form is a concern, chiral assay or enantiomeric impurity testing of the drug product will serve to verify identity.

(e) *Water content:* This test is important in cases where the new drug substance is known to be hygroscopic or degraded by moisture or when the drug substance is known to be a stoichiometric hydrate. The acceptance criteria may be justified with data on the effects of hydration or moisture absorption. In some cases, a loss on drying procedure may be considered adequate; however, a

detection procedure that is specific for water (e.g., Karl Fischer titration) is preferred.

(f) *Inorganic impurities:* The need for inclusion of tests and acceptance criteria for inorganic impurities (e.g., catalysts) should be studied during development and based on knowledge of the manufacturing process. Procedures and acceptance criteria for sulfated ash/residue on ignition should follow pharmacopoeial precedents; other inorganic impurities may be determined by other appropriate procedures, for example, atomic absorption spectroscopy.

(g) *Microbial limits:* There may be a need to specify the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*, *Salmonella*, *Pseudomonas aeruginosa*). These should be suitably determined using pharmacopoeial procedures. The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product. For example, sterility testing may be appropriate for drug substances manufactured as sterile and endotoxin testing may be appropriate for drug substances used to formulate an injectable drug product.

Decision tree 6 provides additional guidance on when microbial limits should be included.

2. New Drug Products

Additional tests and acceptance criteria generally should be included for particular new drug products. The following selection presents a representative sample of both the drug products and the types of tests and acceptance criteria, which may be appropriate. The specific dosage forms addressed include solid oral drug products, liquid oral drug products, and parenterals (small and large volume). Application of the concepts in this guideline to other dosage forms is encouraged. Note that issues related to optically active drug substances and to solid-state considerations for drug products are discussed in part 3.3.1. of this guideline.

a. General Considerations

The following tests are applicable to tablets (coated and uncoated) and hard capsules. One or more of these tests may also be applicable to soft capsules and granules.

(a) *Dissolution:* The specification for solid oral dosage forms normally includes a test to measure release of drug substance from the drug product. Single-point measurements are normally considered to be suitable for immediate-release dosage forms. For modified-release dosage forms, appropriate test conditions and sampling procedures should be established. For example, multiple time point sampling should be performed for extended-release dosage forms, and two-stage testing (using different media in succession or in parallel, as appropriate) may be appropriate for delayed-release dosage forms. In these cases, it is important to consider the populations of individuals who will be taking the drug product (e.g., achlorhydric elderly) when designing the tests and acceptance criteria. In some cases [see 3.3.2.1 b) Disintegration], dissolution testing may be replaced by disintegration testing [see Decision Tree 7 (1)].

For immediate-release drug products where changes in dissolution rate have been demonstrated to significantly affect bioavailability, it is desirable to develop test conditions, which can distinguish batches with unacceptable bioavailability. If changes in formulation or process variables significantly affect dissolution and such changes are not controlled by another aspect of the specification, it may also be appropriate to adopt dissolution test conditions, which can distinguish these changes [see Decision Tree 7(2)].

Where dissolution significantly affects bioavailability, the acceptance criteria should be set to reject batches with unacceptable bioavailability. Otherwise, test conditions and acceptance criteria should be established which pass clinically acceptable batches [see Decision Tree 7(2)]. For extended-release drug products, in vitro/in vivo correlation may be used to establish acceptance criteria when human bioavailability data are available for formulations exhibiting different release rates. Where such data are not available, and drug release cannot be shown to be independent of in vitro test conditions, then acceptance criteria should be established on the basis of available batch data. Normally, the permitted variability in mean release rate at any given time point should not exceed a total numerical difference of $+/-10\%$ of the labeled content of drug substance (i.e., a total variability of 20%: a requirement of 50% $+/-10\%$ thus means an acceptable range from 40% to 60%), unless a wider range is supported by a bioequivalency study [see Decision Tree 7(3)].

(b) *Disintegration:* For rapidly dissolving (dissolution $>80\%$ in 15 minutes at pH 1.2, 4.0, and 6.8) products containing drugs which are highly soluble throughout the physiological range (dose/solubility volume <250 mL from pH 1.2 to 6.8), disintegration may be substituted for dissolution. Disintegration testing is most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution. In such cases, dissolution testing may not be necessary. It is expected that development information will be provided to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution versus disintegration testing [see Decision Tree 7(1)].

(c) *Hardness/friability:* It is normally appropriate to perform hardness and/or friability testing as an in-process control (see section 2.3). Under these circumstances, it is normally not necessary to include these attributes in the specification. If the characteristics of hardness and friability have a critical impact on drug product quality (e.g., chewable tablets), acceptance criteria should be included in the specification.

(d) *Uniformity of dosage units:* This term includes both the mass of the dosage form and the content of the active substance in the dosage form; a pharmacopoeial procedure should be used. In general, the specification should include one or the other but not both. If appropriate, these tests may be performed in-process; the acceptance criteria should be included in the specification. When weight variation is applied for new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate.

(e) *Water content:* A test for water content should be included when appropriate. The acceptance criteria may be justified with data on the effects of hydration or water absorption on the drug product. In some cases, a loss on drying procedure may be considered adequate; however, a detection procedure, which is specific for water (e.g., Karl Fischer titration) is preferred.

(f) *Microbial limits:* Microbial limit testing is seen as an attribute of Good Manufacturing Practice, as well as of quality assurance. In general, it is advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination or proliferation. It should be noted that, whereas this guideline does not directly address excipients, the principles discussed here may be applicable to excipients as well as to new drug products. Skip testing may be an appropriate approach in both cases where permissible. (See Decision Tree 6 for microbial testing of excipients.)

Acceptance criteria should be set for the total count of aerobic microorganisms, the total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *S. aureus*, *E. coli*, *Salmonella*, *Pseudomonas aeruginosa*). These should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture, which is justified by data and experience. The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product. With acceptable scientific justification, it should be possible to propose no microbial limit testing for solid oral dosage forms.

Decision tree 8 provides additional guidance on the use of microbial limits testing.

b. Oral liquids

One or more of the following specific tests will normally be applicable to oral liquids and to powders intended for reconstitution as oral liquids.

(a) *Uniformity of dosage units:* This term includes both the mass of the dosage form and the content of the active substance in the dosage form; a pharmacopoeial procedure should be used. In general, the specification should include one or the other but not both. When weight variation is applied for new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate.
If appropriate, tests may be performed in-process; however, the acceptance criteria should be included in the specification. This concept may be applied to both single-dose and multiple-dose packages.

The dosage unit is considered to be the typical dose taken by the patient. If the actual unit dose, as taken by the patient, is controlled, it may either be measured directly or calculated, based on the total measured weight or volume of drug divided by the total number of doses expected. If dispensing equipment (such as medicine droppers or dropper tips for bottles) is an integral part of the packaging, this equipment should be used to measure the dose. Otherwise, a standard volume measure should be used. The dispensing equipment to be used is normally determined during development.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

(b) *pH:* Acceptance criteria for pH should be provided where applicable and the proposed range justified.

(c) *Microbial limits:* Microbial limit testing is seen as an attribute of Good Manufacturing Practice, as well as of quality assurance. In general, it is advisable to test the drug product unless its components are tested before manufacture and the manufacturing process is known, through validation studies, not to carry a significant risk of microbial contamination or proliferation. It should be noted that, whereas this guideline does not directly address excipients, the principles discussed here may be applicable to excipients as well as to new drug products. Skip testing may be an appropriate approach in both cases where permissible. With acceptable scientific justification, it may be possible to propose no microbial limit testing for powders intended for reconstitution as oral liquids.

Acceptance criteria should be set for the total count of aerobic microorganisms, total count of yeasts and molds, and the absence of specific objectionable bacteria (e.g., *S. aureus*, *E. coli*, *Salmonella*, *Pseudomonas aeruginosa*). These should be determined by suitable procedures, using pharmacopoeial procedures, and at a sampling frequency or time point in manufacture, which is justified by data and experience.

Decision tree 8 provides additional guidance on the use of microbial limits testing.

(d) *Antimicrobial preservative content:* For oral liquids needing an antimicrobial preservative, acceptance criteria for preservative content should be established. Acceptance criteria for preservative content should be based upon the levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Testing for antimicrobial preservative content should normally be performed at release. Under certain circumstances, in-process testing may suffice in lieu of release testing. When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.

Antimicrobial preservative effectiveness should be demonstrated during development, during scale-up, and throughout the shelf life (e.g., in stability testing: see the ICH Guideline, "Stability Testing of New Drug Substances and Products"), although chemical testing for preservative content is the attribute normally included in the specification.

(e) *Antioxidant preservative content:* Release testing for antioxidant content should normally be performed. Under certain circumstances, where justified by developmental and stability data, shelf-life testing may be unnecessary, and in-process testing may suffice in lieu of release testing where permitted. When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.

(f) *Extractables*: Generally, where development and stability data show evidence that extractables from the container/closure systems are consistently below levels that are demonstrated to be acceptable and safe, elimination of this test can normally be accepted. This should be reinvestigated if the container/closure system or formulation changes.

Where data demonstrate the need, tests and acceptance criteria for extractables from the container/closure system components (e.g., rubber stopper, cap liner, plastic bottle, etc.) are considered appropriate for oral

solutions packaged in nonglass systems, or in glass containers with nonglass closures. The container/closure components should be listed, and data collected for these components as early in the development process as possible.

(g) *Alcohol content:* Where it is declared quantitatively on the label in accordance with pertinent regulations, the alcohol content should be specified. It may be assayed or calculated.

(h) *Dissolution:* In addition to the attributes recommended immediately above, it may be appropriate (e.g., insoluble drug substance) to include dissolution testing and acceptance criteria for oral suspensions and dry powder products for resuspension. Dissolution testing should be performed at release. This test may be performed as an in-process test when justified by product development data. The testing apparatus, media, and conditions should be pharmacopoeial, if possible, or otherwise justified. Dissolution procedures using either pharmacopoeial or nonpharmacopoeial apparatus and conditions should be validated.

Single-point measurements are normally considered suitable for immediate-release dosage forms. Multiple-point sampling, at appropriate intervals, should be performed for modified-release dosage forms. Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

(i) *Particle size distribution:* Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for oral suspensions. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure for these formulations.

Particle size distribution testing should be performed at release. It may be performed as an in-process test when justified by product development data. If these products have been demonstrated during development to have consistently rapid drug-release characteristics, exclusion of a particle size distribution test from the specification may be proposed.

Particle size distribution testing may also be proposed in place of dissolution testing; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and/or lower particle size limits should be well defined.

Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo, as well as the intended use of the product. The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

(j) *Redispersibility:* For oral suspensions, which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate procedure.

The procedure (mechanical or manual) should be indicated. Time required to achieve resuspension by the indicated procedure should be clearly defined. Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

(k) *Rheological properties:* For relatively viscous solutions or suspensions, it may be appropriate to include rheological properties (viscosity/specific gravity) in the specification. The test and acceptance criteria should be stated. Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

(l) *Reconstitution time:* Acceptance criteria for reconstitution time should be provided for dry powder products, which require reconstitution. The choice of diluent should be justified. Data generated during product development may be sufficient to justify skip lot testing or elimination of this attribute from the specification may be proposed.

(m) *Water content:* For oral products requiring reconstitution, a test and acceptance criterion for water content should be proposed when appropriate. Loss on drying is generally considered sufficient if the effect of absorbed moisture versus water of hydration has been adequately characterized during the development of the product. In certain cases, a more specific procedure (e.g., Karl Fischer titration) may be preferable.

c. Parenteral Drug Products

The following tests may be applicable to parenteral drug products.

(a) *Uniformity of dosage units:* This term includes both the mass of the dosage form and the content of the active substance in the dosage form; a pharmacopoeial procedure should be used. In general, the specification should one or the other but not both and is applicable to powders for reconstitution. When weight variation is applied for new drug products exceeding the threshold value to allow testing uniformity by weight variation, applicants should verify during drug development that the homogeneity of the product is adequate.

If appropriate (see section 2.3), these tests may be performed in-process; the acceptance criteria should be included in the specification. This test may be applied to both single-dose and multiple-dose packages.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

(b) *pH:* Acceptance criteria for pH should be provided where applicable and the proposed range justified.

(c) *Sterility:* All parenteral products should have a test procedure and acceptance criterion for evaluation of sterility. Where data generated during development and validation justify parametric release, this approach may be proposed for terminally sterilized drug products (see section 2.6).

(d) *Endotoxins/pyrogens:* A test procedure and acceptance criterion for endotoxins, using a procedure such as the limulus amoebocyte lysate test, should be included in the specification. Pyrogenicity testing may be proposed as an alternative to endotoxin testing where justified.

(e) *Particulate matter:* Parenteral products should have appropriate acceptance criteria for particulate matter. This will normally include acceptance criteria for visible particulates and/or clarity of solution, as well as for subvisible particulates as appropriate.

(f) *Water content:* For nonaqueous parenterals, and for parenteral products for reconstitution, a test procedure and acceptance criterion for water content should be proposed when appropriate. Loss on drying is generally

considered sufficient for parenteral products, if the effect of absorbed moisture versus water of hydration has been adequately characterized during development. In certain cases a more specific procedure (e.g., Karl Fischer titration) may be preferred.

(g) *Antimicrobial preservative content:* For parenteral products needing an antimicrobial preservative, acceptance criteria for preservative content should be established. Acceptance criteria for preservative content should be based upon the levels of antimicrobial preservative necessary to maintain microbiological quality of the product at all stages throughout its proposed usage and shelf life. The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using a pharmacopoeial antimicrobial preservative effectiveness test.

Testing for antimicrobial preservative content should normally be performed at release. Under certain circumstances, in-process testing may suffice in lieu of release testing where permitted. When antimicrobial preservative content testing is performed as an in-process test, the acceptance criteria should remain part of the specification.

Antimicrobial preservative effectiveness should be demonstrated during development, during scaleup, and throughout the shelf life (e.g., in stability testing: see the ICH Guideline, "Stability Testing of New Drug Substances and Products"), although chemical testing for preservative content is the attribute normally included in the specification.

(h) *Antioxidant preservative content:* Release testing for antioxidant content should normally be performed. Under certain circumstances, where justified by developmental and stability data, shelf life testing may be unnecessary and in-process testing may suffice in lieu of release testing. When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.

(i) *Extractables:* Control of extractables from container/closure systems is considered significantly more important for parenteral products than for oral liquids. However, where development and stability data show evidence that extractables are consistently below the levels that are demonstrated to be acceptable and safe, elimination of this test can normally be accepted. This should be reinvestigated if the container/closure system or formulation changes.

Where data demonstrate the need, acceptance criteria for extractables from the container/closure components are considered appropriate for parenteral products packaged in nonglass systems or in glass containers with elastomeric closures. This testing may be performed at release only, where justified by data obtained during development. The container/closure system components (e.g., rubber stopper, etc.) should be listed, and data collected for these components as early in the development process as possible.

(j) *Functionality testing of delivery systems:* Parenteral formulations packaged in prefilled syringes, autoinjector cartridges, or the equivalent should have test procedures and acceptance criteria related to the functionality of the delivery system. These may include control of syringeability, pressure, and seal integrity (leakage), and/or parameters such as tip cap removal force, piston release force, piston travel force, and power injector function force. Under certain circumstances these tests may be performed in process. Data generated during product development may be sufficient to justify skip lot testing or elimination of some or all attributes from the specification.

(k) *Osmolarity:* When the tonicity of a product is declared in its labeling, appropriate control of its osmolarity should be performed. Data generated during development and validation may be sufficient to justify performance of this procedure as an in-process control, skip lot testing, or direct calculation of this attribute.

(l) *Particle size distribution:* Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for injectable suspensions. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

Particle size distribution testing should be performed at release. It may be performed as an in-process test when justified by product development data. If the product has been demonstrated during development to have consistently rapid drug release characteristics, exclusion of particle size controls from the specification may be proposed.

Particle size distribution testing may also be proposed in place of dissolution testing, when development studies demonstrate that particle size is the primary factor influencing dissolution; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper, and/or lower particle size limits should be well defined.

Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo and the intended use of the product. The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

(m) *Redispersibility:* For injectable suspensions, which settle on storage (produce sediment), acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate procedure. The procedure (mechanical or manual) should be indicated. Time required to achieve resuspension by the indicated procedure should be clearly defined. Data generated during product development may be sufficient to justify skip lot testing, or elimination of this attribute from the specification may be proposed.

(n) *Reconstitution time:* Acceptance criteria for reconstitution time should be provided for all parenteral products, which require reconstitution. The choice of diluent should be justified. Data generated during product development and process validation may be sufficient to justify skip lot testing or elimination of this attribute from the specification for rapidly dissolving products.

GLOSSARY

The following definitions are presented for the purpose of this guideline.

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

Chiral—Not superimposable with its mirror image, as applied to molecules, conformations, and macroscopic objects, such as crystals. The term has been extended to samples of substances whose molecules are chiral, even if the macroscopic assembly of such molecules is racemic.

Combination Product—A drug product which contains more than one drug substance.

Degradation Product—A molecule resulting from a chemical change in the drug molecule brought about over time and/or by the action of for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Also called decomposition product.

Delayed Release—Release of a drug (or drugs) at a time other than immediately following oral administration.

Enantiomers—Compounds with the same molecular formula as the drug substance, which differ in the spatial arrangement of atoms within the molecule and are nonsuperimposable mirror images.

Extended Release—Products which are formulated to make the drug available over an extended period after administration.

Highly Water Soluble Drugs—Drugs with a dose/solubility volume of less than or equal to 250 mL over a pH range of 1.2 to 6.8. (e.g., Compound A has as its lowest solubility at 37°C± 0.5°C, 1.0 mg/mL at pH 6.8, and is available in 100-, 200-, and 400-mg strengths. This drug would be considered a low solubility drug as its dose/solubility volume is greater than 250 mL (400 mg/1.0 mg/mL = 400 mL).

Immediate Release—Allows the drug to dissolve in the gastrointestinal contents, with no intention of delaying or prolonging the dissolution or absorption of the drug.

Impurity—(1) Any component of the new drug substance which is not the chemical entity defined as the new drug substance. (2) Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product.

Identified Impurity—An impurity for which a structural characterization has been achieved.

In-Process Tests—Tests which may be performed during the manufacture of either the drug substance or drug product, rather than as part of the formal battery of tests which are conducted prior to release.

Modified Release—Dosage forms whose drug-release characteristics of time course and/or location are chosen to accomplish therapeutic or convenience objectives not offered by conventional dosage forms such as a solution or an immediate release dosage form. Modified release solid oral dosage forms include both delayed and extended release drug products.

New Drug Product—A pharmaceutical product type, for example, tablet, capsule, solution, cream, etc., which has not previously been registered in a region or Member State, and which contains a drug ingredient generally, but not necessarily, in association with excipients.

New Drug Substance—The designated therapeutic moiety, which has not previously been registered in a region or Member State (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved drug substance.

Polymorphism—The occurrence of different crystalline forms of the same drug substance. This may include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.

Quality—The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity.

Racemate—A composite (solid, liquid, gaseous, or in solution) of equimolar quantities of two enantiomeric species. It is devoid of optical activity.

Rapidly Dissolving Products—An immediate release solid oral drug product is considered rapidly dissolving when not less than 80% of the label amount of the drug substance dissolves within 15 minutes in each of the following media: (1) pH 1.2, (2) pH 4.0, and (3) pH 6.8.

Reagent—A substance, other than a starting material or solvent, which is used in the manufacture of a new drug substance.

Solvent—An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance or the manufacture of a new drug product.

Specification—A list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance or drug product should conform to be considered acceptable for its intended use. "Conformance to specifications" means that the drug substance and/or drug product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.

Specific Test—A test which is considered to be applicable to particular new drug substances or particular new drug products depending on their specific properties and/or intended use.

Specified Impurity—An identified or unidentified impurity that is selected for inclusion in the new drug substance or new drug product specification and is individually listed and limited in order to assure the quality of the new drug substance or new drug product.

Unidentified Impurity—An impurity which is defined solely by qualitative analytical properties, (e.g., chromatographic retention time).

Universal Test—A test which is considered to be potentially applicable to all new drug substances, or all new drug products; for example, appearance, identification, assay, and impurity tests.

REFERENCES

International Conference on Harmonisation. *Impurities in New Drug Substances*, 1995.

International Conference on Harmonisation; *Impurities in New Drug Products*, 1996.

International Conference on Harmonisation; *Stability Testing of New Drug Substances and Products*, 1994.

International Conference on Harmonisation; *Text on Validation of Analytical Procedures*, 1994.

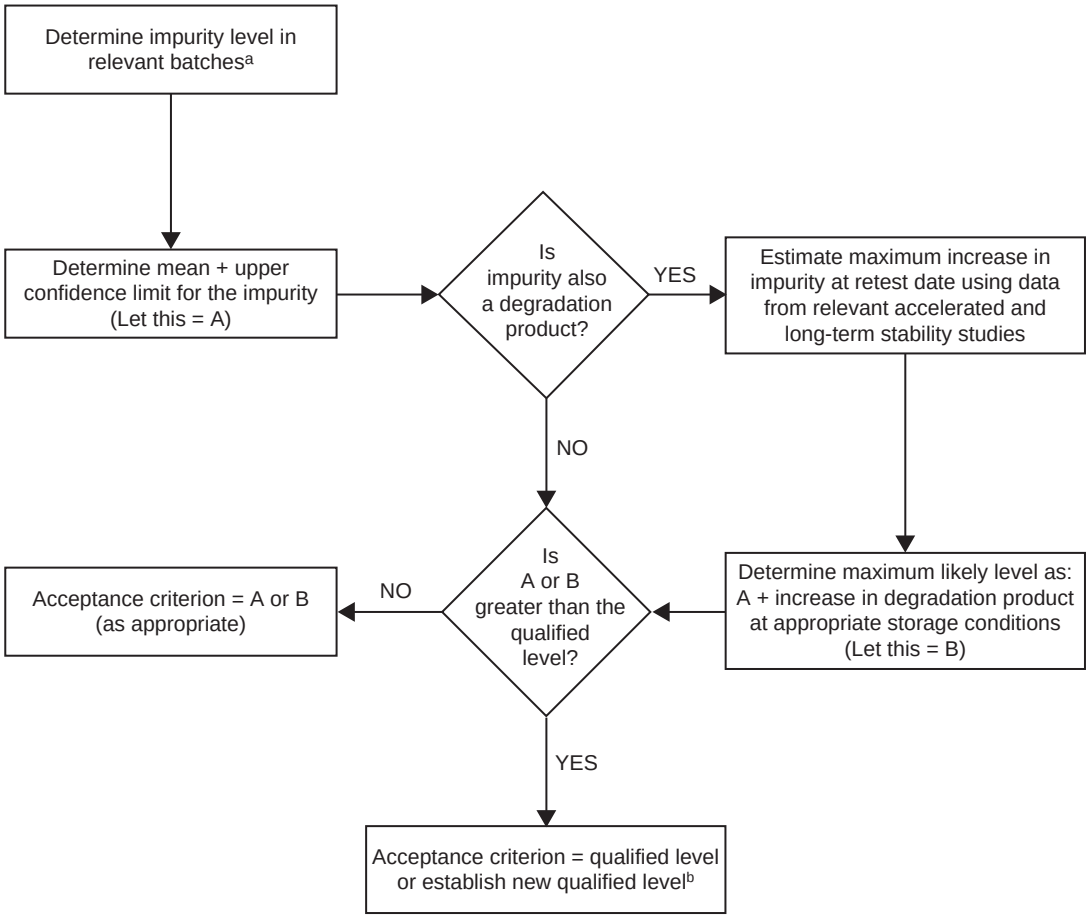
International Conference on Harmonisation; *Validation of Analytical Procedures: Methodology*, 1996.

International Conference on Harmonisation, *Residual Solvents in Pharmaceuticals*, 1996.

International Conference on Harmonisation, *Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products*, 1999.

IV. ATTACHMENTS

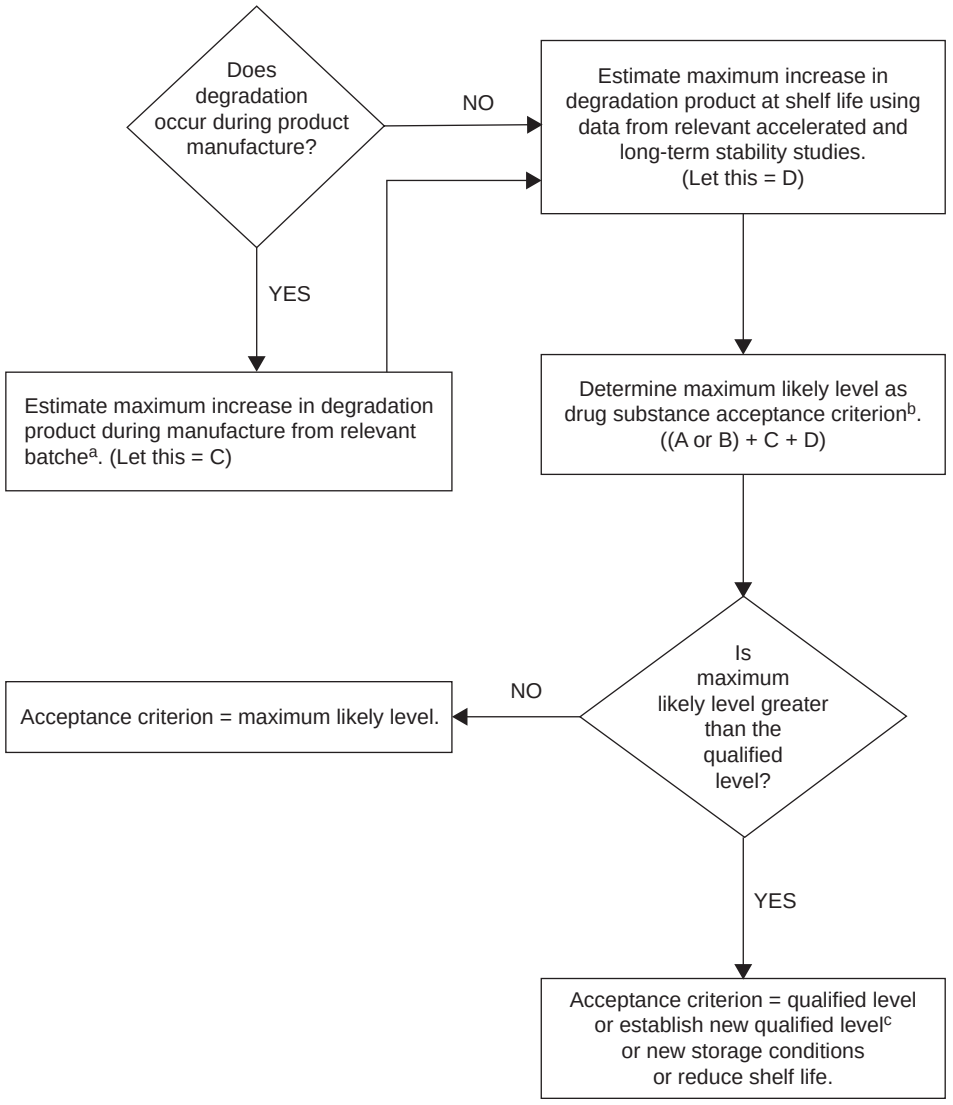
Decision Tree #1: Establishing Acceptance Criterion
for a Specified Impurity in a New Drug Substance



[a]Relevant batches are those from development, pilot and scale-up studies.
[b]Refer to ICH Guideline on Impurities in New Drug Substances.

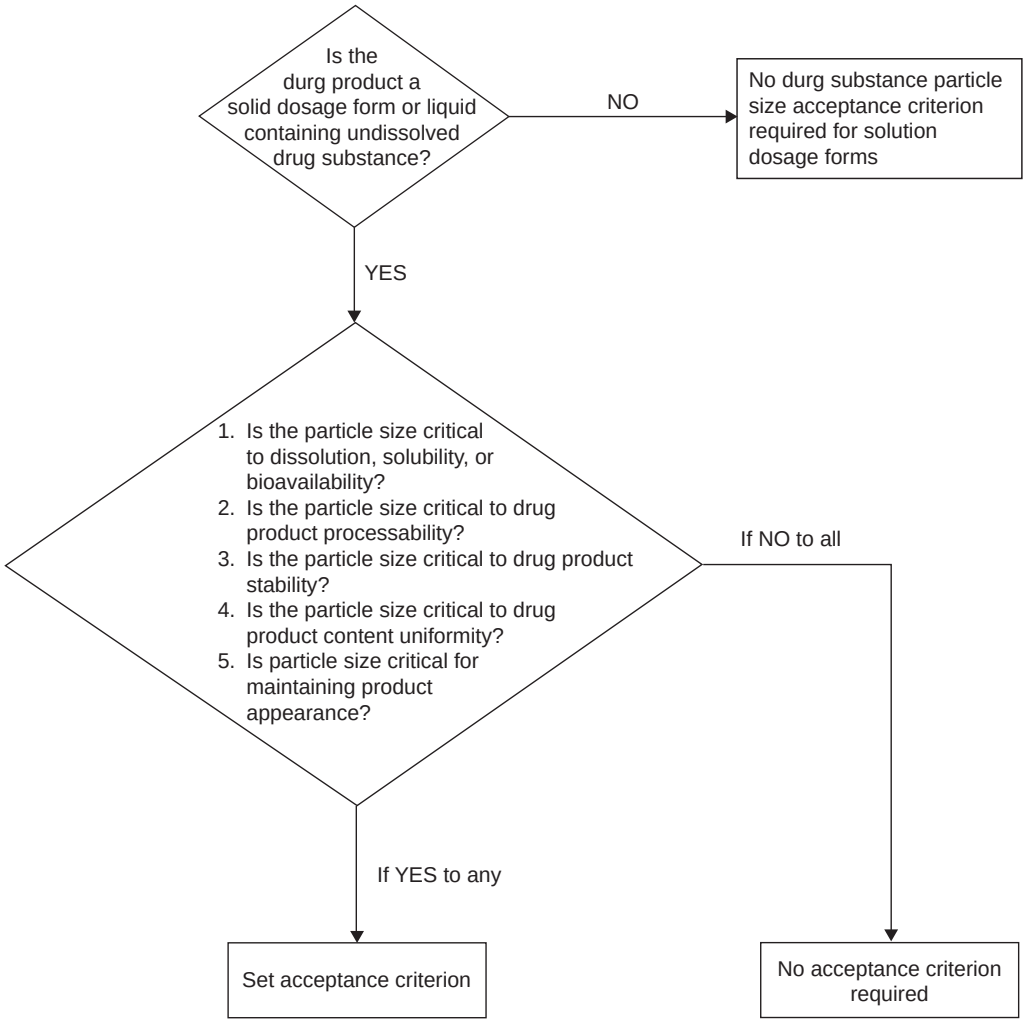
Definition: upper confidence limit = three times the standard deviation of batch analysis data.

Decision Tree #2: Establishing Acceptance Criterion
for a Degradation Product in a New Drug Product

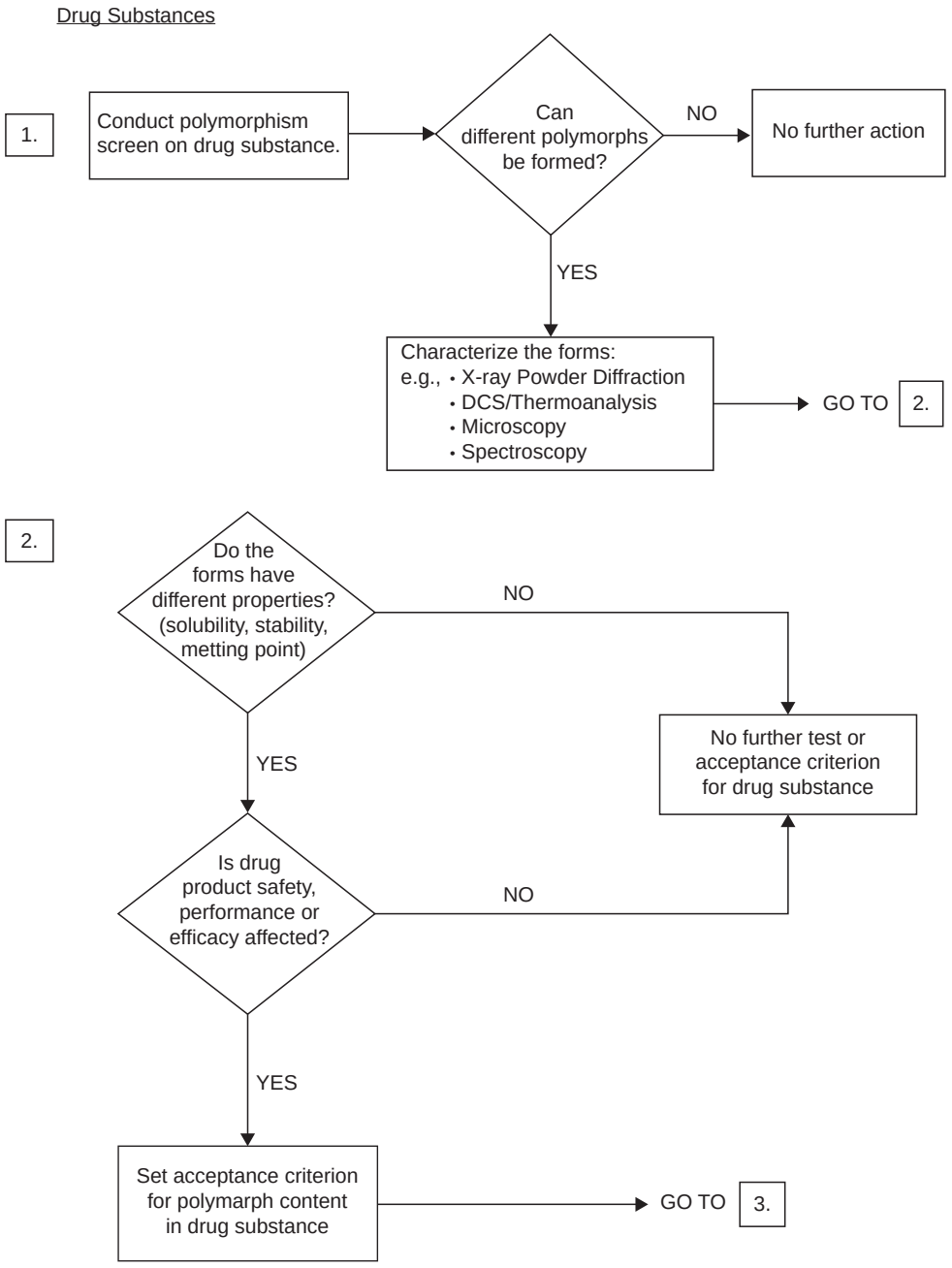


[a]Relevant batches are those from development, pilot and scale-up studies.
[b]Refer to Decision Tree 1 for information regarding A and B.
[c]Refer to ICH Guideline on Impurities in New Drug Products.

Decision Tree #3: Setting Acceptance Criteria for Drug Substance Particle size Distribution



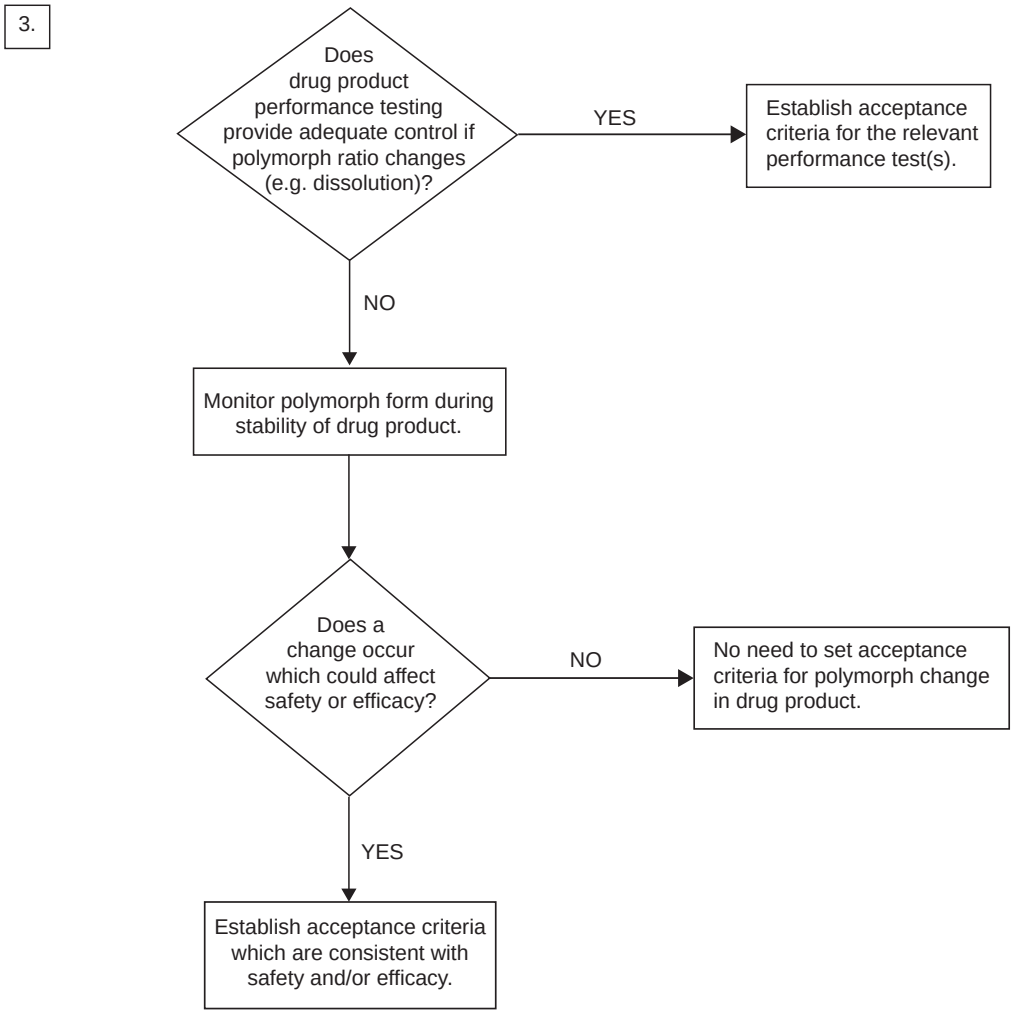
Decision Tree #4: Investigating the Need to set Acceptance Criteria for Polymorphism in Drug Substances and Drug Products



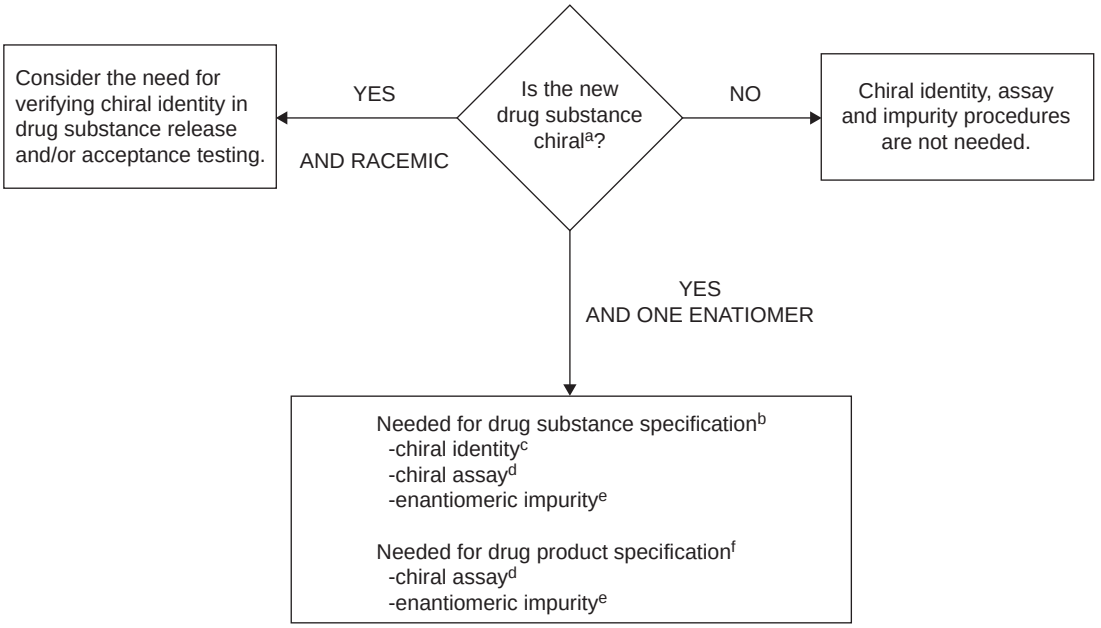
Decision Tree #4: Investigating the Need to Set Acceptance Criteria for Polymorphism in Drug Substances and Drug Products

Drug Product - Solid Dosage Form or Liquid Containing Undissolved Drug Substance

N.B.: Undertake the following processes only technically possible to measure polymorph content in the drug product.



Decision Tree #5: Establishing Identity, Assay and Enantiomeric Impurity Procedures for Chiral New Drug Substances and New Drug Products Containing Chiral Drug Substances



[a]Chiral substances of natural origin are not addressed in this Guideline.

[b]As with other impurities arising in and from raw materials used in drug substance synthesis, control of chiral quality could be established alternatively by applying limits to appropriate starting materials or intermediates when justified from developmental studies. This essentially will be the case when there are multiple chiral centers (e.g., three or more), or when control as a step prior to production of the final drug substance is desirable.

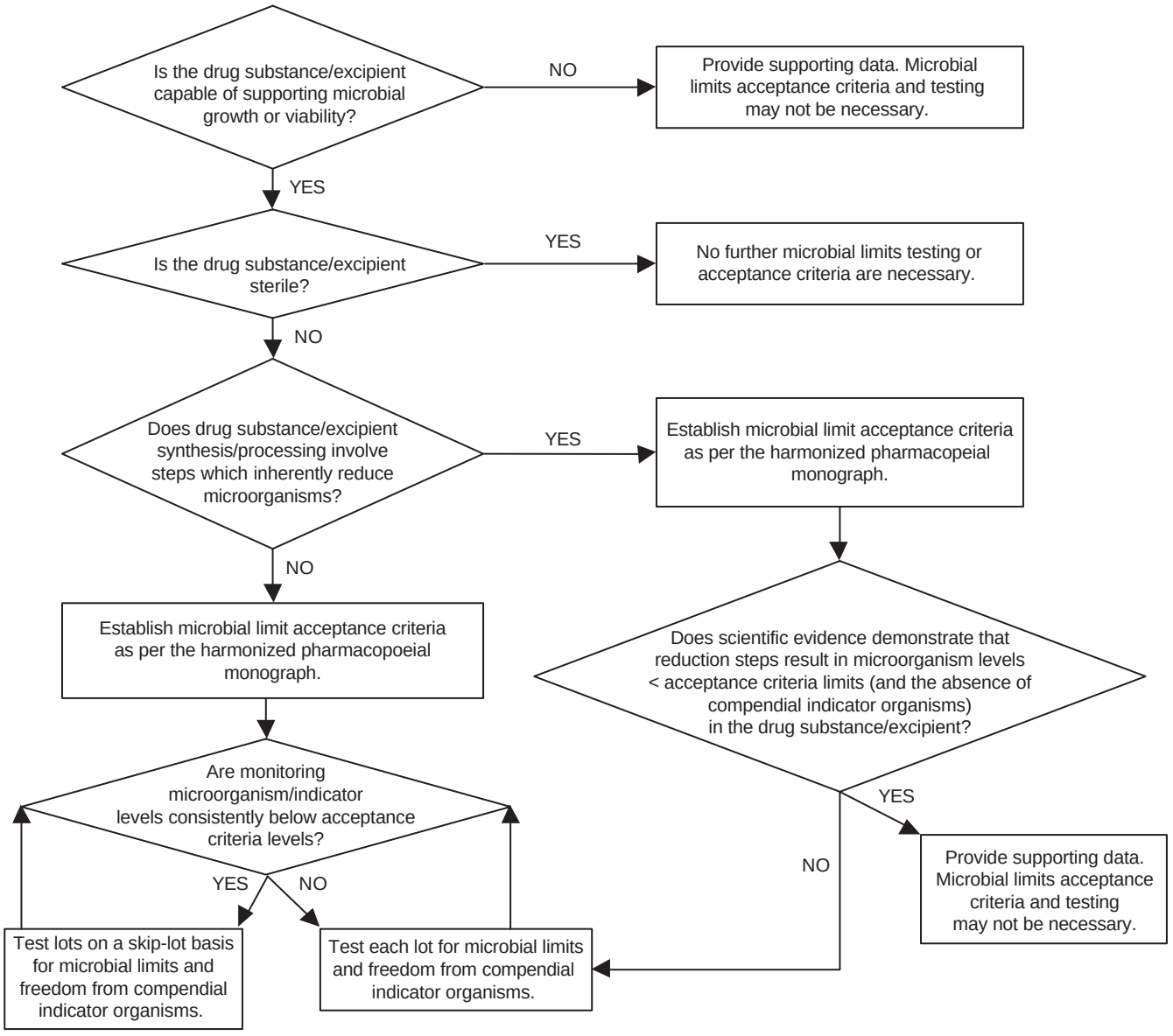
[c]A chiral assay or an enantiomeric impurity procedure may be acceptable in lieu of a chiral identity procedure.

[d]An achiral assay combined with a method for controlling the opposite enantiomer is acceptable in lieu of a chiral assay.

[e]The level of the opposite enantiomer of the drug substance may be derived from chiral assay data or from a separate procedure.

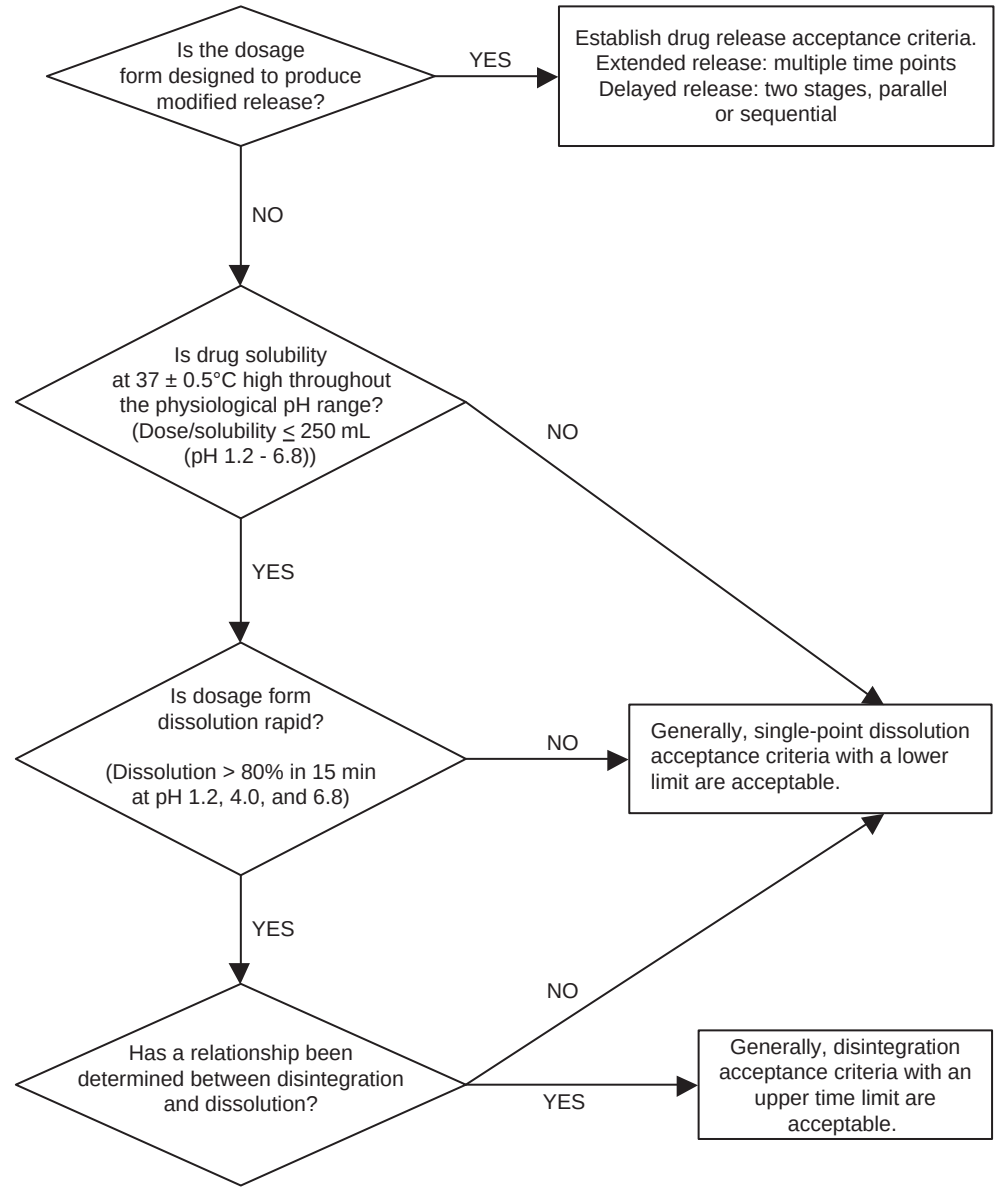
[f]Stereospecific testing of drug product may not be necessary if racerization has been demonstrated to be insignificant during drug product manufacture and during storage of the finished dosage form.

Decision Tree #6: Microbiological Quality Attributes of Drug Substance and Excipients



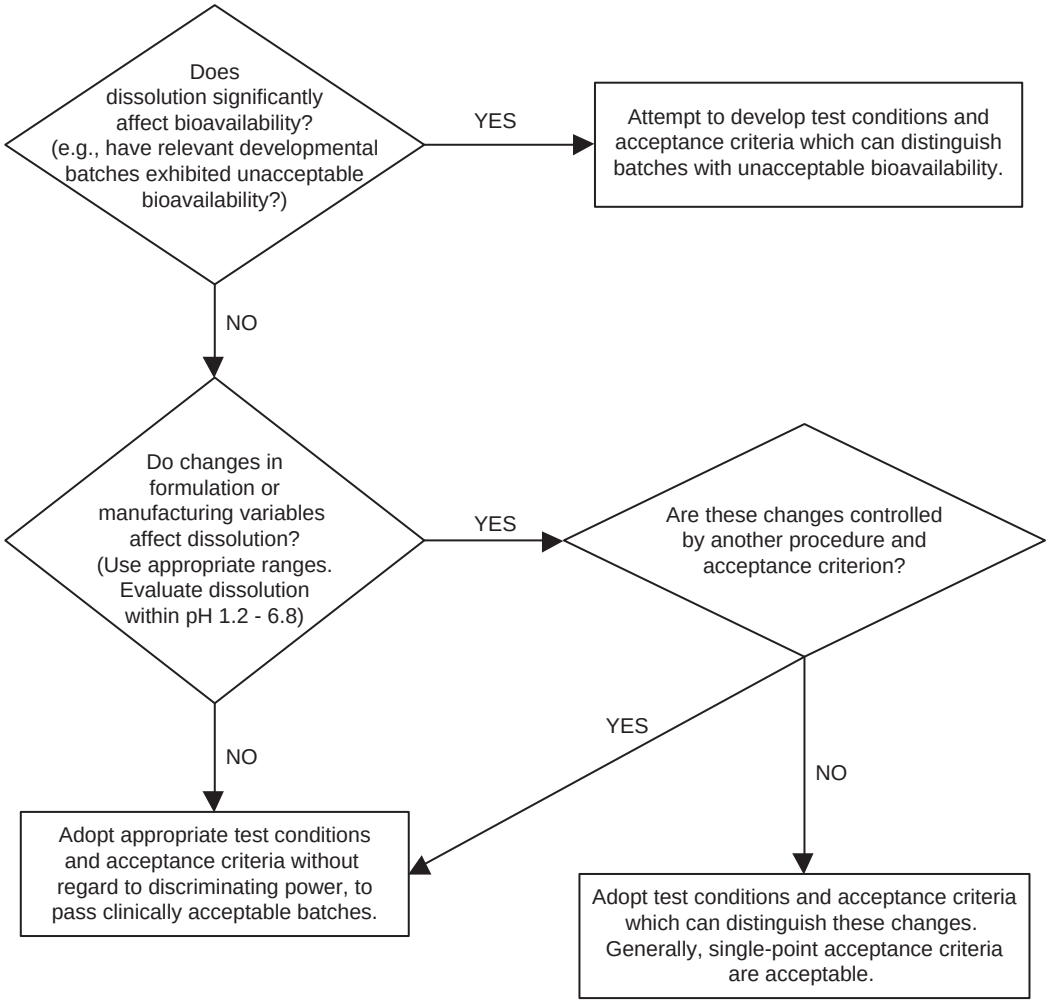
Decision Trees #7: Setting Acceptance Criteria for Drug Product Dissolution

1. What type of drug release acceptance criteria are appropriate?

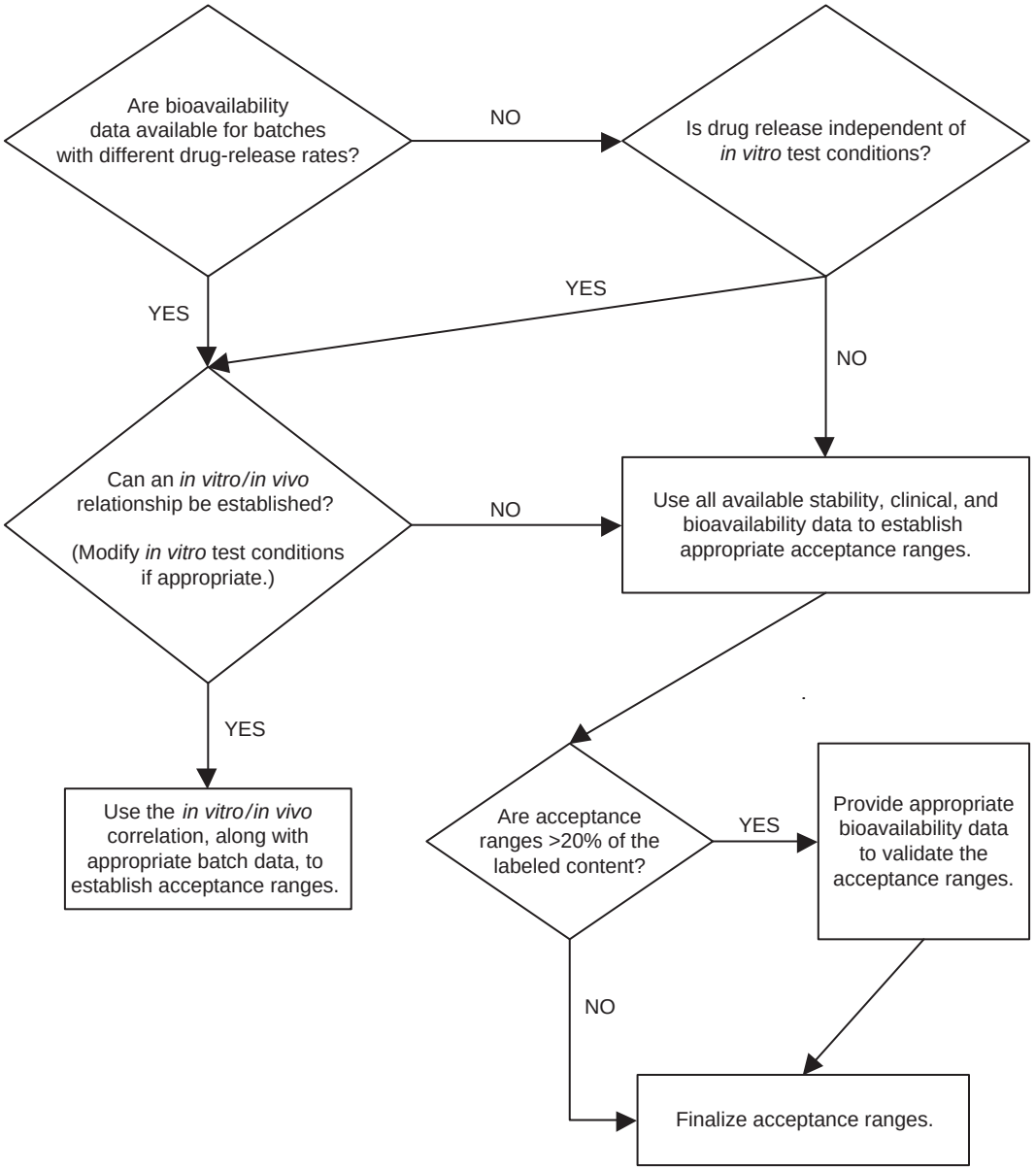


Continued on next page.

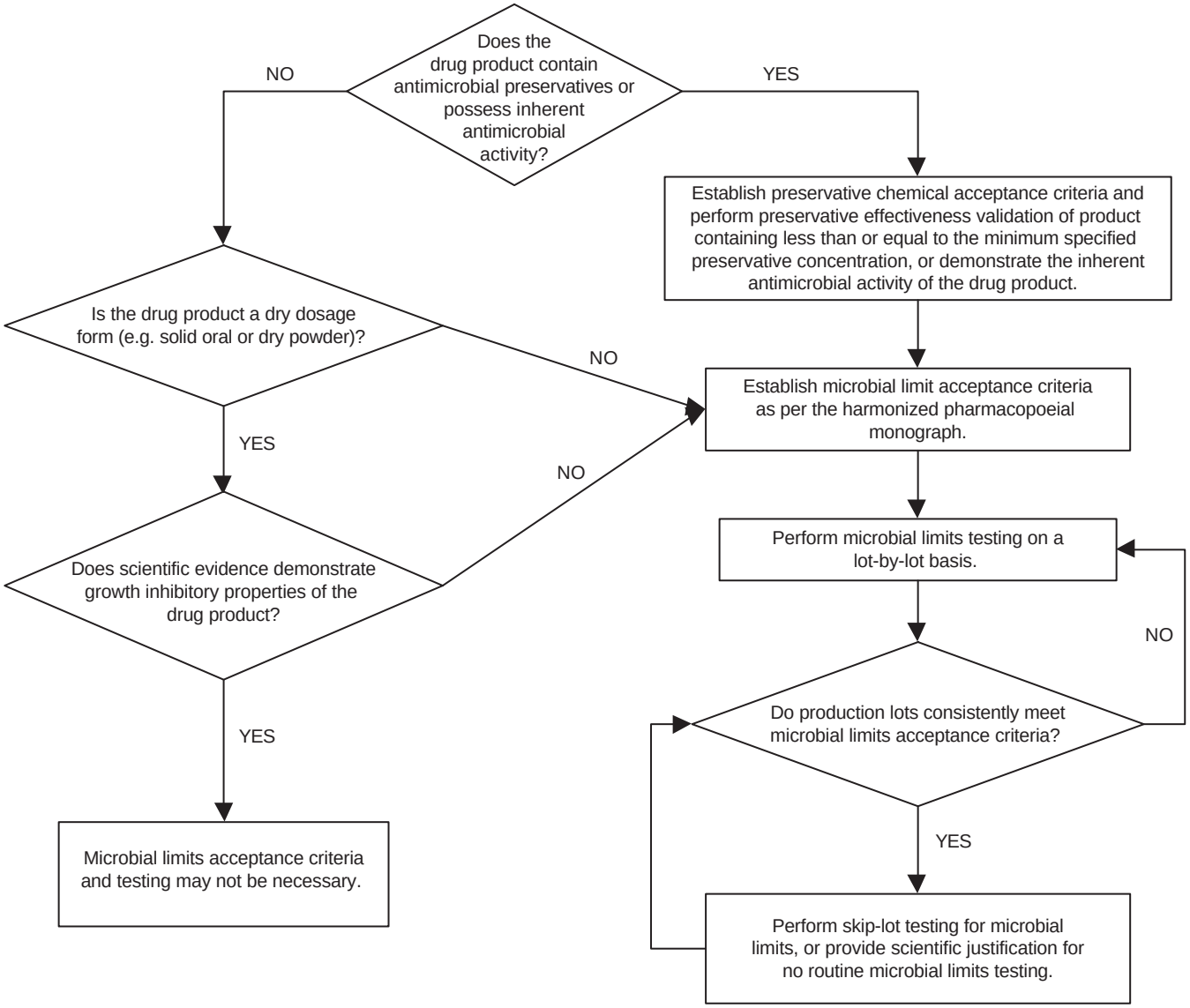
2. What specific test conditions and acceptance criteria are appropriate? [immediate release]



3. What are appropriate acceptance ranges? [extended release]



Decision Tree #8: Microbiological Attributes of Nonsterile Drug Products



14

Skin Irritation and Sensitization Testing of Generic Transdermal Drug Products

To fully evaluate the equivalence of a transdermal product for an abbreviated new drug application to a reference-listed drug, skin irritation and sensitization should be assessed because the condition of the skin may affect the absorption of a drug from a transdermal system. More severe skin irritation may affect the efficacy or safety of the product.

Transdermal products have properties that may lead to skin irritation or sensitization. The delivery system, or the system in conjunction with the drug substance, may cause these reactions. In the development of transdermal products, dermatologic adverse events are evaluated primarily with animal studies and safety evaluations in the context of large clinical trials generally associated with the submission of new drug applications. Separate skin irritation and skin sensitization studies also are used for this purpose. These latter studies are designed to detect irritation and sensitization under conditions of maximal stress and may be used during the assessment of transdermal drug products for abbreviated new drug applications.

I. STUDY DESIGNS

Recommended designs for skin irritation and skin sensitization studies for the comparative evaluation of transdermal drug products for an abbreviated new drug application are delineated below. Other proposals for studies may be suggested, but potential applicants are advised to consult the Office of Generic Drugs about alternative study designs before the initiation of such a study.

A. Recommendations for a Cumulative Skin Irritation Study

1. Sample Size
The sample size should be 30 subjects.

2. Exclusion Criteria
Dermatologic disease that might interfere with the evaluation of test site reaction should be grounds for exclusion.

3. Duration of Study
The study should last for 22 days.

4. Study Design
The study should be a randomized, controlled, repeat patch test study that compares the test patch with the innovator patch. Placebo patches (transdermal patch without active drug substance) or high- and low-irritancy controls (e.g., sodium lauryl sulfate 0.1% and 0.9% saline) can be included as additional test arms.

5. Patch Application
Each subject applies one of each of the patches to be tested. Test sites should be randomized among patients. Patches should be applied for 23 hours (±1 hour) daily for 21 days to the same skin site. At each patch removal, the site should be evaluated for reaction and the patch reapplied.

Application of a test patch should be discontinued at a site if predefined serious reactions occur at the site of repeated applications. Application at a different site may subsequently be initiated.

6. Evaluations
Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale.

Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritations. (See Appendix A for an example of a scoring system that can be used.) The percentage adherence of the transdermal patches should be assessed using a 5-point scale (see Appendix B).

7. Data Presentation and Analysis
Individual daily observations should be provided, as well as a tabulation that presents the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score, the total cumulative irritation score, and the number of days until sufficient irritation occurred to preclude patch application for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed (see Appendix C).

B. Recommendations for a Skin Sensitization Study (Modified Draize Test)

1. Sample Size
Two hundred subjects should be sampled.

2. Exclusion Criteria
Exclusion criteria include

a. dermatologic disease that might interfere with the evaluation of the test site reactions and
b. use of systemic or topical analgesics or antihistamines within 72 hours of study enrollment or systemic or topical corticosteroids within 3 weeks of study enrollment

3. Duration of Study
The study should last for 6 weeks.

4. Study Design
The study should be a randomized, controlled study on three test products: the test transdermal patch, the innovator patch, and the placebo patch (transdermal patch without the active drug substance).

5. Patch Application
Test sites should be randomized among patients. The study is divided into three sequential periods.

a. Induction Phase
Applications of the test materials should be made to the same skin sites three times weekly for 3 weeks, for a total of nine applications. The patches should remain in place for 48 hours on weekdays and for 72 hours on weekends. Scoring of skin reactions and patch adherence should be performed by a trained and blinded observer at each patch removal, using an appropriate scale.

Dermal reactions should be scored on a scale that describes the amount of erythema, edema, and other features indicative of irritation. (See Appendix A for an example of a scoring system that can be used.) The percentage adherence of the transdermal patches should be assessed using a 5-point scale (see Appendix B).

b. Rest Phase
The induction phase is followed by a rest phase of 2 weeks, during which no applications are made.

c. Challenge Phase
The patches should be applied to new skin sites for 48 hours. Evaluation of skin reactions should be made by a trained blinded observer at 30 minutes and at 24, 48, and 72 hours after patch removal. (See Appendix A for an example of a scoring system that can be used.)

6. Data Presentation and Analysis
The individual daily observations should be provided, as well as a tabulation of the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score and the total cumulative irritation score for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed.

A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of contact sensitization.

C. Combined Studies
Alternatively, the cumulative skin irritation study and the skin sensitization study can be combined into a single study. The study design would be identical to that described for the skin sensitization study (see section I.B), except that patch application during the induction phase should be daily for 23 hours (±1 hour) each day over 21 days.

Appendix A: Skin Irritation Scoring Systems
The following scoring system for irritation or sensitization reactions is included as an example of a scoring system that can be used for these studies. Other validated scoring systems can be used in quantifying skin reactions. The inclusion of this system should not be interpreted as an endorsement of the system by the agency. It is provided as an example only.

1. Dermal response:
   0 = no evidence of irritation
   1 = minimal erythema, barely perceptible
   2 = definite erythema, readily visible; minimal edema or minimal papular response
   3 = erythema and papules
   4 = definite edema
   5 = erythema, edema, and papules
   6 = vesicular eruption
   7 = strong reaction spreading beyond test site
2. Other effects:
   A = slight glazed appearance
   B = marked glazing
   C = glazing with peeling and cracking
   D = glazing with fissures
   E = film of dried serous exudate covering all or part of the patch site
   F = small petechial erosions or scabs

Appendix B: Adhesion Score
The following scoring system is included as an example of a scoring system that can be used for this type of study. Other validated scoring systems may be equally effective in quantifying comparative adhesion of transdermal systems. The inclusion of this system is not to be interpreted as an endorsement of the system by the agency. It is provided as an example only.

An estimate of the adherence of the transdermal system will be rated as follows:

0 ≥ 90% adhered (essentially no lift off the skin)
1 ≥ 75% to <90% adhered (some edges only lifting off the skin)
2 ≥ 50% to <75% adhered (less than half of the system lifting off the skin)
3 ≥ 50% adhered but not detached (more than half the system lifting off the skin without falling off)
4 = patch detached (patch completely off the skin)

Appendix C: Statistics
To be considered equivalent for a particular response, the average response for the generic (μ_T) should be between 80% and 125% of the average response for the innovator (μ_R). It is recommended that the response of the generic be equivalent to or better than the innovator. This implies a one-sided test.

For a variable for which low scores are better, such as mean irritation score or total cumulative irritation score, the hypotheses would be

$$H_0: \mu_T/\mu_R > 1.25$$

$$H_1: \mu_T/\mu_R \geq 1.25$$

which (assuming that $\mu_R > 0$) implies

$$H_0: \mu_T - 1.25\ \mu_R > 0$$

$$H_1: \mu_T - 1.25\ \mu_R \geq 0$$

The null hypothesis H_0 will be rejected when the upper limit of the 90% confidence interval (that is, the 95% upper confidence bound) for the quantity $\mu_T - 1.25\ \mu_R$ is less than or equal to zero.

For a variable for which high values are better, such as time to removal score, the hypotheses would be

$$H_0: \mu_T/\mu_R < 0.80$$

$$H_1: \mu_T/\mu_R \geq 0.80$$

which (assuming that $\mu_R > 0$) implies

$$H_0: \mu_T - 0.80\ \mu_R < 0$$

$$H_1: \mu_T - 0.80\ \mu_R \geq 0$$

The null hypothesis H_0 will be rejected in this case when the lower limit of the 90% confidence interval (i.e., the 95% lower confidence bound) for the quantity $_T\ 0.80\ _R$ is greater than or equal to zero.

In either case, if the null hypothesis H_0 is rejected, the generic should be considered equivalent or better than the innovator.

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Holdiness MR (1989). A review of contact dermatitis associated with transdermal therapeutic systems. Contact Dermatitis 20(1): 3–9.

Lanman BM, Elvers EB, Howard CJ (1968). The role of human patch testing in a product development program. Joint Conference on Cosmetic Sciences, The Toilet Goods Association (currently, the Cosmetic, Toiletry and Fragrance Association), April, 21–23, 1968; Washington, DC.

Patel SM, Patrick E, Maibach HI (1977). Animal, human, and *in vitro* test methods for predicting skin irritation. In: Marzulli FN, Maibach HI, eds. Dermatotoxicology, 5th ed. New York, NY: Taylor and Francis, chap. 33.

15

Impurities in New Drug Substances

I. PREAMBLE

This document is intended to provide guidance for registration applications on the content and qualification of impurities in new drug substances produced by chemical syntheses and not previously registered in a region or member state. It is not intended to apply to new drug substances used during the clinical research stage of development. The following types of drug substances are not covered in this guideline: biological/biotechnological, peptide, oligonucleotide, radiopharmaceutical, fermentation product and semisynthetic products derived therefrom, herbal products, and crude products of animal or plant origin.

Impurities in new drug substances are addressed from the following two perspectives:

Chemistry Aspects include classification and identification of impurities, report generation, listing of impurities in specifications, and a brief discussion of analytical procedures.

Safety Aspects include specific guidance for qualifying those impurities that were not present, or were present at substantially lower levels, in batches of a new drug substance used in safety and clinical studies.

II. CLASSIFICATION OF IMPURITIES

Impurities can be classified into the following categories:

- Organic impurities (process and drug related)
- Inorganic impurities
- Residual solvents

Organic impurities can arise during the manufacturing process and/or storage of the new drug substance. They can be identified or unidentified, volatile or non-volatile, and include

- starting materials;
- by-products;
- intermediates;
- degradation products; and
- reagents, ligands, and catalysts.

Inorganic impurities can result from the manufacturing process. They are normally known and identified and include

- reagents, ligands, and catalysts;
- heavy metals or other residual metals;
- inorganic salts; and
- other materials (e.g., filter aids, charcoal).

Solvents are inorganic or organic liquids used as vehicles for the preparation of solutions or suspensions in the synthesis of a new drug substance. Since these are generally of known toxicity, the selection of appropriate controls is easily accomplished (see ICH Guideline Q3C on Residual Solvents).

Excluded from this document are (1) extraneous contaminants that should not occur in new drug substances and are more appropriately addressed as GMP issues, (2) polymorphic forms, and (3) enantiomeric impurities.

III. RATIONALE FOR THE REPORTING AND CONTROL OF IMPURITIES

A. Organic Impurities

The applicant should summarize the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the new drug substance. This summary should be based on sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products. This discussion can be limited to those impurities that might reasonably be expected based on knowledge of the chemical reactions and conditions involved.

In addition, the applicant should summarize the laboratory studies conducted to detect impurities in the new drug substance. This summary should include test results of batches manufactured during the development process and batches from the proposed commercial process, as well as the results of stress testing (see ICH Guideline Q1A on Stability) used to identify potential impurities arising during storage. The impurity profile of the drug substance batches intended for marketing should be compared with those used in development, and any differences discussed.

The studies conducted to characterize the structure of actual impurities present in the new drug substance at a level greater than (>) the identification threshold given in Attachment 1 (e.g., calculated using the response factor of the drug substance) should be described. Note that any impurity at a level greater than (>) the identification threshold in any batch manufactured by the proposed commercial process should be identified. In addition, any degradation product observed in stability studies at recommended storage conditions at a level greater than (>) the identification threshold should be identified. When identification of an impurity is not feasible, a summary of the laboratory studies demonstrating the unsuccessful effort should be included in the application. Where attempts have been made to identify impurities present at levels of not more than (≤) the identification thresholds, it is useful also to report the results of these studies.

Identification of impurities present at an apparent level of not more than (≤) the identification threshold is generally not considered necessary. However, analytical procedures should be developed for those potential impurities that are expected to be unusually potent, producing toxic or pharmacological effects at a level not more than (≤) the identification threshold. All impurities should be qualified as described later in this guideline.

B. Inorganic Impurities

Inorganic impurities are normally detected and quantified using pharmacopoeial or other appropriate procedures. Carryover of catalysts to the new drug substance should be evaluated during development. The need for inclusion or exclusion of inorganic impurities in the new drug substance specification should be discussed. Acceptance criteria should be based on pharmacopoeial standards or known safety data.

C. Solvents

The control of residues of the solvents used in the manufacturing process for the new drug substance should be discussed and presented according to the ICH Q3C Guideline for Residual Solvents.

IV. ANALYTICAL PROCEDURES

The registration application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantification of impurities (see ICH Q2A and Q2B Guidelines for Analytical Validation). Technical factors (e.g., manufacturing capability and control methodology) can be considered as part of the justification for selection of alternative thresholds based on manufacturing experience with the proposed commercial process. The use of two decimal places for thresholds (see Attachment 1) does not necessarily reflect the precision of the analytical procedure used for routine quality control purposes. Thus, the use of lower precision techniques (e.g., thin-layer chromatography) can be acceptable where justified and appropriately validated. Differences in the analytical procedures used during development and those proposed for the commercial product should be discussed in the registration application.

The quantitation limit for the analytical procedure should be not more than ($\leq$) the reporting threshold.

Organic impurity levels can be measured by a variety of techniques, including those that compare an analytical response for an impurity to that of an appropriate reference standard or to the response of the new drug substance itself. Reference standards used in the analytical procedures for control of impurities should be evaluated and characterized according to their intended uses. The drug substance can be used as a standard to estimate the levels of impurities. In cases where the response factors of the drug substance and the relevant impurity are not close, this practice can still be appropriate, provided a correction factor is applied or the impurities are, in fact, being overestimated. Acceptance criteria and analytical procedures used to estimate identified or unidentified impurities can be based on analytical assumptions (e.g., equivalent detector response). These assumptions should be discussed in the registration application.

V. REPORTING IMPURITY CONTENT OF BATCHES

Analytical results should be provided in the application for all batches of the new drug substance used for clinical, safety, and stability testing, as well as for batches representative of the proposed commercial process. Quantitative results should be presented numerically, and not in general terms such as "complies," "meets limit," etc. Any impurity at a level greater than (>) the reporting threshold (see Attachment 1) and total impurities observed in these batches of the new drug substance should be reported with the analytical procedures indicated. Below 1.0%, the results should be reported to two decimal places (e.g., 0.06%, 0.13%); at and above 1.0%, the results should be reported to one decimal place (e.g., 1.3%). Results should be rounded using conventional rules (see Attachment 2). A tabulation (e.g., spreadsheet) of the data is recommended. Impurities should be designated by code number or by an appropriate descriptor, for example, retention time. If a higher reporting threshold is proposed, it should be fully justified. All impurities at a level greater than (>) the reporting threshold should be summed and reported as total impurities.

When analytical procedures change during development, reported results should be linked to the procedure used, with appropriate validation information provided. Representative chromatograms should be provided. Chromatograms of representative batches from analytical validation studies showing separation and detectability of impurities (e.g., on spiked samples), along with any other impurity tests routinely performed, can serve as the representative impurity profiles. The applicant should ensure that complete impurity profiles (e.g., chromatograms) of individual batches are available, if requested.

A tabulation should be provided that links the specific new drug substance batch to each safety study and each clinical study in which the new drug substance has been used.

For each batch of the new drug substance, the report should include

- batch identity and size;
- date of manufacture;
- site of manufacture;
- manufacturing process;
- impurity content, individual and total;
- use of batches; and
- reference to analytical procedure used.

VI. LISTING OF IMPURITIES IN SPECIFICATIONS

The specification for a new drug substance should include a list of impurities. Stability studies, chemical development studies, and routine batch analyses can be used to predict those impurities likely to occur in the commercial product. The selection of impurities in the new drug substance specification should be based on the impurities found in batches manufactured by the proposed commercial process. Those individual impurities with specific acceptance criteria included in the specification for the new drug substance are referred to as "specified impurities" in this guideline. Specified impurities can be identified or unidentified.

A rationale for the inclusion or exclusion of impurities in the specification should be presented. This rationale should include a discussion of the impurity profiles observed in the safety and clinical development batches, together with a consideration of the impurity profile of batches manufactured by the proposed commercial process. Specified identified impurities should be included along with specified unidentified impurities estimated to be present at a level greater than (>) the identification threshold given in Attachment 1. For impurities known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the level at which the impurities should be controlled. For unidentified impurities, the procedure used and assumptions made in establishing the level of the impurity should be clearly stated. Specified, unidentified impurities should be

referred to by an appropriate qualitative analytical descriptive label (e.g., "unidentified A," "unidentified with relative retention of 0.9"). A general acceptance criterion of not more than (≤) the identification threshold (Attachment 1) for any unspecified impurity and an acceptance criterion for total impurities should be included.

Acceptance criteria should be set no higher than the level that can be justified by safety data, and should be consistent with the level achievable by the manufacturing process and the analytical capability. Where there is no safety concern, impurity acceptance criteria should be based on data generated on batches of the new drug substance manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variation and the stability characteristics of the new drug substance. Although normal manufacturing variations are expected, significant variation in batch-to-batch impurity levels can indicate that the manufacturing process of the new drug substance is not adequately controlled and validated (see ICH Q6A Guideline on Specifications, Decision Tree no. 1, for establishing an acceptance criterion for a specified impurity in a new drug substance). The use of two decimal places for thresholds (see Attachment 1) does not necessarily indicate the precision of the acceptance criteria for specified impurities and total impurities.

In summary, the new drug substance specification should include, where applicable, the following list of impurities:

Organic Impurities
- Each specified identified impurity
- Each specified unidentified impurity
- Any unspecified impurity with an acceptance criterion of not more than (≤) the identification threshold
- Total impurities

Residual Solvents
Inorganic Impurities

VII. QUALIFICATION OF IMPURITIES

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified. The applicant should provide a rationale for establishing impurity acceptance criterion that includes safety considerations. The level of any impurity present in a new drug substance that has been adequately tested in safety and/or clinical studies would be considered qualified. Impurities that are also significant metabolites present in animal and/or human studies are generally considered qualified. A level of a qualified impurity higher than that present in a new drug substance can also be justified based on an analysis of the actual amount of impurity administered in previous relevant safety studies.

If data are unavailable to qualify the proposed acceptance criterion of an impurity, studies to obtain such data can be appropriate when the usual qualification thresholds given in Attachment 1 are exceeded.

Higher or lower thresholds for qualification of impurities can be appropriate for some individual drugs based on scientific rationale and level of concern, including drug class effects and clinical experience. For example, qualification can be especially important when there is evidence that such impurities in certain drugs or therapeutic classes have previously been associated with adverse reactions in patients. In these instances, a lower qualification threshold can be appropriate. Conversely, a higher qualification threshold can be appropriate for individual drugs when the level of concern for safety is less than usual based on similar considerations (e.g., patient population, drug class effects, clinical considerations). Proposals for alternative thresholds would be considered on a case-by-case basis.

The "Decision Tree for Identification and Qualification" (Attachment 3) describes considerations for the qualification of impurities when thresholds are exceeded. In some cases, decreasing the level of impurity to not more than the threshold can be simpler than providing safety data. Alternatively, adequate data could be available in the scientific literature to qualify an impurity. If neither is the case, additional safety testing should be considered. The studies considered appropriate to qualify an impurity will depend on a number of factors, including the patient population, daily dose, and route and duration of drug administration. Such studies can be conducted on the new drug substance containing the impurities to be controlled, although studies using isolated impurities can sometimes be appropriate.

Although this guideline is not intended to apply during the clinical research stage of development, in the later stages of development the thresholds in this guideline can be useful in evaluating new impurities observed in drug substance batches prepared by the proposed commercial process. Any new impurity observed in later stages of development should be identified if its level is greater than (>) the identification threshold given in Attachment 1 (see the "Decision Tree for Identification and Qualification" in Attachment 3). Similarly, the qualification of the impurity should be considered if its level is greater than (>) the qualification threshold given in Attachment 1. Safety assessment studies to qualify an impurity should compare the new drug substance containing a representative amount of the new impurity with previously qualified material. Safety assessment studies using a sample of the isolated impurity can also be considered.

GLOSSARY

Chemical Development Studies—Studies conducted to scale up, optimize, and validate the manufacturing process for a new drug substance.

Enantiomeric Impurity—A compound with the same molecular formula as the drug substance that differs in the spatial arrangement of atoms within the molecule and is a nonsuperimposable mirror image.

Extraneous Contaminant—An impurity arising from any source extraneous to the manufacturing process.

Herbal Products—Medicinal products containing, exclusively, plant material and/or vegetable drug preparations as active ingredients. In some traditions, materials of inorganic or animal origin can also be present.

Identified Impurity—An impurity for which a structural characterization has been achieved.

Identification Threshold—A limit above (>) which an impurity should be identified.

Impurity—Any component of the new drug substance that is not the chemical entity defined as the new drug substance.

Impurity Profile—A description of the identified and unidentified impurities present in a new drug substance.

Intermediate—A material produced during steps of the synthesis of a new drug substance that undergoes further chemical transformation before it becomes a new drug substance.

Ligand—An agent with a strong affinity to a metal ion.

New Drug Substance—The designated therapeutic moiety that has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It can be a complex, simple ester, or salt of a previously approved drug substance.

Polymorphic Forms—Different crystalline forms of the same drug substance. These can include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms.

Potential Impurity—An impurity that theoretically can arise during manufacture or storage. It may or may not actually appear in the new drug substance.

Qualification—The process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

Qualification Threshold—A limit above (>) which an impurity should be qualified.

Reagent—A substance other than a starting material, intermediate, or solvent that is used in the manufacture of a new drug substance.

Reporting Threshold—A limit above (>) which an impurity should be reported. Reporting threshold is the same as reporting level in Q2B.

Solvent—An inorganic or an organic liquid used as a vehicle for the preparation of solutions or suspensions in the synthesis of a new drug substance.

Specified Impurity—An impurity that is individually listed and limited with a specific acceptance criterion in the new drug substance specification. A specified impurity can be either identified or unidentified.

Starting Material—A material used in the synthesis of a new drug substance that is incorporated as an element into the structure of an intermediate and/or of the new drug substance. Starting materials are normally commercially available and of defined chemical and physical properties and structure.

Unidentified Impurity—An impurity for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Unspecified Impurity—An impurity that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the new drug substance specification.

Attachment 1: Thresholds

Maximum Daily Dose[a]	Reporting Threshold[b,c]	Identification Threshold[c]	Qualification Threshold[c]
≤ 2 g/day	0.05%	0.10% or 1.0 mg/day intake (whichever is lower)	0.15% or 1.0 mg/day intake (whichever is lower)
> 2 g/day	0.03%	0.05%	0.05%

[a]The amount of drug substance administered per day.
[b]Higher reporting thresholds should be scientifically justified.
[c]Lower thresholds can be appropriate if the impurity is unusually toxic.

Attachment 2: Illustration of Reporting Impurity Results for Identification and Qualification in an Application

The attachment is only illustrative and is not intended to serve as template how results on impurities should be presented in an application file. Normally raw data are not presented.

Example 1: 0.5 g Maximum Daily Dose

Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 0.15%

"Raw" Result (%)	Reported Result (%) Reporting Threshold = 0.05%	Calculated Total Daily Intake (TDI) (mg) of the Impurity (Rounded Result in mg)	Action: Identification (Threshold 0.10% Exceeded?)	Action: Qualification (Threshold 0.15% Exceeded?)
0.044	Not reported	0.2	None	None
0.0963	0.10	0.5	None	None
0.12	0.12[a]	0.6	Yes	None[a]
0.1649	0.16[a]	0.8	Yes	Yes[a]

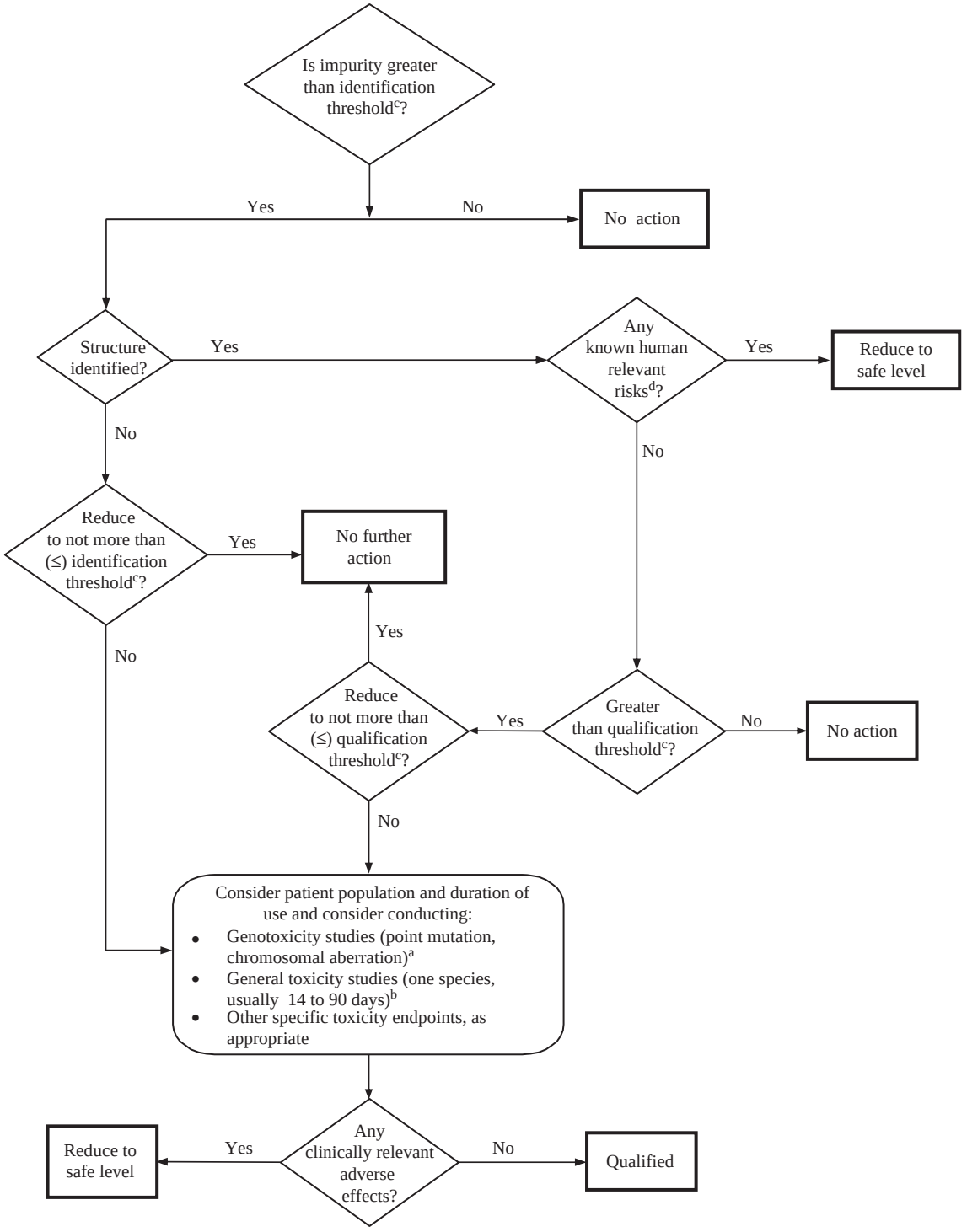
Example 2: 0.8 g Maximum Daily Dose

Reporting threshold = 0.05%
Identification threshold = 0.10%
Qualification threshold = 1.0 mg TDI

"Raw" Result (%)	Reported Result (%) Reporting Threshold = 0.05%	Calculated Total Daily Intake (TDI) (mg) of the Impurity (Rounded Result in mg)	Action: Identification (Threshold 0.10% Exceeded?)	Action: Qualification (Threshold 1.0 mg TDI Exceeded?)
0.066	0.07	0.6	None	None
0.124	0.12	1.0	Yes	None[a,b]
0.143	0.14	1.1	Yes	Yes[a]

[a]After identification, if the response factor is determined to differ significantly from the original assumptions, it may be appropriate to remeasure the actual amount of the impurity present and reevaluate against the qualification threshold (see Attachment 1).
[b]To verify if a threshold is exceeded, a reported result has to be evaluated against the thresholds as follows: when the threshold is described in %, the reported result rounded to the same decimal place as the threshold should be compared directly to the threshold. When the threshold is described in TDI, the reported result should be converted to TDI, rounded to the same decimal place as the threshold and compared to the threshold. For example the amount of impurity at 0.12% level corresponds to a TDI of 0.96 mg (absolute amount), which is then rounded up to 1.0 mg; so the qualification threshold expressed in TDI (1.0 mg) is not exceeded.

Attachment 3: Decision Tree for Identification and Qualification



[a]If considered desirable, a minimum screen (e.g., genotoxic potential) should be conducted. A study to detect point mutations and to detect chromosomal aberrations, both in vitro, is considered an appropriate minimum screen

[b]If general toxicity studies are desirable, one or more studies should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximize the potential to detect the toxicity of an impurity. On a case-by-case basis, single-dose studies can be appropriate, especially for single-dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days would be considered appropriate.

[c]Lower thresholds can be appropriate if the impurity is unusually toxic.

[d]For example, do known safety data for this impurity or its structural class preclude human exposure at the concentration present?

16

Impurities in New Drug Products

I. INTRODUCTION

A. Objective of the Guideline

This document provides guidance for registration applications on the content and qualification of impurities in new drug products produced from chemically synthesized new drug substances not previously registered in a region or member state.

B. Background

This guideline is complementary to the ICH Q3A(R) guideline "Impurities in New Drug Substances," which should be consulted for basic principles. The ICH Q3C guideline "Residual Solvents" should also be consulted, if appropriate.

C. Scope of the Guideline

This guideline addresses only those impurities in new drug products classified as degradation products of the drug substance or reaction products of the drug substance with an excipient and/or immediate container closure system (collectively referred to as "degradation products" in this guideline). Generally, impurities present in the new drug substance need not be monitored or specified in the new drug product unless they are also degradation products (see ICH Q6A guideline on specifications).

Impurities arising from excipients present in the new drug product or extracted or leached from the container closure system are not covered by this guideline. This guideline also does not apply to new drug products used during the clinical research stages of development. The following types of products are not covered in this guideline: biological/biotechnological products, peptides, oligonucleotides, radiopharmaceuticals, fermentation products and semisynthetic products derived therefrom, herbal products, and crude products of animal or plant origin. Also excluded from this document are (1) extraneous contaminants that should not occur in new drug products and are more appropriately addressed as good manufacturing practice (GMP) issues, (2) polymorphic forms, and (3) enantiomeric impurities.

II. RATIONALE FOR THE REPORTING AND CONTROL OF DEGRADATION PRODUCTS

The applicant should summarize the degradation products observed during manufacture and/or stability studies of the new drug product. This summary should be based on sound scientific appraisal of potential degradation pathways in the new drug product and impurities arising from the interaction with excipients and/or the immediate container closure system. In addition, the applicant should summarize any laboratory studies conducted to detect degradation products in the new drug product. This summary should also include test results of batches manufactured during the development process and batches representative of the proposed commercial process. A rationale should be provided for exclusion of those impurities that are not degradation products (e.g., process impurities from the drug substance and impurities arising from excipients). The impurity profiles of the batches representative of the proposed commercial process should be compared with the profiles of batches used in development and any differences discussed.

Any degradation product observed in stability studies conducted at the recommended storage condition should be identified when present at a level greater than (>) the identification thresholds given in Attachment 1. When identification of a degradation product is not feasible, a summary of the laboratory studies demonstrating the unsuccessful efforts to identify it should be included in the registration application.

Degradation products present at a level of not more than (≤) the identification threshold generally would not need to be identified. However, analytical procedures should be developed for those degradation products that are suspected to be unusually potent, producing toxic or significant pharmacological effects at levels not more than (≤) the identification threshold. In unusual circumstances, technical factors (e.g., manufacturing capability, a low drug substance to excipient ratio, or the use of excipients that are crude products of animal or plant origin) can be considered as part of the justification for selection of alternative thresholds based upon manufacturing experience with the proposed commercial process.

III. ANALYTICAL PROCEDURES

The registration application should include documented evidence that the analytical procedures have been validated and are suitable for the detection and quantitation of degradation products (see ICH Q2A and Q2B guidelines on analytical validation). In particular, analytical procedures should be validated to demonstrate specificity for the specified and unspecified degradation products. As appropriate, this validation should include samples stored under relevant stress conditions: light, heat, humidity, acid/base hydrolysis, and oxidation. When an analytical procedure reveals the presence of other peaks in addition to those of the degradation products (e.g., the drug substance, impurities arising from the synthesis of the drug substance, excipients and impurities arising from the excipients), these peaks should be labeled in the chromatograms and their origin(s) discussed in the validation documentation.

The quantitation limit for the analytical procedure should be not more than (≤) the reporting threshold.

Degradation product levels can be measured by a variety of techniques, including those that compare an analytical response for a degradation product to that of an appropriate reference standard or to the response of the new drug substance itself. Reference standards used in the analytical procedures for control of degradation products should

be evaluated and characterized according to their intended uses. The drug substance can be used to estimate the levels of degradation products. In cases where the response factors are not close, this practice can still be used if a correction factor is applied or the degradation products are, in fact, being overestimated. Acceptance criteria and analytical procedures, used to estimate identified or unidentified degradation products, are often based on analytical assumptions (e.g., equivalent detector response). These assumptions should be discussed in the registration application.

Differences between the analytical procedures used during development and those proposed for the commercial product should also be discussed.

IV. REPORTING DEGRADATION PRODUCTS CONTENT OF BATCHES

Analytical results should be provided in the registration application for all relevant batches of the new drug product used for clinical, safety, and stability testing, as well as batches that are representative of the proposed commercial process. Quantitative results should be presented numerically, and not in general terms such as "complies," "meets limit," etc. Any degradation product at a level greater than (>) the reporting threshold (see Attachment 1), and total degradation products observed in the relevant batches of the new drug product, should be reported with the analytical procedures indicated. Below 1.0%, the results should be reported to the number of decimal places (e.g., 0.06%) in the applicable reporting threshold; at and above 1.0%, the results should be reported to one decimal place (e.g., 1.3%). Results should be rounded using conventional rules (see Attachment 2). A tabulation (e.g., spreadsheet) of the data is recommended. Degradation products should be designated by code number or by an appropriate descriptor, for example, retention time. If a higher reporting threshold is proposed, it should be fully justified. All degradation products at a level greater than (>) the reporting threshold should be summed and reported as total degradation products.

Chromatograms with peaks labeled (or equivalent data if other analytical procedures are used) from representative batches, including chromatograms from analytical procedure validation studies and from long-term and accelerated stability studies, should be provided. The applicant should ensure that complete degradation product profiles (e.g., chromatograms) of individual batches are available, if requested.

For each batch of the new drug product described in the registration application, the documentation should include

- batch identity, strength, and size;
- date of manufacture;
- site of manufacture;
- manufacturing process;
- immediate container closure;
- degradation product content, individual and total;
- use of batch (e.g., clinical studies, stability studies);
- reference to analytical procedure used;
- batch number of the drug substance used in the new drug product; and
- storage conditions for stability studies.

V. LISTING OF DEGRADATION PRODUCTS IN SPECIFICATIONS

The specification for a new drug product should include a list of degradation products expected to occur during manufacture of the commercial product and under recommended storage conditions. Stability studies, knowledge of degradation pathways, product development studies, and laboratory studies should be used to characterize the degradation profile. The selection of degradation products in the new drug product specification should be based on the degradation products found in batches manufactured by the proposed commercial process. Those individual degradation products with specific acceptance criteria included in the specification for the new drug product are referred to as "specified degradation products" in this guideline. Specified degradation products can be identified or unidentified. A rationale for the inclusion or exclusion of degradation products in the specification should be presented. This rationale should include a discussion of the degradation profiles observed in the safety and clinical development batches and in stability studies, together with a consideration of the degradation profile of batches manufactured by the proposed commercial process. Specified identified degradation products should be included along with specified unidentified degradation products estimated to be present at a level greater than (>) the identification threshold given in Attachment 1. For degradation products known to be unusually potent or to produce toxic or unexpected pharmacological effects, the quantitation/detection limit of the analytical procedures should be commensurate with the level at which the degradation products should be controlled. For unidentified degradation products, the procedure used and assumptions made in establishing the level of the degradation product should be clearly stated. Specified unidentified degradation products should be referred to by an appropriate qualitative analytical descriptive label (e.g., "unidentified A," "unidentified with relative retention of 0.9"). A general acceptance criterion of not more than (≤) the identification threshold (Attachment 1) for any unspecified degradation product and an acceptance criterion for total degradation products should also be included.

For a given degradation product, its acceptance criterion should be established by taking into account its acceptance criterion in the drug substance (if applicable), its qualified level, its increase during stability studies, and the proposed shelf life and recommended storage conditions for the new drug product. Furthermore, each acceptance criterion should be set no higher than the qualified level of the given degradation product.

Where there is no safety concern, degradation product acceptance criteria should be based on data generated from batches of the new drug product manufactured by the proposed commercial process, allowing sufficient latitude to deal with normal manufacturing and analytical variation and the stability characteristics of the new drug product. Although normal manufacturing variations are expected, significant variation in batch-to-batch degradation product levels can indicate that the manufacturing process of the new drug product is not adequately controlled and validated (see ICH Q6A guideline on specifications, decision tree no. 2, for establishing an acceptance criterion for a specified degradation product in a new drug product).

In this guideline, the use of two decimal places for thresholds (See Attachment 1) does not necessarily indicate the precision of the acceptance criteria for specified degradation products and total degradation products.

In summary, the new drug product specification should include, where applicable, the following list of degradation products:

- Each specified identified degradation product
- Each specified unidentified degradation product
- Any unspecified degradation product with an acceptance criterion of not more than (≤) the identification threshold
- Total degradation products.

VI. QUALIFICATION OF DEGRADATION PRODUCTS

Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual degradation product or a given degradation profile at the level(s) specified. The applicant should provide a rationale for establishing degradation product acceptance criteria that includes safety considerations. The level of any degradation product present in a new drug product that has been adequately tested in safety and/or clinical studies would be considered qualified. Therefore, it is useful to include any available information on the actual content of degradation products in the relevant batches at the time of use in safety and/or clinical studies. Degradation products that are also significant metabolites present in animal and/or human studies are generally considered qualified. Degradation products could be considered qualified at levels higher than those administered in safety studies based on a comparison between actual doses given in the safety studies and the intended dose of the new drug product. Justification of such higher levels should include consideration of factors such as (1) the amount of degradation product administered in previous safety and/or clinical studies and found to be safe, (2) the increase in the amount of the degradation product, and (3) other safety factors, as appropriate.

If the qualification thresholds given in Attachment 1 are exceeded and data are unavailable to qualify the proposed acceptance criterion of a degradation product, additional studies to obtain such data can be appropriate (see Attachment 3).

Higher or lower thresholds for qualification of degradation products can be appropriate for some individual new drug products based on scientific rationale and level of concern, including drug class effects and clinical experience. For example, qualification can be especially important when there is evidence that such degradation products in certain new drug products or therapeutic classes have previously been associated with adverse reactions in patients. In these instances, a lower qualification threshold can be appropriate. Conversely, a higher qualification threshold can be appropriate for individual new drug products when the level of concern for safety is less than usual based on similar considerations (e.g., patient population, drug class effects, and clinical considerations). Proposals for alternative thresholds would be considered on a case-by-case basis.

The "Decision Tree for Identification and Qualification of a Degradation Product" (Attachment 3) describes considerations for the qualification of degradation products when thresholds are exceeded. In some cases, reducing the level of degradation product (e.g., use of a more protective container closure or modified storage conditions) to not more than (≤) the threshold can be simpler than providing safety data. Alternatively, adequate data could be available in the scientific literature to qualify a degradation product. If neither is the case, additional safety testing should be considered. The studies considered appropriate to qualify a degradation product will depend on a number of factors, including the patient population, daily dose, and route and duration of new drug product administration. Such studies can be conducted on the new drug product or substance containing the degradation products to be controlled, although studies using isolated degradation products can sometimes be appropriate.

Although this guideline is not intended to apply during the clinical research stage of development, in the later stages of development the thresholds in this guideline can be useful in evaluating new degradation products observed in new drug product batches prepared by the proposed commercial process. Any new degradation product observed in later stages of development should be identified (see the "Decision Tree for Identification and Qualification of a Degradation Product" in Attachment 3) if its level is greater than (>) the identification threshold given in Attachment 1. Similarly, qualification of the degradation product should be considered if its level is greater than (>) the qualification threshold given in Attachment 1.

Safety studies should provide a comparison of results of safety testing of the new drug product or drug substance containing a representative level of the degradation product with previously qualified material, although studies using the isolated degradation products can also be considered.

GLOSSARY

Degradation Product—An impurity resulting from a chemical change in the drug substance brought about during manufacture and/or storage of the new drug product by the effect of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container closure system.

Degradation Profile—A description of the degradation products observed in the drug substance or drug product.

Development Studies—Studies conducted to scale up, optimize, and validate the manufacturing process for a drug product.

Identification Threshold—A limit above (>) which a degradation product should be identified.

Identified Degradation Product—A degradation product for which a structural characterization has been achieved.

Impurity—Any component of the new drug product that is not the drug substance or an excipient in the drug product.

Impurity Profile—A description of the identified and unidentified impurities present in a drug product.

New Drug Substance—The designated therapeutic moiety that has not been previously registered in a region or member state (also referred to as a new molecular entity or new chemical entity). It can be a complex, simple ester, or salt of a previously approved substance.

Qualification—The process of acquiring and evaluating data that establishes the biological safety of an individual degradation product or a given degradation profile at the level(s) specified.

Qualification Threshold—A limit above (>) which a degradation product should be qualified.

Reporting Threshold—A limit above (>) which a degradation product should be reported.

Specified Degradation Product—A degradation product that is individually listed and limited with a specific acceptance criterion in the new drug product specification. A

specified degradation product can be either identified or unidentified.

Unidentified Degradation Product—A degradation product for which a structural characterization has not been achieved and that is defined solely by qualitative analytical properties (e.g., chromatographic retention time).

Unspecified Degradation Product—A degradation product that is limited by a general acceptance criterion, but not individually listed with its own specific acceptance criterion, in the new drug product specification.

Attachment 1 Thresholds for Degradation Products in New Drug Products

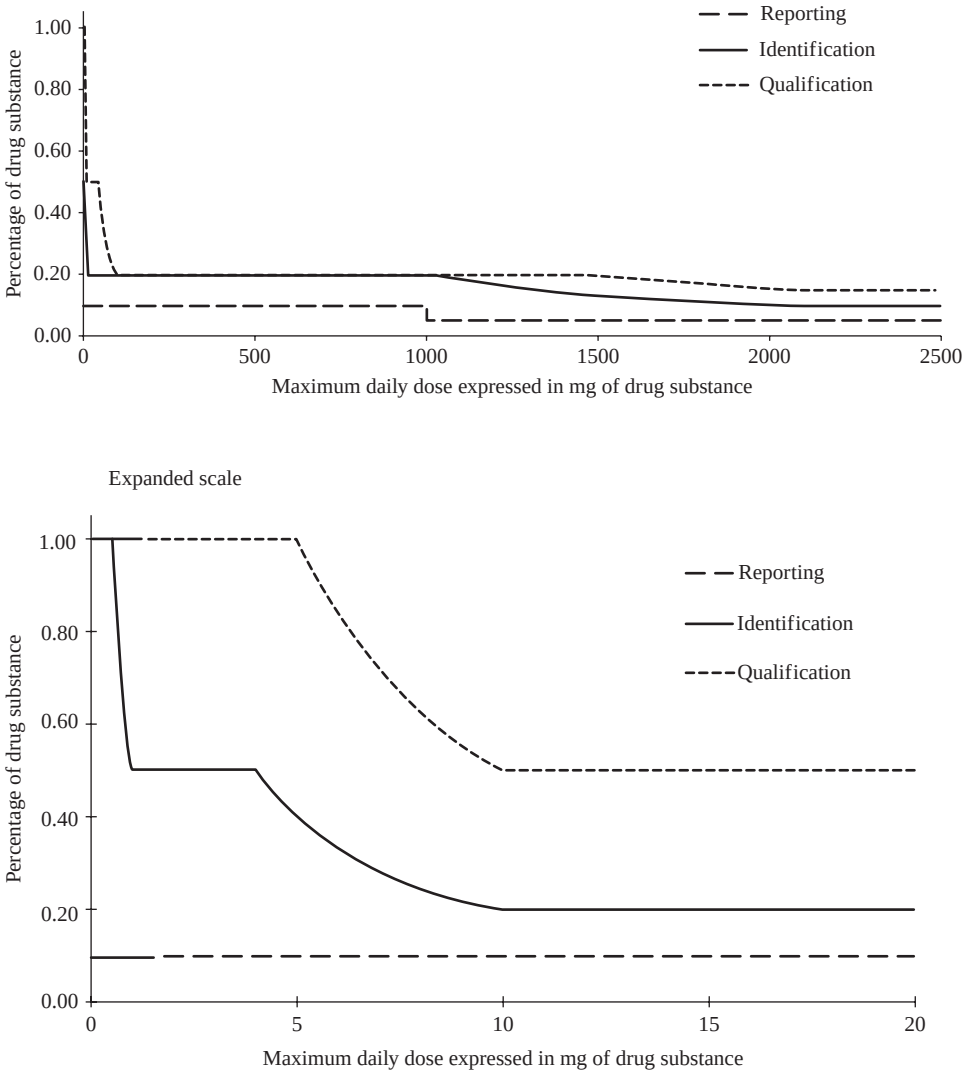
Maximum Daily Dose[a]	Threshold[b,c]
Reporting thresholds	
≤1 g	0.1%
>1 g	0.05%
Identification thresholds	
<1 mg	1.0% or 5 μg TDI, whichever is lower
1 mg–10 mg	0.5% or 20 μg TDI, whichever is lower
>10 mg–2 g	0.2% or 2 mg TDI, whichever is lower
>2 g	0.10%
Qualification thresholds	
<10 mg	1.0% or 50 μg TDI, whichever is lower
10 mg–100 mg	0.5% or 200 μg TDI, whichever is lower
>100 mg–2 g	0.2% or 3 mg TDI, whichever is lower
>2 g	0.15%

[a]The amount of drug substance administered per day.

[b]Thresholds for degradation products are expressed either as a percentage of the drug substance or as total daily intake (TDI) of the degradation product. Lower thresholds can be appropriate if the degradation product is unusually toxic.

[c]Higher thresholds should be scientifically justified.

Illustration of thresholds for reporting, identification, and qualification of degradation products in new drug products as a function of maximum daily dose[a]



[a]*Note*: Actual threshold values should be taken from the preceding table in this attachment.

Attachment 2: Illustration of Reporting Degradation Product Results for Identification and Qualification in an Application

The attachment is only illustrative and is not intended to serve as a template how results on degradation products should be presented in an application file. Normally raw data are not provided.

Example 1: 50 mg Maximum Daily Dose

Reporting threshold: 0.1%
Identification threshold: 0.2%
Qualification threshold: 200 μg

"Raw" Result (%)	Reported Result (%) Reporting Threshold = 0.05%	Total Daily Intake (TDI) of the Degradation Prodution (Rounded Result in μg)	Action Identification Threshold 0.2% Exceeded?	Action Qualification Threshold 200 μg TDI Exceeded?
0.04	Not reported	20	None	None
0.2143	0.2	100	None	None
0.349	0.3[a]	150	Yes	None[a]
0.550	0.6[a]	300	Yes	Yes[a]

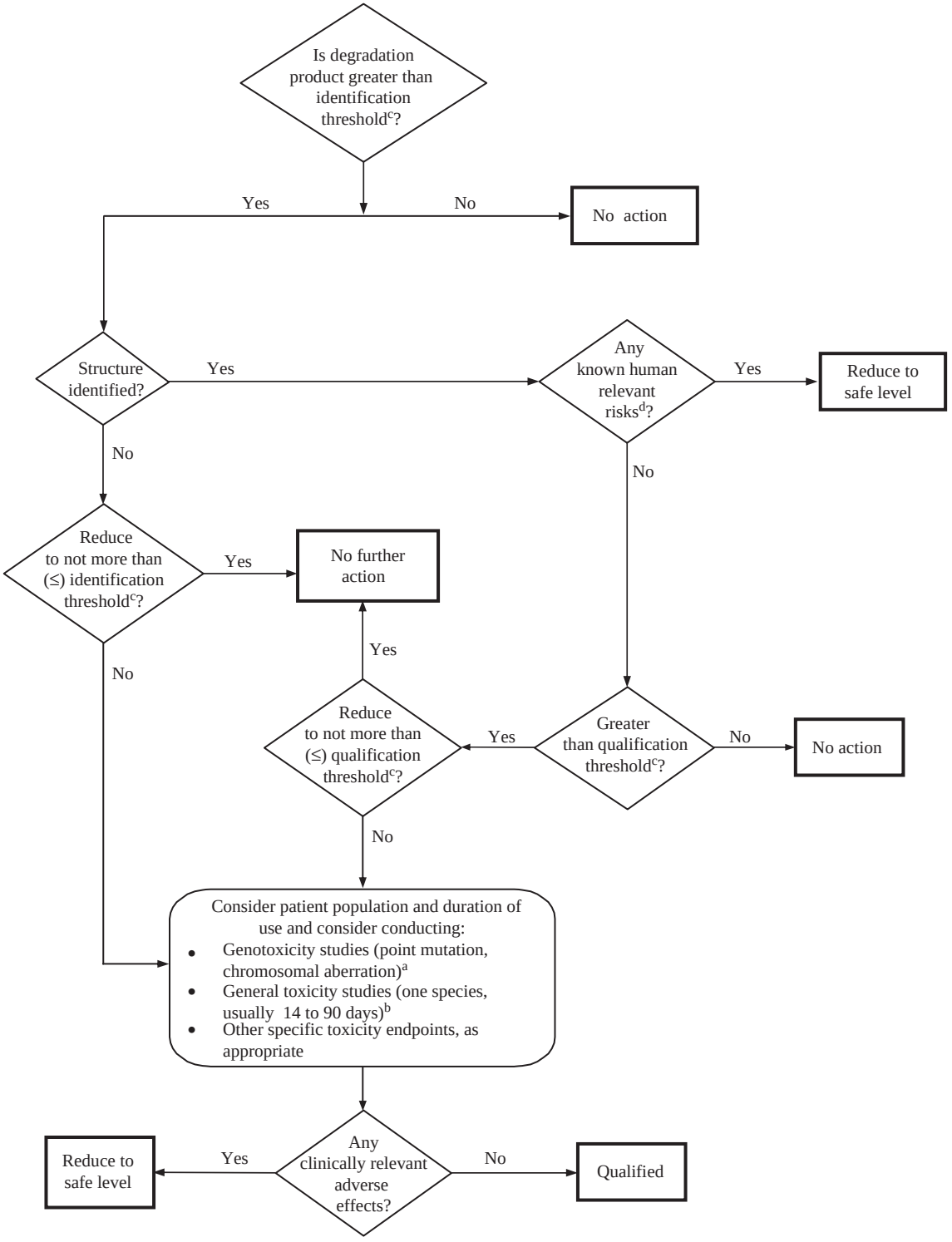
Example 2: 1.9 g Maximum Daily Dose

Reporting threshold: 0.05%
Identification threshold: 2 mg
Qualification threshold: 3 mg

"Raw" Result (%)	Reported Result (%) Reporting Threshold = 0.05%	Total Daily Intake (TDI) of the Degradation Product (Rounded Result in mg)	Action Identification Threshold 2 mg TDI Exceeded?	Action Qualification Threshold 3 mg TDI Exceeded?
0.049	Not reported	1	None	None
0.079	0.08	2	None	None
0.183	0.18[a]	3	Yes	None[a,b]
0.192	0.19[a]	4	Yes	Yes[a]

[a]After identification, if the response factor is determined to differ significantly from the original assumptions, it can be appropriate to remeasure the actual amount of the degradation product present and reevaluate against the qualification threshold (see Attachment 1).
[b]To verify if a threshold is exceeded, a reported result has to be evaluated against the thresholds as follows: when the threshold is described in %, the reported result rounded to the same decimal place as the threshold should be compared directly to the threshold. When the threshold is described in TDI, the reported result should be converted to TDI, rounded to the same decimal place as the threshold and compared to the threshold, for example, an amount of 0.18% degradation level corresponds to a TDI of 3.4 mg impurity (absolute amount), which is then rounded down to 3 mg; so the qualification threshold expressed in TDI (3 mg) is not exceeded.

Attachment 3: Decision Tree for Identification and Qualification of a Degradation Product



[a]If considered desirable, a minimum screen (e.g., genotoxic potential) should be conducted. A study to detect point mutations and to detect chromosomal aberrations, both in vitro, is considered an appropriate minimum screen.

[b]If general toxicity studies are desirable, one or more studies should be designed to allow comparison of unqualified to qualified material. The study duration should be based on available relevant information and performed in the species most likely to maximize the potential to detect the toxicity of a degradation product. On a case-by-case basis, single-dose studies can be appropriate, especially for single-dose drugs. In general, a minimum duration of 14 days and a maximum duration of 90 days would be considered appropriate.

[c]Lower thresholds can be appropriate if the degradation product is unusually toxic.

[d]For example, do known safety data for this degradation product or its structural class preclude human exposure at the concentration present?

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Formulation Factors in Semisolid Dosage Forms

The subjects covered here are generally applicable to all forms of topical drug products, including those that are intended to be sterile. The topics given below address several problem areas that may be encountered in the production of semisolid drug products (including transdermal products) including their potency, active ingredient uniformity, physical characteristics, microbial purity, and chemical purity.

I. POTENCY UNIFORMITY

Active ingredient solubility and particle size are generally important ingredient characteristics that need to be controlled to ensure potency uniformity in many topical drug products such as emulsions, creams, and ointments. Crystalline form is also important where the active ingredient is dispersed as a solid phase in either the oil or water phase of an emulsion, cream, or ointment.

It is important that active ingredient solubility in the carrier vehicle be known and quantified at the manufacturing step in which the ingredient is added to the liquid phase. The development data should adequately demon such solubility and its validation.

Substances that are very soluble, as is frequently the case with ointments, would be expected to present less of a problem than if the drug substance were to be suspended, as is the case with creams. If the drug substance is soluble, then potency uniformity would be based largely on adequate distribution of the component throughout the mix.

If the active ingredient is insoluble in the vehicle, then in addition to ensuring uniformity of distribution in the mix, potency uniformity depends on control of particle size and use of a validated mixing process. Particle size can also affect the activity of the drug substance because the smaller the particle size, the greater its surface area, which may influence its activity. Particle size also affects the degree to which the product may be physically irritating when applied; in general, smaller particles are less irritating.

Production controls should be implemented that account for the solubility characteristics of the drug substance; inadequate controls can adversely affect product potency, efficacy, and safety. For example, in one instance, residual water remaining in the manufacturing vessel, used to produce an ophthalmic ointment, resulted in partial solubilization and subsequent recrystallization of the drug substance; the substance recrystallized in a larger particle size than expected and thereby raised questions about the product efficacy.

In addition to ingredient solubility and particle size, other physical characteristics and specifications for both ingredients and finished products are important.

II. EQUIPMENT AND PRODUCTION CONTROL

A. Mixers

There are many different kinds of mixers used in the manufacture of topical products. It is important that the design of a given mixer is appropriate for the type of topical product being mixed. One important aspect of mixer design is how well the internal walls of the mixer are scraped during the mixing process. This can present some problems with stainless steel mixers because scraper blades should be flexible enough to remove interior material, yet not rigid enough to damage the mixer itself. In general, good design of a stainless steel mixer includes blades that are made of some hard plastic, such as Teflon®, which facilitates scrapping of the mixer walls without damaging the mixer.

If the internal walls of the mixer are not adequately scraped during mixing and the residual material becomes part of the batch, the result may be nonuniformity. Such nonuniformity may occur, for example, if operators use handheld spatulas to scrape the walls of the mixer.

Another mixer design concern is the presence of "dead spots" where quantities of the formula are stationary and not subject to mixing. Where such dead spots exist, there should be adequate procedures for recirculation or nonuse of the cream or ointment removed from the dead spots in the tank.

B. Filling and Packaging

Suspension products often require constant mixing of the bulk suspension during filling to maintain uniformity. When validating a suspension manufacturing process, determine how to ensure that the product remains homogeneous during the filling process and establish the data that support the adequacy of the firm's process. When the batch size is large and the bulk suspension is in large tanks, determine how the low levels of bulk suspension near the end of the filling process are handled. If the bulk suspension drops below a level, can this be adequately mixed? This question must be answered. If the residual material transferred to a smaller tank, how is the reliance made on hand mixing of the residual material? The adequacy of the process for dealing with residual material should be demonstrated.

C. Process Temperature Control

Typically, heat is applied in the manufacture of topical products to facilitate mixing or filling operations. Heat may also be generated by the action of high-energy mixers. It is important to control the temperature within spec parameters, not only to facilitate those operations but also to ensure that product stability is not adversely affected. Excessive temperatures may cause physical or chemical degradation of the drug product, vehicle, active ingredient or ingredients, or preservatives. Furthermore, excessive temperatures may cause insoluble ingredients to dissolve, reprecipitate, or change particle size or crystalline form.

Temperature control is also important where microbial quality of the product is a concern. The processing of topical products at higher temperatures can destroy some of the objectionable microorganisms that may be present. However, elevated temperatures may also promote incubation of microorganisms.

Temperature uniformity within a mixer should be controlled. In addressing temperature uniformity, one should consider the complex interaction among vat size, mixer speed, blade design, viscosity of contents, and rate of heat transfer. Where temperature control is critical, use of recording thermometers to continuously monitor and document temperature measurements is preferred to frequent manual checks. Where temperature control is not critical, it may be adequate to manually monitor and document temperatures periodically by use of handheld thermometers.

III. CLEANING VALIDATION

It is current good manufacturing practice for a manufacture to establish and follow written standard operating procedures to clean production equipment in a manner that precludes contamination of current and future batches. This is especially critical where contamination may present direct safety concerns, as with a potent drug such as a steroid (e.g., cortisone, and estrogen), antibiotic, or sulfa drug, where there are hypersensitivity concerns.

The insolubility of some excipients and active substance used in the manufacture of topical products makes some equipment, such as mixing vessels, pipes, and plastic hoses, difficult to clean. Often piping and transfer lines are inaccessible to direct physical cleaning. Some firms address this problem by dedicating lines and hoses to specific products or product classes.

It is therefore important that the following considerations be adequately addressed in a cleaning validation protocol and in the procedures that are established for production batches.

A. Detailed Cleaning Procedures

Cleaning procedures should be detailed and provide specific understandable instructions. The procedure should identify equipment, cleaning methods, solvents and detergents approved for use, inspection and release mechanisms, and documentation. For some of the more complex systems, such as clean-in-place systems, it is usually necessary both to provide a level of detail that includes drawings and to provide provision to label valves. The time that may elapse from completion of a manufacturing operation to initiation of equipment cleaning should also be stated where excessive delay may affect the adequacy of the established cleaning procedure. For example, residual product may dry and become more difficult to clean.

B. Sampling Plan for Contaminants

As part of the validation of the cleaning method, the cleaned surface is sampled for the presence of residues. Sampling should be made by an appropriate method, selected on the basis of factors such as equipment and solubility of residues. For example, representative swabbing of surfaces is often used, especially in areas that are hard to clean or where the residue is relatively insoluble. Analysis of rinse solutions for residues has also been shown to be of value where the residue is soluble or difficult to access for direct swabbing. Both methods are useful when there is a direct measurement of the residual substance. However, it is unacceptable to test rinse solutions (such as purified water) for conformance to the purity specifications for those solutions instead of testing directly for the presence of possible residues.

C. Equipment Residue Limits

Because of improved technology, analytical methods are becoming much more sensitive and capable of determining very low levels of residues. Thus, it is important to establish appropriate limits on levels of post–equipment-cleaning residues. Such limits must be safe, practical, achievable, and verifiable and must ensure that residues remaining in the equipment will not cause the quality of subsequent batches to be altered beyond established product specifications. The rationale for residue limits should be established. Because surface residues will not be uniform, it should be recognized that a detected residue level may not represent the maximum amount that may be present. This is particularly true when surface sampling by swabs is performed on equipment.

IV. MICROBIOLOGICAL

A. Controls (Nonsterile Topicals)

The extent of microbiological controls needed for a given topical product will depend on the nature of the product, the use of the product, and the potential hazard to users posed by microbial contamination. This concept is reflected in the current good manufacturing practice regulations at 21 CFR 211.113(a) (Control of Microbiological Contamination), and in the U.S. Pharmacopeia (USP). It is therefore vital that manufacturers assess the health hazard of all organ isolated from the product.

1. Deionized Water Systems for Purified Water

The microbiological control of deionized water systems used to produce purified water is important. Deionizers are usually excellent breeding areas for microorganisms. The microbial population tends to increase as the length of time between deionizer service periods increases. Other factors that influence microbial growth include flow rates, temperature, surface area of resin beds, and, of course, the microbial quality of the feed water. These factors should be considered in assessing the suitability of deionizing systems where microbial integrity of the product incorporating the purified water is significant. There should be a suitable routine water monitoring program and a program of other controls as necessary.

It is not necessary to assess and monitor the suitability of a deionizer by relying solely on representations of the deionizer manufacturer. Specifically, product quality could be compromised if a deionizer is serviced at intervals based not on validation studies but, rather, on the "recharge" indicator built into the unit. Unfortunately, such indicators are not triggered by microbial population but, rather, are typically triggered by measures of electrical conductivity or resistance. If a unit is infrequently used, sufficient time could elapse between recharging and sanitizing to allow the microbial population to increase significantly.

Preuse validation of deionizing systems used to produce purified water should include consideration of such factors as microbial quality of feed water (and residual chlorine levels of feed water where applicable), surface area of ionexchange resin beds, temperature range of water during processing, operational range of flow rates, recirculation systems to minimize intermittent use and low flow, frequency of use, quality of regenerant chemicals, and frequency and method of sanitization.

A monitoring program used to control deionizing systems should include established water quality and conductivity monitoring intervals, measurement of conditions and quality at significant stages through the deionizer (influent,

postcation, postanion, postmixed bed, etc.), microbial conditions of the bed, and specific methods of microbial testing. Frequency of monitoring should be based on the firm's experience with the systems.

Other methods of controlling deionizing systems include establishment of water-quality specifications and corresponding action levels, remedial action when microbial levels are exceeded, documentation of regeneration, and a description of sanitization and sterilization procedures for piping, filters, and so forth.

2. Microbiological Specifications and Test Methods

Microbiological specifications and microbial test methods for each topical product should be well-established to ensure that they are consistent with any described in the relevant application or USP. In general, product specifications should cover the total number of organisms permitted, as well as specific organisms that must not be present. These specifications must be based on use of specified sampling and analytical procedures. Where appropriate, the specifications should describe action levels where additional sampling or speciation of organisms is necessary.

Manufacturers must demonstrate that the test methods and specifications are appropriate for their intended purpose. Where possible, firms should use methods that isolate and identify organisms that may present a hazard to the user under the intended use. It should be noted that the USP does not state methods that are specific for water-insoluble topical products.

One test deficiency to be aware of is inadequate dispersement of a cream or ointment on microbial test plates. Firms may claim to follow USP procedures, yet in actual practice they may not disperse product over the test plate, resulting in inhibited growth as a result of concentrated preservative in the nondispersed inoculate. The spread technique is critical, and the firm should document that the personnel performing the technique have been adequately trained and are capable of performing the task. Validation of the spread-plate technique is particularly important when the product has a potential antimicrobial affect.

In assessing the significance of microbial contamination of a topical product, both the identification of the isolated organisms and the number of organisms found are significant. For example, the presence of a high number of organisms may indicate that the manufacturing process, component quality, or container integrity may be deficient. Although high numbers of nonpathogenic organisms may not pose a health hazard, they may affect product efficacy and physical/chemical stability. Inconsistent batch-to-batch microbial levels may indicate some process or control failure in the batch. The batch release evaluation should extend to both organism identification and numbers and, if limits are exceeded, there should be an investigation into the cause.

B. Preservative Activity

Manufacturing controls necessary to maintain the antimicrobiological effectiveness of preservatives should be evaluated. For example, for those products that separate on standing, there should be data available that show the continued effectiveness of the preservative throughout the product's shelf life.

For preservative-containing products, finished product testing must ensure that the specified level of preservative is present before release. In addition, preservative effectiveness must be monitored as part of the final ongoing stability program. This can be accomplished through analysis for the level of preservative previously shown to be effective or through appropriate microbiological challenge at testing intervals.

For concepts relating to sterility assurance and bioburden controls on the manufacture of sterile topicals, see the Guideline on Sterile Drug Products Produced by Aseptic Processing.

V. CHANGE CONTROL

As with other dosage forms, it is important to carefully control how changes are made in the production of topical products. The procedures should be able to support changes that represent departures from approved and validated manufacturing processes. There should be written change control procedures that have been reviewed and approved by the quality-control unit. The procedures should provide for full description of the proposed change, the purpose of the change, and controls to ensure that the change will not adversely alter product safety and efficacy. Factors to consider include potency or bioactivity, uniformity, particle size (if the active ingredient is suspended), viscosity, chemical and physical stability, and microbiological quality.

Of particular concern are the effects that formulation and process changes may have on the therapeutic activity and uniformity of the product. For example, changes in vehicle can affect absorption, and processing changes can alter the solubility and microbiological quality of the product.

VI. TRANSDERMAL TOPICAL PRODUCTS

The manufacturing of topical transdermal products (patches) has many problems in scale-up and validation. Problems analogous to production of topical creams or ointments include uniformity of the drug substance and particle size in the bulk gel or ointment. Uniformity and particle size are particularly significant when the drug substance is suspended or partially suspended in the vehicle. Viscosity also needs control because it can affect the absorption of the drug; the dissolution test is important in this regard. Other areas that need special inspectional attention are assembly and packaging of the patch, including adhesion, package integrity (regarding pinholes), and controls to ensure that a dose is present in each unit.

Because of the many quality parameters that must be considered in the manufacture and control of a transdermal dosage form, scale-up may be considerably more difficult than for many other dosage forms. Therefore, special attention should be given to evaluating the adequacy of the process validation efforts. As with other dosage forms, process validation must be based on multiple lots, typically at least three consecutive successful batches. Summary data should be augmented by comparison with selected data contained in supporting batch records, particularly where the data appear unusually uniform or disparate. Given the complexities associated with this dosage form, the tolerances or variances may be broader than for other dosage forms. In addition, batches may not be entirely problem free. Nevertheless, there should be adequate rationale for the tolerances and production experiences, based on appropriate developmental efforts and investigation of problems.

A. General Considerations

In general, semisolid dosage forms are complex formulations having complex structural elements. Often they are

composed of two phases (oil and water), one of which is a continuous (external) phase, and the other of which is a dispersed (internal) phase. The active ingredient is often dissolved in one phase, although occasionally the drug is not fully soluble in the system and is dispersed in one or both phases, thus creating a three-phase system. The physical properties of the dosage form depend on various factors, including the size of the dispersed particles, the interfacial tension between the phases, the partition coefficient of the active ingredient between the phases, and the product rheology. These factors combine to determine the release characteristics of the drug as well as other characteristics, such as viscosity.

For a true solution, the order in which solutes are added to the solvent is usually unimportant. The same cannot be said for dispersed formulations, however, because depending on at which phase a particulate substance is added, dispersed matter can distribute differently. In a typical manufacturing process, the critical points are generally the initial separation of a one-phase system into two phases and the point at which the active ingredient is added. Because the solubility of each added ingredient is important for determining whether a mixture is visually a single homogeneous phase, such data, possibly supported by optical microscopy, should usually be available for review. This is particularly important for solutes added to the formulation at a concentration near or exceeding that of their solubility at any temperature to which the product may be exposed. Variations in the manufacturing procedure that occur after either of these events are likely to be critical to the characteristics of the finished product. This is especially true of any process intended to increase the degree of dispersion through reducing droplet or particle size (e.g., homogenization). Aging of the finished bulk formulation before packaging is critical and should be specifically addressed in process validation studies.

B. The Role of In Vitro Release Testing

The key parameter for any drug product is its efficacy as demonstrated in controlled clinical trials. The time and expense associated with such trials make them unsuitable as routine quality control methods. Therefore, in vitro surrogate tests are often used to ensure that product quality and performance are maintained over time and in the presence of change. A variety of physical and chemical tests commonly performed on semisolid products and their components (e.g., solubility, particle size and crystalline form of the active component, viscosity, and homogeneity of the product) have historically provided reasonable evidence of consistent performance. More recently, in vitro release testing has shown promise as a means to comprehensively ensure consistent delivery of the active component or components from semisolid products. An in vitro release rate can reflect the combined effect of several physical and chemical parameters, including solubility and particle size of the active ingredient and rheological properties of the dosage form. In most cases, in vitro release rate is a useful test to assess product sameness between prechange and postchange products. However, there may be instances in which it is not suitable for this purpose. In such cases, other physical and chemical tests to be used as measures of sameness should be proposed and discussed with the agency. With any test, the metrics and statistical approaches to documentation of "sameness" in quality attributes should be considered. The evidence available at this time for the in vitro–in vivo correlation of release tests for semisolid dosage forms is not as convincing as that for in vitro dissolution as a surrogate for in vivo bioavailability of solid oral dosage forms. Therefore, the FDAs current position concerning in vitro release testing is as follows:

a. In vitro release testing is a useful test to assess product sameness under certain scale-up and postapproval changes for semisolid products.
b. The development and validation of an in vitro release test are not required for approval of an NDA, ANDA, or AADA, nor is the in vitro release test required as a routine batch-to-batch quality control test.
c. In vitro release testing alone is not a surrogate test for in vivo bioavailability or bioequivalence.
d. The in vitro release rate should not be used for comparing different formulations across manufacturers.

In vitro release is one of several standard methods that can be used to characterize performance characteristics of a finished topical dosage form; that is, semisolids such as creams, gels, and 20 ointments. Important changes in the characteristics of a drug product formula or the thermodynamic properties of the drug or drugs it contains should show up as a difference in drug release. Release is theoretically proportional to the square root of time when the formulation in question is in control of the release process because the release is from a receding boundary. In vitro release method for topical dosage forms is based on an open chamber diffusion cell system such as a Franz cell system, fitted usually with a synthetic membrane. The test product is placed on the upper side of the membrane in the open donor chamber of the diffusion cell, and a sampling fluid is placed on the other side of the membrane in a receptor cell. Diffusion of drug from the topical product to and across the membrane is monitored by assay of sequentially collected samples of the receptor fluid. The in vitro release methodology should be appropriately validated. Sample collection can be automated. Aliquots removed from the receptor phase can be analyzed for drug content by high-pressure liquid chromatography or other analytical methodology. A plot of the amount of drug released per unit area (mcg/cm) against the square root of time yields a straight line, the slope of which represents the release rate. This release rate measure is formulation specific and can be used to monitor product quality. The release rate of the biobatch or currently manufactured batch should be compared with the release rate of the product prepared after a change, as defined in this guidance.

C. In Vivo Bioequivalence Studies

The design of in vivo bioequivalence studies for semisolid dosage forms varies depending on the pharmacological activity of the drug and dosage form. A brief general discussion of such tests follows. The objective is to document the bioequivalence of the drug product for which the manufacture has been changed, as defined in this guidance, compared with the drug product manufactured before the change or with the reference-listed drug. The study design is dependent on the nature of the active drug. The bioequivalence study can be a comparative skin-blanching study as in glucocorticoids (FDA, 1995) or a comparative clinical trial or any other appropriate validated bioequivalence study (e.g., dermatopharmacokinetic study) for the topical dermatological drug product. The assay methodology selected should ensure specificity, accuracy, interday and intraday precision, linearity of standard curves, and adequate sensitivity, recovery, and stability of the samples under the storage and handling conditions associated with the analytical method. (See Van Buskirk et al, 1994.)

REFERENCES

FDA (1995). Topical Dermatological Corticosteroids: In Vivo Bioequivalence. www.fda.gov/OHRMS/DOCKETS/98fr/3659bg.pdf.

Van Buskirk GA, Shah VP, Adair D, et al (1994). Workshop report: scale-up of liquid and semi-solids disperse systems. Pharm Res 11:1216–1220.

GLOSSARY

Approved Target Composition—Components and amount of each ingredient for a drug product used in an approved pivotal clinical study or bioequivalence study.

Batch—Specific quantity of a drug or other material produced according to a single manufacturing order during the same cycle of manufacture and intended to have uniform character and quality, within specified limits [21 CFR 210.3(b)(2)].

Contiguous Campus—Contiguous or unbroken site or a set of buildings in adjacent city blocks.

Creams/Lotions—Semisolid emulsions that contain fully dissolved or suspended drug substances for external application. Lotions are generally of lower viscosity.

Diluent—Vehicle in a pharmaceutical formulation commonly used for making up volume or weight (e.g., water, paraffin base).

Drug Product—Finished dosage form (e.g., cream, gel, or ointment) in its marketed package. It also can be a finished dosage form (e.g., tablet, capsule, or solution) that contains a drug substance, generally, but not necessarily, in association with one or more other ingredients [21 CFR 314.3(b)].

Drug Release—Disassociation of a drug from its formulation, thereby allowing the drug to be distributed into the skin or be absorbed into the body, where it may exert its pharmacological effect.

Drug Substance—Active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease or to affect the structure or any function of the human body, but that does not include intermediates used in the synthesis of such ingredient [21 CFR 314.3(b)].

Emulsion—Two-phase systems in which an immiscible liquid (dispersed phase) is dispersed throughout another liquid (continuous phase or external phase) as small droplets. Where oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water emulsion. Conversely, where water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil emulsion. Emulsions are stabilized by emulsifying agents that prevent coalescence, the merging of small droplets into larger droplets and, ultimately, into a single separated phase. Emulsifying agents (surfactants) do this by concentration in the interface between the droplet and external phase and by providing a physical barrier around the particle to coalesce. Surfactants also reduce the interfacial tension between the phases, thus increasing the ease of emulsification on mixing. Emulsifying agents substantially prevent or delay the time needed for 27 emulsion droplets to coalesce. Emulsification is the act of forming an emulsion. Emulsification can involve the incorporation of a liquid within another liquid to form an emulsion or a gas in a liquid to form a foam.

Formulation—Listing of the ingredients and quantitative composition of the dosage form.

Gel—Semisolid system in which a liquid phase is constrained within a three-dimensional, cross-linked matrix. The drug substance may be either dissolved or suspended within the liquid phase.

Homogenization—Method of atomization and thereby emulsification of one liquid in another in which the liquids are pressed between a finely ground valve and seat under high pressure (e.g., up to 5000 psi).

Internal Phase—Internal phase or dispersed phase of an emulsion that comprises the droplets that are found in the emulsion.

In Vitro Release Rate—Rate of release of the active drug from its formulation, generally expressed as amount/unit area/time.

Ointment—Unctuous semisolid for topical application. Typical ointments are based on petrolatum. An ointment does not contain sufficient water to separate into a second phase at room temperature. Water-soluble ointments may be formulated with polyethylene glycol.

Pilot-Scale Batch—Manufacture of drug product by a procedure fully representative of and simulating that intended to be used for full manufacturing scale.

Preservative—Agent that prevents or inhibits microbial growth in a formulation to which it has been added.

Process—Series of operations, actions, and controls used to manufacture a drug product.

Scale-down—Process of decreasing the batch size.

Scale-up—Process of increasing the batch size.

Shear—Strain resulting from applied forces that cause or tend to cause contiguous parts of a body to slide relative to one another in direction parallel to their plane of contact. In emulsification and suspensions, it is the strain produced on passing a system through a homogenizer or other milling device. Low shear: Processing in which the strain produced through mixing or emulsifying shear is modest. High shear: Forceful processes that, at point of mixing or emulsification, place a great strain on the product. Homogenization, by its very nature, is a high-shear process that leads to a small and relatively uniform emulsion droplet size. Depending on their operation, mills and mixers are categorized as either high-shear or low-shear devices.

Significant Body of Information—A significant body of information on the stability of the product is likely to exist after 5 years of commercial experience for new molecular entities or 3 years of commercial experience for new dosage forms.

Strength—Strength is the concentration of the drug substance (e.g., weight/weight, weight/volume, or unit dose/volume basis) or the potency, that is, the therapeutic activity of the drug product as indicated by appropriate laboratory tests or by adequately developed and controlled clinical data (e.g., expressed in terms of units by reference to a standard) [21 CFR 210.3(b)(16)]. For semisolid dosage forms the strength is usually stated as a weight/weight or weight/volume percentage.

Structure-Forming Excipient—Excipient that participates in the formation of the structural matrix that gives an ointment, cream, gel, etc., its semisolid character. Examples are gel-forming polymers, petrolatum, certain

colloidal inorganic solids (e.g., bentonite), waxy solids (e.g., cetyl alcohol, stearic acid), and emulsifiers used in creams.

Suspending Agent—Excipient added to a suspension to control the rate of sedimentation of the active ingredients.

Technical Grade—Technical grades of excipients differ in their specifications and intended use. Technical grades may differ in specifications or functionality, impurities, and impurity profiles.

Validation—Procedure to establish documented evidence that provides a high degree of assurance that a specific process or test will consistently produce a product or test outcome meeting its predetermined specifications and quality attributes. A validated manufacturing process or test is one that has been proven to do what it purports to or is represented to do. The proof of process validation is obtained through collection and evaluation of data, preferably beginning with the process development phase and continuing through the production phase. Process validation necessarily includes process qualification (the qualification of materials, equipment, systems, building, and personnel), but it also includes the control of the entire processes for repeated batches or runs.

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GMP Audit Template, EU Guidelines (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm)

		Compliance 1 2 3[a]	Remarks	EU Guide
1	**PERSONNEL**			
1.1	Qualified personnel available?	☐ ☐ ☐		2.1
1.2	Organization charts available?	☐ ☐ ☐		2.2
1.3	Job descriptions available?	☐ ☐ ☐		2.2
1.4	Responsibilities clearly defined?	☐ ☐ ☐		2.2
	Key personnel			
	Responsible persons designated for			
1.5	• production?	☐ ☐ ☐		2.5
1.6	• quality control?	☐ ☐ ☐		2.6
1.7	Are they independent from each other?	☐ ☐ ☐		2.3
1.8	Are joint functions clearly defined?	☐ ☐ ☐		2.7
1.9	Are the responsible persons working full time?	☐ ☐ ☐		2.3
1.10	Do the responsible persons have the appropriate formation, knowledge, and experience?	☐ ☐ ☐		2.1/2.2
1.11	Do the relevant departments have enough personnel?	☐ ☐ ☐		2.1
	Training			
1.12	Continuous training programs for the production and QC staff?	☐ ☐ ☐		2.8
1.13	Initial job training for all employees?	☐ ☐ ☐		2.9
1.14	Teaching aids (videos, slides, and brochures) available?	☐ ☐ ☐		2.9
1.15	External training courses for the staff?	☐ ☐ ☐		2.9
1.16	Training records?	☐ ☐ ☐		2.9
1.17	Special training in sensitive areas? (sterile prod. and toxic subs.)	☐ ☐ ☐		2.10
1.18	Information for visitors to the manufacturing area?	☐ ☐ ☐		2.11
2	**HYGIENE**			
	Personnel hygiene			
	Detailed written hygiene programs for			
2.1	• clothing?	☐ ☐ ☐		2.13
2.2	• use of washrooms?	☐ ☐ ☐		2.13
2.3	• behavior in production areas?	☐ ☐ ☐		2.13
2.4	Precautions against sick or personnel with open wounds in production?	☐ ☐ ☐		2.14
	Medical examination			
2.5	• on recruitment?	☐ ☐ ☐		2.15
2.6	• regular reexaminations?	☐ ☐ ☐		2.15

		Compliance 1 2 3[a]	Remarks	EU Guide
	Duty of notification after			
2.7	• trips to tropical countries?	☐ ☐ ☐		2.15
2.8	• cases of contagious illness in the family?	☐ ☐ ☐		2.15
2.9	Instructions for appropriate working clothes?	☐ ☐ ☐		2.16
2.10	Absence of food and drinks (chewing gum!) in the working area?	☐ ☐ ☐		2.17
2.11	Measures against contact with open product (gloves etc.)?	☐ ☐ ☐		2.18
2.12	Instructions for hand washing in production?	☐ ☐ ☐		2.19
2.13	Change of clothes when entering and leaving the production area?	☐ ☐ ☐		5.19
2.14	Change rooms and toilets easily within reach?	☐ ☐ ☐		3.31
2.15	Toilets and restrooms sufficiently separated from production areas?	☐ ☐ ☐		3.30/3.31
2.16	Workshops separate from production areas?	☐ ☐ ☐		3.32
2.17	Laboratory animal rooms totally segregated from production rooms?	☐ ☐ ☐		3.33
3	**WAREHOUSE**			
	Rooms, general			
3.1	Suitable for the intended use?	☐ ☐ ☐		3
3.2	• adequate size?	☐ ☐ ☐		3
3.3	• clean?	☐ ☐ ☐		3
3.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
3.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
3.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
3.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
3.8	Recording of temperature and humidity?	☐ ☐ ☐		
3.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
3.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
	Type of warehousing:			
3.11	Separation of goods sufficient?	☐ ☐ ☐		3.18
3.12	Provision for different storage temperatures?	☐ ☐ ☐		3.19
3.13	Goods receiving zone weather protected?	☐ ☐ ☐		3.20
3.14	Cleaning zone for incoming goods?	☐ ☐ ☐		3.20
3.15	Separate quarantine area with controlled access?	☐ ☐ ☐		3.21
3.16	Separate, protected sampling area?	☐ ☐ ☐		3.22
	Separate and safe storage of			
3.17	• returned goods?	☐ ☐ ☐		3.23
3.18	• rejected goods?	☐ ☐ ☐		3.23
3.19	Separate and safe storage of highly active, toxic, or dangerous substances?	☐ ☐ ☐		3.24
3.20	Safe storage of narcotics?	☐ ☐ ☐		3.24
3.21	Safe storage of printed packaging materials?	☐ ☐ ☐		3.25
3.22	Security measurements against theft?	☐ ☐ ☐		3.25
3.23	Smoke detectors?	☐ ☐ ☐		3.25
3.24	Fire extinguishing system?	☐ ☐ ☐		3.25

			Compliance 1 2 3[a]	Remarks	EU Guide
	Operations				
3.25	Reception, sampling, and labeling according to written procedures?		☐ ☐ ☐		5.2
3.26	Is a sampling plan available?		☐ ☐ ☐		suppl. 4
3.27	Cleaning of incoming containers?		☐ ☐ ☐		5.3
3.28	Investigation and recording of damaged deliveries?		☐ ☐ ☐		5.4
3.29	FIFO principle?		☐ ☐ ☐		5.7
3.30	Inventory system?		☐ ☐ ☐		5.8
3.31	The location of materials can be detected at all times?		☐ ☐ ☐		
3.32	Incoming goods: containers and seals intact?		☐ ☐ ☐		5.27
3.33	Incoming goods: conformity with bill of delivery?		☐ ☐ ☐		5.27
	Labeling of incoming containers with:				
3.34	• internal name and code?		☐ ☐ ☐		5.29
3.35	• allocated batch number?		☐ ☐ ☐		5.29
3.36	• quarantine status?		☐ ☐ ☐		5.29
3.37	• expiry date or reanalysis date?		☐ ☐ ☐		5.29
3.38	Identity test for each incoming container?		☐ ☐ ☐		5.29
3.39	Are the sampled containers marked?		☐ ☐ ☐		5.30
3.40	Are reference samples taken?		☐ ☐ ☐		5.30
3.41	Safe storage of printed packaging materials?		☐ ☐ ☐		5.41
3.42	Lot tracing of all packaging materials possible?		☐ ☐ ☐		5.42
3.43	Are excessive packaging materials destroyed?		☐ ☐ ☐		5.43
	Release of starting materials by				
	physical/inventory checks on raw materials, packaging materials, and finished goods:				
	Item:	Stocks: Physical:	Stocks: Inventory:	Storage conditions:	
4	**DISPENSING/ASSEMBLING**				
	Rooms, general				
4.1	Suitable for the intended use?		☐ ☐ ☐		3
4.2	• adequate size?		☐ ☐ ☐		3
4.3	• clean?		☐ ☐ ☐		3
4.4	Located and designed to exclude external contamination?		☐ ☐ ☐		3.1
4.5	Appropriate level of maintenance?		☐ ☐ ☐		3.2
4.6	Maintenance works possible without contamination risk?		☐ ☐ ☐		3.2

		Compliance 1 2 3[a]	Remarks	EU Guide
4.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
4.8	Recording of temperature and humidity?	☐ ☐ ☐		
4.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
4.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
4.11	Segregated from production and warehouse?	☐ ☐ ☐		3.13
4.12	Separate weighing cabins?	☐ ☐ ☐		3.13
4.13	Separate AHU for each cabin?	☐ ☐ ☐		3.12
	Air pressure gradient from weighing cabin → corridor:			3.3
4.14	Dust extraction systems available?	☐ ☐ ☐		5.11
	Operations			
4.15	Balances regularly calibrated?	☐ ☐ ☐		3.41
4.16	Only pharmaceutical raw materials in this area?	☐ ☐ ☐		5.17
4.17	Check on remains from previous materials before entering of new materials into a weighing cabin?	☐ ☐ ☐		5.9/5.35
4.18	Only one material in one cabin?	☐ ☐ ☐		5.9
4.19	Are dispensed materials correctly labeled?	☐ ☐ ☐		5.29
4.20	Only released products in the dispensing?	☐ ☐ ☐		5.31
4.21	Cleaning SOPs for the dispensing?	☐ ☐ ☐		4.28
4.22	Previously dispensed material recorded on weighing protocol?	☐ ☐ ☐		4.8
4.23	Safety measures against mix-ups during assembling (e.g. cage pallets)?	☐ ☐ ☐		5.32/5.34
5	**SOLIDS MANUFACTURING**			
	Field of activity:			
	• Granulation	☐		
	• Compression	☐		
	• Encapsulation	☐		
	• Film and sugar coating	☐		
	• Visual inspection (Capsules, tablets, etc.)	☐		
	• Premix (Human)	☐		
	Rooms, general			
5.1	Suitable for the intended use?	☐ ☐ ☐		3
5.2	• adequate size?	☐ ☐ ☐		3
5.3	• clean?	☐ ☐ ☐		3
5.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
5.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
5.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
5.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
5.8	Recording of temperature and humidity?	☐ ☐ ☐		
5.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
5.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
5.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6

		Compliance 1 2 3[a]	Remarks	EU Guide
5.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
5.13	Logical flow of materials?	☐ ☐ ☐		3.7
5.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
5.15	Easy cleaning possible?	☐ ☐ ☐		3.10
5.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
5.17	Appropriate air-handling system?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
5.18	Appropriate dust extraction system?	☐ ☐ ☐		3.14
5.19	Appropriate lighting?	☐ ☐ ☐		3.16
5.20	Separate rest rooms?	☐ ☐ ☐		3.30
5.21	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
5.22	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
5.23	Suitable for the intended use?	☐ ☐ ☐		3.34
5.24	Well maintained?	☐ ☐ ☐		3.34
5.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
5.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
5.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
5.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
5.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
5.30	Calibration records available?	☐ ☐ ☐		3.41
5.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
5.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
5.33	Not functioning equipment in the production area (if yes: clearly marked)?	Y N ☐ ☐ ☐		3.44
5.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
5.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
5.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
5.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
5.38	Check of each single container of the starting materials (contents, weight, and identity)?	☐ ☐ ☐		5.3
5.39	Limits for yields?	☐ ☐ ☐		5.8
5.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
5.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
5.42	Appropriate measures against generation of dust (e.g. closed systems)?	☐ ☐ ☐		5.11
	Correct labeling of containers, materials, equipment, and rooms with			5.12

		Compliance 1 2 3[a]	Remarks		EU Guide
5.43	• product name and batch no.	☐ ☐ ☐			5.12
5.44	• quarantine status?	☐ ☐ ☐			5.12
5.45	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐			5.14
5.46	Special procedures for the production of antibiotics, hormones, etc.?	☐ ☐ ☐			5.19
5.47	• Campaign production?	☐ ☐ ☐			5.19
5.48	• Special monitoring?	☐ ☐ ☐			5.19
5.49	• Validated decontamination procedure?	☐ ☐ ☐			5.19
5.50	Double check on weight?	☐ ☐ ☐			5.34
5.51	Line clearance before start of production?	☐ ☐ ☐			5.35
5.52	Investigation of deviations in yields?	☐ ☐ ☐			5.39
5.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐			5.62
5.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐			5.63
5.55	Special release procedure (QA) for those batches?	☐ ☐ ☐			5.64
5.56	Use of protective clothing (hair cover, shoes, masks, and gloves)?	☐ ☐ ☐			2.16
5.57	Clothing regulation for visitors?	☐ ☐ ☐			2.11
	IPC				5.38
	Who performs IPC?				
5.58	Are IPC methods approved by QC?	☐ ☐ ☐			6.18
	Performance of IPCs:	*During Start-up?* **Yes No**	*Frequency*	*Automatic data recording?* **Yes No**	
	Tablets/kernels				
5.59	Individual weights	☐ ☐		☐ ☐	
5.60	Disintegration	☐ ☐		☐ ☐	
5.61	Thickness	☐ ☐		☐ ☐	
5.62	Hardness	☐ ☐		☐ ☐	
5.63	Friability/Abrasion	☐ ☐		☐ ☐	
	Sugar-/film-coated tablets				
5.64	Weights	☐ ☐		☐ ☐	
5.65	Disintegration	☐ ☐		☐ ☐	
5.66	Residual absolute humidity (IR or)	☐ ☐		☐ ☐	
	Capsules				
5.67	Individual weights	☐ ☐		☐ ☐	
5.68	Disintegration	☐ ☐		☐ ☐	
	Validation				
5.69	Validation according to fixed procedures?	☐ ☐ ☐			5.21
5.70	New procedures released only after validation?	☐ ☐ ☐			5.22
	Validation of changes of				
5.71	• processes?	☐ ☐ ☐			5.23
5.72	• starting materials?	☐ ☐ ☐			5.23
5.73	• equipment?	☐ ☐ ☐			5.23

		Compliance 1 2 3[a]	Remarks	EU Guide
5.74	Revalidation in fixed intervals?	☐ ☐ ☐		5.24
5.75	Procedures for the retrospective validation of old procedures?	☐ ☐ ☐		
6	**LIQUIDS MANUFACTURING**			
	Operations carried out:			
	• Dispensing (if different from solid)	☐ ☐ ☐		
	• Syrups and suspensions	☐ ☐ ☐		
	• Drops	☐ ☐ ☐		
	• Ointment manufacture	☐ ☐ ☐		
	• Ointment filling	☐ ☐ ☐		
	• Ampoule solution manufacture	☐ ☐ ☐		
	• Sterile or aseptic ampoule filling	☐ ☐ ☐		
	• Sterile freeze drying	☐ ☐ ☐		
	• Sterile powder filling	☐ ☐ ☐		
	Rooms, general			
6.1	Suitable for the intended use?	☐ ☐ ☐		3
6.2	• adequate size?	☐ ☐ ☐		3
6.3	• clean?	☐ ☐ ☐		3
6.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
6.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
6.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
6.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
6.8	Recording of temperature and humidity?	☐ ☐ ☐		
6.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
6.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
6.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6
6.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
6.13	Logical flow of materials?	☐ ☐ ☐		3.7
6.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
6.15	Easy cleaning possible?	☐ ☐ ☐		3.10
6.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
6.17	Appropriate air-handling system with filtered air where open products are exposed to the environment?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
6.18	Appropriate lighting?	☐ ☐ ☐		3.16
6.19	Separate rest rooms?	☐ ☐ ☐		3.30
6.20	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
6.21	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
6.22	Suitable for the intended use?	☐ ☐ ☐		3.34
6.23	Well maintained?	☐ ☐ ☐		3.34
6.24	Tanks, containers, pipework, and pumps designed for easy cleaning and sanitation (dead legs!)?	☐ ☐ ☐		Suppl. 2

		Compliance 1 2 3[a]	Remarks	EU Guide
6.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
6.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
6.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
6.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
6.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
6.30	Calibration records available?	☐ ☐ ☐		3.41
6.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
6.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
6.33	Not functioning equipment in the production area (if yes: clearly marked)?	Y N ☐ ☐ ☐		3.44
6.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
6.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
6.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
6.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
6.38	Check of each single container of the starting materials (contents, weight, and identity)?	☐ ☐ ☐		5.3
6.39	Limits for yields?	☐ ☐ ☐		5.8
6.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
6.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
	Correct labeling of containers, materials, equipment, and rooms with			5.12
6.42	• product name and batch no.	☐ ☐ ☐		5.12
6.43	• quarantine status?	☐ ☐ ☐		5.12
6.44	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐		5.14
6.45	Special procedures for the production of antibiotics, hormones, etc.?	☐ ☐ ☐		5.19
6.46	• Campaign production?	☐ ☐ ☐		5.19
6.47	• Special monitoring?	☐ ☐ ☐		5.19
6.48	• Validated decontamination procedure?	☐ ☐ ☐		5.19
6.49	Double check on weight?	☐ ☐ ☐		5.34
6.50	Line clearance before start of production?	☐ ☐ ☐		5.35
6.51	Investigation of deviations in yields?	☐ ☐ ☐		5.39
6.52	Specification of max. storage time and storage conditions if products are not immediately filled or packaged?	☐ ☐ ☐		Suppl. 9
6.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐		5.62
6.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐		5.63
6.55	Special release procedure (QA) for those batches?	☐ ☐ ☐		5.64
6.56	Use of protective clothing (hair cover, shoes, masks, and gloves)?	☐ ☐ ☐		2.16
6.57	Clothing regulation for visitors?	☐ ☐ ☐		2.11

		Compliance 1 2 3[a]	Remarks	EU Guide
	Water			
6.58	Loop system for purified water?	☐ ☐ ☐		Suppl. 4
6.59	Antimicrobial treatment of purified water?	☐ ☐ ☐		Suppl. 4
6.60	Loop system for water for injection?	☐ ☐ ☐		Suppl. 4
	Storage temperature of water for injection:			Suppl. 4
6.61	Loop system constructed to avoid deadlegs?	☐ ☐ ☐		Suppl. 4
6.62	Regular microbiological monitoring?	☐ ☐ ☐		Suppl. 4
6.63	Regular endotoxin control?	☐ ☐ ☐		Suppl. 4
	Special requirements for sterile and aseptic products			**Suppl.**
	Rooms and equipment			
6.64	Access of staff and materials to clean areas *only* through air locks?	☐ ☐ ☐		1
6.66	Rooms classified according EC guide?	☐ ☐ ☐		3
	Classification for products to be sterilized:			
6.67	• Solution preparation (EC: class C, with special precautions class D):	Class:		5
6.68	• Filling (EC: under LF in class C):	Class:		5
	Classification for aseptic products:			
6.69	• Handling of starting materials that can be sterile filtered (EC: class C):	Class:		6
6.70	• Handling of starting materials that cannot be sterile filtered (EC: class A in class B):	Class:		6
6.71	• Handling and filling of bulk (EC: class A in Class B):	Class:		6
6.72	All rooms easy to clean disinfect?	☐ ☐ ☐		17
6.73	Doors, windows, frames, lighting, etc. without edges?	☐ ☐ ☐		18
6.74	Suspended ceilings (if yes: sealed?)?	☐ ☐ ☐		19
6.75	Traps constructed to avoid microb. contamination?	☐ ☐ ☐		21
6.76	Appropriate constructed changing rooms?	☐ ☐ ☐		22
6.77	Measures against opening of both doors of air locks?	☐ ☐ ☐		23
6.78	Overpressure gradient from cleanest areas to others?	☐ ☐ ☐		24
6.79	AHU validated and regularly revalidated?	☐ ☐ ☐		25
6.80	Control instruments for pressure gradient?	☐ ☐ ☐		26
6.81	Warning system for errors in air supply?	☐ ☐ ☐		26
6.82	Recording of pressure gradients?	☐ ☐ ☐		26
6.83	Do conveyor belts leave sterile areas?	☐ ☐ ☐		28
6.84	Maintenance works outside from clean areas possible?	☐ ☐ ☐		28
6.85	Cleaning and disinfection procedure after maintenance works?	☐ ☐ ☐		29
6.86	Regular revalidation of all equipment and systems?	☐ ☐ ☐		30
6.87	Water prepared, circulated, and stored to exclude microb. contamination?	☐ ☐ ☐		31
6.88	Cleaning and disinfection of rooms according to validated SOPs rooms?	☐ ☐ ☐		32
	• Disinfection methods?			
6.89	Microb. monitoring of cleaning and disinfection agents?	☐ ☐ ☐		33

		Compliance 1 2 3[a]	Remarks	EU Guide
6.90	Microb. monitoring program of production areas?	☐ ☐ ☐		35
6.91	Results recorded and considered for the release?	☐ ☐ ☐		35
	Personnel and hygiene			
6.92	Minimal no. of personnel in clean areas?	☐ ☐ ☐		7
6.93	Special and regular training?	☐ ☐ ☐		8
6.94	Regular medical examinations?	☐ ☐ ☐		10
6.95	Appropriate clean room clothes (material, design)?	☐ ☐ ☐		12
6.96	Protective clothes worn correctly?	☐ ☐ ☐		12
6.97	Prohibition of cosmetics, jewellery, and watches?	☐ ☐ ☐		13
6.98	New clean room clothes for each working cycle?	☐ ☐ ☐		15
6.99	Appropriate washing and sterilization of clothes?	☐ ☐ ☐		16
	Operations			
6.100	Validation (media filling) in regular intervals?	☐ ☐ ☐		38
	Monitoring of water preparation system, frequency:			
6.101	• microbiological:			40
6.102	• chemical:			40
6.103	• particles:			40
6.104	• endotoxins:			40
6.105	Microbiological monitoring of starting materials?	☐ ☐ ☐		42
6.106	Max. storage times defined for sterilized equipment?	☐ ☐ ☐		45
6.107	Max. storage time defined between solution preparation and filtration?	☐ ☐ ☐		46
6.108	Material transfer to clean areas through double door autoclaves?	☐ ☐ ☐		48
	Sterilization processes			
6.109	All processes validated?	☐ ☐ ☐		50
6.110	Sterilized and nonsterilized materials clearly separated?	☐ ☐ ☐		54
	Trays and boxes clearly labeled with			
6.111	• product name and code	☐ ☐ ☐		54
6.112	• batch no.	☐ ☐ ☐		54
6.113	• status: sterilized or nonsterilized	☐ ☐ ☐		54
	Sterilizers:			
6.114	• Recording of temp., pressure, and time?	☐ ☐ ☐		55
6.115	• Coldest point determined?	☐ ☐ ☐		55
6.116	• Independent counter check probe?	☐ ☐ ☐		55
6.117	• Heat-up time for each product determined?	☐ ☐ ☐		56
6.118	• Sterile cooling media?	☐ ☐ ☐		57
6.119	• Tightness tests for vacuum autoclaves?	☐ ☐ ☐		58
6.120	• Clean steam for steam autoclaves?	☐ ☐ ☐		58
6.121	• Circulated air with overpressure?	☐ ☐ ☐		61
6.122	• Recirculated air: sterile filtered?	☐ ☐ ☐		61
6.123	• Ethylene oxide autoclaves: humidity, temp., and time recorded?	☐ ☐ ☐		69
6.124	• Ethylene oxide autoclaves: use of bioindicators?	☐ ☐ ☐		70

		Compliance 1 2 3[a]	Remarks	EU Guide
	Filtration			
6.125	Double filtration?	☐ ☐ ☐		75
6.126	Integrity testing of filters immediately after use?	☐ ☐ ☐		77
6.127	Are results part of the batch protocol?	☐ ☐ ☐		77
6.128	Optical control of each single container of ampoules, vials, and infusions?	☐ ☐ ☐		82
	IPC			
6.129	Written IPC procedures and SOPs?	☐ ☐ ☐		
	Particle testing of			
6.130	• rooms	☐ ☐ ☐		
6.131	• primary packaging materials	☐ ☐ ☐		
6.132	• system of warning and action limits?	☐ ☐ ☐		
	Microbiological monitoring of			
6.133	• rooms			
6.134	• personnel			
6.135	• equipment			
6.136	Residual O_2 of ampoules, infusions, and syrups?	☐ ☐ ☐		
6.137	Endotoxin testing of water and packaging materials?	☐ ☐ ☐		
6.138	Calibration of equipment?	☐ ☐ ☐		
6.139	Regular revalidation of equipment?	☐ ☐ ☐		
7	**PACKAGING**			
	Operations carried out: • Blistering • Foil–packaging • Filling into tablet glasses • Effervescent packaging • Powder filling • Syrup/drops filling • Ointment filling	 ☐ ☐ ☐ ☐ ☐ ☐ ☐		
	Rooms			
7.1	Suitable for the intended use?	☐ ☐ ☐		3
7.2	• adequate size?	☐ ☐ ☐		3
7.3	• clean?	☐ ☐ ☐		3
7.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
7.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
7.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
7.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
7.8	Recording of temperature and humidity?	☐ ☐ ☐		
7.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
7.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
7.11	Adequate separation of the packaging lines?	☐ ☐ ☐		3.15
	Operations			
7.12	Only *one* product per line?	☐ ☐ ☐		5.44

		Compliance 1 2 3[a]	Remarks	EU Guide
7.13	Check list for clearance before processing a new product/new batch?	☐ ☐ ☐		5.45
7.14	Adequate labeling of the lines (product name and code)?	☐ ☐ ☐		5.46
7.15	Check of all materials delivered to the line (quantity, identity, and conformity with order)?	☐ ☐ ☐		5.47
7.16	Cleaning of primary packaging materials?	☐ ☐ ☐		5.48
7.17	Immediate labeling after filling?	☐ ☐ ☐		5.49
7.18	Careful check of all printing processes (code and expiry date)?	☐ ☐ ☐		5.50
7.19	Special safety measures for off-line printing?	☐ ☐ ☐		5.51
7.20	Regular checks of all control devices (code reader, counter, etc.)?	☐ ☐ ☐		5.52
7.21	Printings clear and durable?	☐ ☐ ☐		5.53
7.22	Balancing of printed packaging materials and bulk?	☐ ☐ ☐		5.56
7.23	Destruction of excessive coded packaging material after completion of an order?	☐ ☐ ☐		5.57
7.24	Are the finished products kept in quarantine until final release?	☐ ☐ ☐		5.58
7.25	Appropriate storage after release?	☐ ☐ ☐		5.60
	IPC			
7.26	Checks on identity of bulk and packaging materials?	☐ ☐ ☐		5.47
	Regular line checks on			
7.27	• aspect of the packages	☐ ☐ ☐		5.54a
7.28	• completeness	☐ ☐ ☐		5.54b
7.29	• conformity of quantity and quality of materials with packaging order	☐ ☐ ☐		5.54c
7.30	• correct imprint	☐ ☐ ☐		5.54d
7.31	• correct function of control devices	☐ ☐ ☐		5.54d
	Are the following IPC checks performed?			
7.32	• Leaking	☐ ☐ ☐		
7.33	• Release torque of screw caps	☐ ☐ ☐		
7.34	• pH, density, drop weight, viscosity, and sedimentation	☐ ☐ ☐		
8	**DOCUMENTATION**			
	Specifications			
8.1	Specifications for raw/packaging materials available?	☐ ☐ ☐		4.10
	Do they include			
8.2	• internal name and code	☐ ☐ ☐		4.11
8.3	• name of supplier and/or manufacturer?	☐ ☐ ☐		4.11
8.4	• reference sample (printed pack.mat.)?	☐ ☐ ☐		4.11
8.5	• sampling procedure?	☐ ☐ ☐		4.11
8.6	• qualitative/quantitative specifications with limits?	☐ ☐ ☐		4.11
8.7	• storage conditions?	☐ ☐ ☐		4.11
8.8	• maximum storage period?	☐ ☐ ☐		4.11
	Goods receiving?			
8.9	Written procedures for the reception of deliveries?	☐ ☐ ☐		4.19

		Compliance 1 2 3[a]	Remarks	EU Guide
	Do records receipt include			
8.10	• product name on labels and delivery note?	☐ ☐ ☐		4.20
8.11	• internal name and code?	☐ ☐ ☐		4.20
8.12	• receiving date?	☐ ☐ ☐		4.20
8.13	• name of supplier and/or manufacturer?	☐ ☐ ☐		4.20
8.14	• batch number of supplier?	☐ ☐ ☐		4.20
8.15	• total quantity and number of containers?	☐ ☐ ☐		4.20
8.16	• allocated internal batch number?	☐ ☐ ☐		4.20
8.17	SOPs for labeling, quarantine, and storage conditions of all incoming goods available?	☐ ☐ ☐		4.21
	Sampling procedures (SOPs) include			
8.18	• authorized sampling personnel?	☐ ☐ ☐		4.22
8.19	• methods, equipment, and quantities?	☐ ☐ ☐		4.22
8.20	• safety measures?	☐ ☐ ☐		4.22
	Master formulae			
8.21	Are master formulae for each product and batch size available?	☐ ☐ ☐		4.3
8.22	Is the master formula approved and signed by the authorized persons?	☐ ☐ ☐		4.3
	The master formula includes			
8.23	• product name and code?	☐ ☐ ☐		4.14a
8.24	• description of galenical form, dosage, and batch size?	☐ ☐ ☐		4.14b
8.25	• all active ingredients with name, code, and weight?	☐ ☐ ☐		4.14c
8.26	• all excipients used during manufacture with name, code, and weight?	☐ ☐ ☐		4.14c
8.27	• yields with limits?	☐ ☐ ☐		4.14d
	Does the working procedure include			
8.28	• the production line?	☐ ☐ ☐		4.15a
8.29	• equipment to be used?	☐ ☐ ☐		4.15a
8.30	• reference to methods for cleaning, assembling, and calibration of machines?	☐ ☐ ☐		4.15b
8.31	• detailed stepwise manufacturing prescription?	☐ ☐ ☐		4.15c
8.32	• IPCs to be performed with limits?	☐ ☐ ☐		4.15d
8.33	• precautions to be followed?	☐ ☐ ☐		4.15e
8.34	Are batch records kept for each batch processed?	☐ ☐ ☐		4.17
	Do batch records include			
8.35	• protocol of line clearance?	☐ ☐ ☐		4.17
8.36	• name of the product and batch no.?	☐ ☐ ☐		4.17a
8.37	• date and time of start and end of production?	☐ ☐ ☐		4.17b
8.38	• name and initials of responsible workers for each step?	☐ ☐ ☐		4.17c, d
8.39	• batch and analytical no. and actual weight of all starting materials?	☐ ☐ ☐		4.17e
8.40	• equipment used?	☐ ☐ ☐		4.17f
8.41	• results of IPCs with initials of person who carries them out?	☐ ☐ ☐		4.17g
8.42	• yields of the relevant manufacturing steps?	☐ ☐ ☐		4.17h
8.43	• detailed notes on problems and process deviations?	☐ ☐ ☐		4.17i

		Compliance 1 2 3[a]	Remarks	EU Guide
8.44	Records on reprocessing of batches?	☐ ☐ ☐		
	Packaging instructions			
8.45	Packaging instructions for each product, package size, and presentation?	☐ ☐ ☐		4.16
	Do they include			
8.46	• product name?	☐ ☐ ☐		4.16a
8.47	• description of galenical form and strength?	☐ ☐ ☐		4.16b
8.48	• package size?	☐ ☐ ☐		4.17c
8.49	• list of all packaging materials with code for a standard batch size?	☐ ☐ ☐		4.17d
8.50	• samples of printed packaging materials?	☐ ☐ ☐		4.17e
8.51	• special precautions?	☐ ☐ ☐		4.17f
8.52	• description of the process and equipment?	☐ ☐ ☐		4.17g
8.53	• IPCs to be performed with sampling instruction?	☐ ☐ ☐		4.17h
8.54	Are packaging batch records kept for each batch or part batch?	☐ ☐ ☐		4.18
	Do the packaging batch records include			
8.55	• protocol of line clearance?	☐ ☐ ☐		4.18
8.56	• name of the product?	☐ ☐ ☐		4.18a
8.57	• date and time when operations have been performed?	☐ ☐ ☐		4.18b
8.58	• name of the responsible person?	☐ ☐ ☐		4.18c
8.59	• initials of workers carrying out operations?	☐ ☐ ☐		4.18d
8.60	• notes on identity checks and conformity with packaging instructions?	☐ ☐ ☐		4.18e
8.61	• results of IPCs	☐ ☐ ☐		4.18e
8.62	• details of operations and equipment used?	☐ ☐ ☐		4.18f
8.63	• samples of printed packaging materials with codes (MFD, EXP, batch no., etc.)?	☐ ☐ ☐		4.18g
8.64	• record of problems and process deviations?	☐ ☐ ☐		4.18h
8.65	• quantities of packaging materials delivered, used, destroyed, or returned?	☐ ☐ ☐		4.18i
8.66	• no. of packs consumed?	☐ ☐ ☐		4.18j
	Testing			
	Do the written testing procedures include			
8.67	• test methods?	☐ ☐ ☐		4.23
8.68	• equipment for testing?	☐ ☐ ☐		4.23
8.69	Tests documented?	☐ ☐ ☐		4.23
	Others			
8.70	Procedures for release and rejection of materials and finished products?	☐ ☐ ☐		4.24
8.71	Final release by authorized person?	☐ ☐ ☐		4.24
8.72	Records about distribution of each batch?	☐ ☐ ☐		4.25
	Procedures and protocols about			
8.73	• validation?	☐ ☐ ☐		4.26

		Compliance 1 2 3[a]	Remarks	EU Guide
8.74	• set up and calibration of equipment?	☐ ☐ ☐		4.26
8.75	• maintenance, cleaning, and disinfection?	☐ ☐ ☐		4.26
8.76	• training records?	☐ ☐ ☐		4.26
8.77	• environmental monitoring of production areas?	☐ ☐ ☐		4.26
8.78	• pest control?	☐ ☐ ☐		4.26
8.79	• complaints?	☐ ☐ ☐		4.26
8.80	• recalls?	☐ ☐ ☐		4.26
8.81	• returned goods?	☐ ☐ ☐		4.26
8.82	Instructions for use of manufacturing and testing equipment?	☐ ☐ ☐		4.27
	Logbooks for major equipment incl. date and name of persons who performed			
8.83	• validation?	☐ ☐ ☐		4.28
8.84	• calibration?	☐ ☐ ☐		4.28
8.85	• maintenance, cleaning, and repair works?	☐ ☐ ☐		4.28
8.86	Chronological records of use of major equipment and manufacturing areas?	☐ ☐ ☐		4.29
9	**QUALITY CONTROL**			**6**
	General requirements			
9.1	Independent QC department available?	☐ ☐ ☐		6.1
9.2	Head of QC well qualified and sufficiently experienced?	☐ ☐ ☐		6.1
9.3	Qualified personnel available?	☐ ☐ ☐		2.1
9.4	Organization charts available?	☐ ☐ ☐		2.2
9.5	Job descriptions available?	☐ ☐ ☐		2.2
9.6	Responsibilities clearly defined?	☐ ☐ ☐		2.2
9.7	Continuous training programs for QC staff?	☐ ☐ ☐		2.2
9.8	Initial job training for all employees?	☐ ☐ ☐		2.9
9.9	Training records?	☐ ☐ ☐		
9.10	QC personnel admitted to the production rooms for sampling etc.?	☐ ☐ ☐		
	QC Laboratories			
9.11	Suitable for the intended use?	☐ ☐ ☐		3.26
9.12	Laboratories of adequate size?	☐ ☐ ☐		3.26
9.13	Appropriate level of maintenance?	☐ ☐ ☐		3.1
9.14	Adequate separation from the production area?	☐ ☐ ☐		3.26
9.15	Controlled access of authorized personnel only?	☐ ☐ ☐		3.5
9.16	Special laboratory to handle biological samples available?	☐ ☐ ☐		3.29
9.17	Special laboratory to handle radioactive material available?	☐ ☐ ☐		3.29
9.18	Separate recreation rooms for the personnel available?	☐ ☐ ☐		3.30
9.19	Animal laboratories present?	☐ ☐ ☐		3.33
9.20	Animal laboratories separated from other areas?	☐ ☐ ☐		3.33
9.21	Animal laboratories equipped with a separate air-handling system?	☐ ☐ ☐		3.33

		Compliance 1 2 3[a]	Remarks	EU Guide
	QC Documentation			
9.22	Do procedures exist for • self inspection? • release or rejection of products or raw material? • product complaints? • product recalls? • local stability testing? • storage of reference samples? • validation of analytical procedures?	 ☐		
9.23	Specifications available for • raw materials? • bulk products? • packaging materials?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.7
9.24	Analytical procedures for every product?	☐ ☐ ☐		
9.25	Are Basel methods followed?	☐ ☐ ☐		
9.26	Validation of locally developed test methods?	☐ ☐ ☐		
9.27	Sampling procedures available for • raw materials? • bulk products? • packaging materials?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.7
9.28	Suppliers certificates available?	☐ ☐ ☐		6.7
9.29	Calibration program for analytical instruments installed?	☐ ☐ ☐		6.7
9.30	Maintenance program for analytical instruments?	☐ ☐ ☐		6.7
9.31	Retention system for QC records?	☐ ☐ ☐		6.8
9.32	Batch documents stored for expiry + 1 year or 5 years (EEC 75/319, article 22) minimum?	☐ ☐ ☐		6.8
9.33	Are original data like notebooks stored in addition to the batch documents?	☐ ☐ ☐		6.10
9.34	Can the original data be traced back easily and quickly from the analytical report number or batch number?	☐ ☐ ☐		6.10
9.35	Are trend analyses being performed for • analytical results? • yields? • environmental monitoring data?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.9
	Sampling			
9.36	Written procedures for taking samples?	☐ ☐ ☐		6.11
9.37	Do procedures define • method of sampling? • necessary equipment? • quantity of the sample? • subdivision of the sample? • sample container? • labeling of samples? • storage conditions? • cleaning and storage of sampling equipment? • identification of containers sampled	 ☐		
9.38	Are samples representative for the batch they are taken from? (sampling plan)	☐ ☐ ☐		6.12
9.39	Are critical steps being surveilled and validated by additional sampling (e.g., beginning or end of a process).	☐ ☐ ☐		6.12

		Compliance 1 2 3[a]	Remarks	EU Guide
9.40	Sample containers labeled with • name of the content • batch number • date of sampling • batch containers sampled	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.13
9.41	Are samples taken by QC/QA?	☐ ☐ ☐		
9.42	Reference samples retained for validity plus 1 year?	☐ ☐ ☐		6.14
9.43	Storage of reference samples under the recommended storage conditions?	☐ ☐ ☐		6.14
9.44	Finished products stored in the final packaging?	☐ ☐ ☐		6.14
9.45	Quantity of the reference sample makes 1 (better 2) complete reanalysis possible?	☐ ☐ ☐		6.14
9.46	Sample room secure?	☐ ☐ ☐		
9.47	Sample room neatly organized and not overcrowded?	☐ ☐ ☐		
	Testing			
9.48	Are the applied analytical methods validated?	☐ ☐ ☐		6.15
9.49	Analytical methods in compliance with the registration?	☐ ☐ ☐		6.16
9.50	Are all results recorded and checked for correctness?	☐ ☐ ☐		6.16
9.51	Are all calculations checked?	☐ ☐ ☐		6.16
9.52	Do the testing protocols contain • name and galenical form of material? • batch number? • supplier if applicable? • specification reference? • method reference? • analytical results? • reference to analytical certificates? • date of the analysis? • name of the analyst? • name of the person verifying the data? • statement of release or rejection? • date and sign of the release person?	 ☐		6.17
9.53	Are all IPC methods in production approved by QC?	☐ ☐ ☐		6.18
9.54	Are written methods available for the preparation of reagents and volumetric solutions?	☐ ☐ ☐		6.19
9.55	Is a record maintained of standardization of volumetric solutions?	☐ ☐ ☐		6.2
9.56	Are reagents for prolonged use labeled with • date of the preparation? • sign of the preparator?	 ☐ ☐ ☐ ☐ ☐ ☐		6.20
9.57	Are unstable reagents labeled with • expiry date? • storage conditions?	 ☐ ☐ ☐ ☐ ☐ ☐		6.20
9.58	Are volumetric solutions labeled with • the last date of standardization? • last current factor?	 ☐ ☐ ☐ ☐ ☐ ☐		6.20
9.59	Are reference standards labeled with • name and potency • suppliers reference • date of receipt • date of expiry	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.21

		Compliance 1 2 3[a]	Remarks	EU Guide
9.60	Are reference standards stored properly and under the control of a designated person?	☐ ☐ ☐		
9.61	Are animals used for testing of components, materials or products • quarantined before use? • checked for suitability? • Are records maintained showing the history of their use?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		
10	**COMPLAINTS AND PRODUCT RECALLS**			**8**
	Complaints			8.1
10.1	Does a written complaint procedure exist?	☐ ☐ ☐		8.2
10.2	Are product complaints carefully reviewed?	☐ ☐ ☐		8.1
10.3	Is a person designated to handle complaints and to decide on measures to be taken?	☐ ☐ ☐		8.1
10.4	Is each complaint concerning a product recorded with all original details?	☐ ☐ ☐		8.3
10.5	Are product complaints thoroughly investigated?	☐ ☐ ☐		8.3
10.6	Is a responsible person of QC involved in the study?	☐ ☐ ☐		8.3
10.7	Is it considered that other batches might be concerned as well?	☐ ☐ ☐		8.4
10.8	Are decisions and measures as a result recorded?	☐ ☐ ☐		8.5
10.9	Is this record added to the corresponding batch documents?	☐ ☐ ☐		8.5
10.10	Are the complaint records regularly revised with respect to specific or recurring problems?	☐ ☐ ☐		8.6
10.11	Are the authorities informed of serious quality problems with a product?	☐ ☐ ☐		8.7
	Recalls			8.8
10.12	Does a written recall procedure exist?	☐ ☐ ☐		8.9
10.13	Is a person nominated responsible for the execution and coordination of a recall?	☐ ☐ ☐		8.8
10.14	Responsible person independent of the marketing and sales organization?	☐ ☐ ☐		8.8
10.15	Are the competent authorities informed of an imminent recall?	☐ ☐ ☐		8.11
10.16	Does the person responsible for a recall have access to the distribution records?	☐ ☐ ☐		8.12
10.17	Do the distribution records contain sufficient information on customers with • addresses? • phone numbers inside or outside working hours? • Batches and amounts delivered? • Medical samples?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		8.12
10.18	Are recalled products stored separately in a secure area?	☐ ☐ ☐		8.13
10.19	Is a final record made including a reconciliation between the delivered and recovered quantities?	☐ ☐ ☐		8.14
10.20	Is the effectiveness of the arrangements for recalls checked critically from time to time?	☐ ☐ ☐		8.15
11	**SELF INSPECTION**			**9**
11.1	Does a self-inspection procedure exist which defines frequency and program?	☐ ☐ ☐		9.1
11.2	Are self-inspections carried out to check compliance with GMP rules?	☐ ☐ ☐		9.1

		Compliance 1 2 3[a]	Remarks	EU Guide
11.3	Are self-inspections conducted in an • independent and detailed way? • by designated competent persons from the company or external experts?	 ☐ ☐ ☐ ☐ ☐ ☐		9.2 9.2
11.4	Are self-inspections recorded?	☐ ☐ ☐		9.3
11.5	Do reports contain the observations made during a self-inspection? Proposals for corrective measures?	☐ ☐ ☐ ☐ ☐ ☐		9.3
11.6	Are actions subsequently taken recorded?	☐ ☐ ☐		9.3
12	**CONTRACT MANUFACTURE AND ANALYSIS**			**7**
12.1	Written contract between contract giver and contract acceptor available?	☐ ☐ ☐		7.1
12.2	Are responsibilities and duties clearly defined?	☐ ☐ ☐		7
12.3	All arrangements in accordance with the marketing authorization of the product concerned?	☐ ☐ ☐		7.2
	The contract giver			
12.4	Competence of the acceptor to carry out the work successful and according to GMP assessed?	☐ ☐ ☐		7.3
12.5	Acceptor provided with all the informations necessary to carry out the contract work?	☐ ☐ ☐		7.4
12.6	Acceptor informed of safety aspects?	☐ ☐ ☐		7.4
12.7	Conformance of products supplied by the acceptor ensured?	☐ ☐ ☐		7.5
12.8	Product released by a qualified person on the acceptor's side?	☐ ☐ ☐		7.5
	The contract acceptor			
12.9	Does the acceptor have • adequate premises and equipment? • knowledge and experience? • competent personnel? • a manufacturing authorization?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.6 7.6
12.10	Does the acceptor ensure that all products or materials delivered to him are suitable?	☐ ☐ ☐		7.7
12.11	There must be no work passed to a third party without the permission of the giver.	☐ ☐ ☐		7.8
12.12	If a third party is involved, it must have the necessary manufacturing and analytical information.	☐ ☐ ☐		7.8
	The contract			
12.13	Does the written contract specify the responsibilities?	☐ ☐ ☐		7.10
12.14	Have technical aspects been drawn up by competent persons?	☐ ☐ ☐		7.10
12.15	Release of material and check for compliance with the marketing authorization defined?	☐ ☐ ☐		7.11
12.16	Is it defined who is responsible for • purchasing of materials? • IPC controls • testing and release of materials? • manufacturing and quality control? • sampling? • storage of batch documentation?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.12
12.17	Are manufacturing, analytical, and distribution records available to the contract giver?	☐ ☐ ☐		7.13
12.18	Contract permits the giver to visit the facilities of the acceptor?	☐ ☐ ☐		7.14

		Compliance 1 2 3[a]	Remarks	EU Guide
12.19	In the case of contract analysis: Does the contract acceptor understand that he is subject to inspection by the competent authorities?	☐ ☐ ☐		7.15
13	**AUDIT OF SUPPLIERS**			**2.7**
13.1	Supplier audits performed • excipients? • active substances? • packaging material?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		

[a] 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (or Drug Substance)—Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Air lock—An enclosed space with two or more doors, which is interposed between two or more rooms, for example, of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An air lock is designed for use either by people or for goods and/or equipment.

API Starting Material—A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house. API Starting Materials are normally of defined chemical properties and structure.

Authorized Person—The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested, and approved for release in compliance with the laws and regulations in force in that country.

Batch (or Lot)—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Batch Number (or Lot Number)—A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, etc.

Batch Records—All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bioburden—The level and type (e.g. objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates, or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Bulk Product—Any product that has completed all processing stages up to, but not including, final packaging.

Calibration—The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Clean Area—An area with defined environmental control of particulate and microbial contamination, constructed and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Computer System—A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions. A process or operation integrated with a computer system.

Consignment (or delivery)—The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Contamination—The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, and storage or transport.

Contract Manufacturer—A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical—Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Critical Operation—An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Cross-Contamination—Contamination of a material or product with another material or product. Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Deviation—Departure from an approved instruction or established standard.

Drug (Medicinal) Product—The dosage form in the final immediate packaging intended for marketing. (Reference Q1A).

Drug Substance—See Active Pharmaceutical Ingredient.

Expiry Date (or Expiration Date)—The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf-life specifications if stored under defined conditions, and after which it should not be used.

Finished Product—A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.

Impurity—Any component present in the intermediate or API that is not the desired entity.

Impurity Profile—A description of the identified and unidentified impurities present in an API.

In-Process control—Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate—A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Large-Volume Parenterals—Sterile solutions intended for parenteral application with a volume of 100 mL or more in one container of the finished dosage form.

Lot—See Batch

Lot Number—See Batch Number

Manufacture—All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Manufacturer—A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of pharmaceuticals.

Marketing Authorization (Product License, Registration Certificate)—A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling, and shelf life.

Master Formula—A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master Record—A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Material—A general term used to denote raw materials (starting materials, reagents, and solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother Liquor—The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It may be used for further processing.

Packaging—All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized would not normally be regarded as part of packaging.

Packaging Material—Any material intended to protect an intermediate or API during storage and transport. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical Product—Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Procedure—A documented description of the operations to be performed, the precautions to be taken, and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids—Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon).

Process Control—See In-Process Control.

Production—All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, and labeling and relabeling, to completion of the finished product.

Qualification—Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)—The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)—Checking or testing that specifications are met.

Quality Unit(s)—An organizational unit independent of production, which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine—The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Raw Material—A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reconciliation—A comparison between the theoretical quantity and the actual quantity.

Recovery—The introduction of all or part of previous batches (or of redistilled solvents and similar products) of

the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

Reference Standard, Primary—A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity.

Reference Standard, Secondary—A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing—Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate), or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and preapproved as part of the marketing authorization.

Retest Date—The date when a material should be reexamined to ensure that it is still suitable for use.

Reworking—Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not preapproved as part of the marketing authorization.

Self-Contained Area—Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well-established procedures, controls, and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

Signature (Signed)—See definition for signed.

Signed (Signature)—The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent—An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification—A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Standard Operating Procedure (SOP)—An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g. equipment operation, maintenance, and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting Material—Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Validation—A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity, or system actually leads to the expected results (see also qualification).

Validation Protocol—A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected—The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical—The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

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Dissolution Testing of Semisolid Dosage Forms

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (min)	Date Updated
Prochlorperazine	Suppository	I (Suppository, dissolution baskets, palmieri type)	100	0.1 N HCl at 38°C	900	10, 20, 30, and 45	08/17/2006
Acetaminophen	Suppository	II (Paddle)	50	Phosphate buffer, pH 5	900	15, 30, 45, 60, and 90	08/17/2006
Mesalamine	Suppository	II (Paddle) with option to use a sinker	75 (for 500 mg) & 125 (for 1000 mg)	For 500-mg strength: 0.2 M phosphate buffer, pH 7.5 at 37°C; For 1000-mg strength: 0.2 M phosphate buffer, pH 7.5 at 40°C	900	30, 60, 90, 120, and 150	01/30/2006

Approved Excipients in Semisolid Dosage Forms

Ingredient	Dosage Form	Qty	Unit
1,2,6-hexanetriol	Topical; emulsion, cream	7.5	%
1,3-dimethylol-5,5-dimethyl-hydantoin	Topical; lotion	46.4	%
2-amino-2-methyl-1-propanol	Topical; lotion	0.3	%
2-amino-2-methyl-1-propanol	Topical; emulsion, cream	1	%
2-ethylhexyl salicylate	Transdermal; spray	68.85	%
Acetone	Topical; lotion	10	%
Acrylates copolymer	Topical; gel	10	%
Acrylates copolymer	Topical; emulsion, cream	13.6	%
Acrylates copolymer	Transdermal; film, controlled release	382.22	mg
Acrylic acid/isooctylacrylate copolymer	Transdermal; film, controlled release	24.5	mg
Adcote 72A103	Transdermal; patch, controlled release	3.99	mg
Adcote 72A103	Transdermal; film, controlled release	16	mg
Adhesive tape	Transdermal; film, controlled release	127.85	mg
Aerotex Resin 3730	Transdermal; film, controlled release	1.9	mg
Alcohol	Transdermal; gel	74.1	%
Alcohol	Topical; lotion	80.5	%
Alcohol	Topical; gel	84.95	%
Alcohol	Transdermal; film, controlled release	358.7	mg
Alcohol, dehydrated	Topical; lotion	8.8	%
Alcohol, dehydrated	Transdermal; gel	46.28	%
Alcohol, dehydrated	Topical; gel	94.7808	%
Alcohol, dehydrated	Transdermal; film, controlled release	250	mg
Alcohol, denatured	Topical; lotion	25	%
Alcohol, denatured	Topical; gel	96.9385	%
Allantoin	Topical; gel	0.2	%
Allantoin	Topical; emulsion, cream	1	%
Allantoin	Vaginal; emulsion, cream	2	%
Almond oil	Topical; emulsion, cream	2	%
Alpha-terpineol	Topical; lotion	11	%
Alpha-tocopherol	Topical; ointment	0.002	%
Aluminum acetate	Topical; emulsion, cream	0.0001	%
Aluminum acetate	Topical; lotion	10	%
Aluminum diacetate	Rectal; suppository	75	mg
Aluminum hydroxide	Topical; emulsion, cream	5	%
Aluminum hydroxide gel	Topical; emulsion, cream	5	%
Aluminum hydroxide gel F 500	Topical; emulsion, cream	2	%

Ingredient	Dosage Form	Qty	Unit
Aluminum hydroxide gel F 5000	Topical; emulsion, cream	3	%
Aluminum monostearate	Topical; emulsion, cream	0.01	%
Aluminum polyester	Transdermal; film, controlled release	81	mg
Aluminum potassium sulfate	Vaginal; suppository	17.2	mg
Aluminum starch octenylsuccinate	Topical; emulsion, cream	10	%
Aluminum stearate	Topical; emulsion, cream	0.01	%
Aluminum stearate	Topical; ointment	0.01	%
Aluminum sulfate	Topical; emulsion, cream	0.131	%
Amerchol-cab	Topical; ointment	10	%
Ammonium hydroxide	Topical; emulsion, cream	5.72	%
Ammonyx	Topical; sponge	37500	mg
Amphoteric-9	Topical; emulsion, cream	0.66	%
Anoxid SBN	Topical; emulsion, cream	0.1562	%
Antifoam	Topical; lotion	0.031	%
Apricot kernel oil PEG-6 esters	Topical; emulsion, cream	2.94	%
Apricot kernel oil PEG-6 ESTERS	Vaginal; emulsion, cream	2.94	%
Aquaphor	Topical; emulsion, cream	1	%
Arlacel	Topical; emulsion, cream	1.5	%
Arlatone 289	Topical; emulsion, cream	1.9	%
Ascorbic acid	Topical; gel	0.3	%
Ascorbic acid	Rectal; suppository	3	mg
Ascorbyl palmitate	Topical; emulsion, cream	0.02	%
Ascorbyl palmitate	Rectal; suppository	5.6	mg
Balsam, Canada	Topical; lotion	0.5	%
Balsam, Peru	Rectal; suppository	100	mg
Barium sulfate	Vaginal; drug delivery system	5.9	mg
Beeswax	Topical; emulsion, cream	5	%
Beeswax	Topical; ointment	20	%
Beeswax, synthetic	Topical; emulsion, cream	3.5	%
Bentonite	Transdermal; patch, controlled release	2.47	mg
Bentonite	Topical; lotion	5	%
Bentonite	Transdermal; film, controlled release	9.86	mg
Bentonite	Vaginal; suppository	288.1	mg
Benzalkonium chloride	Topical; lotion	0.1	%
Benzoic acid	Topical; gel	0.1	%
Benzoic acid	Topical; lotion	0.2	%
Benzoic acid	Topical; emulsion, cream	0.25	%
Benzoic acid	Vaginal; emulsion, cream	0.25	%
Benzoic acid	Vaginal; sponge	3	mg
Benzyl alcohol	Topical; cream, augmented	1	%
Benzyl alcohol	Topical; cream, emulsion, sustained release	1	%
Benzyl alcohol	Vaginal; cream, augmented	1	%
Benzyl alcohol	Vaginal; emulsion, cream	1	%

Ingredient	Dosage Form	Qty	Unit
Benzyl alcohol	Topical; lotion	1.3	%
Benzyl alcohol	Topical; ointment	2.2	%
Benzyl alcohol	Topical; emulsion, cream	2.7	%
Benzyl alcohol	Topical; gel	50	%
Betadex	Topical; gel	1	%
Bismuth subgallate	Rectal; suppository	115	mg
Butyl alcohol, tertiary	Topical; gel	0.1186	%
Butyl stearate	Topical; emulsion, cream	3.7	%
Butylated hydroxyanisole	Topical; ointment	0.005	%
Butylated hydroxyanisole	Vaginal; ointment	0.02	%
Butylated hydroxyanisole	Topical; gel	0.05	%
Butylated hydroxyanisole	Topical; emulsion, cream	0.1	%
Butylated hydroxyanisole	Vaginal; emulsion, cream	0.125	%
Butylated hydroxyanisole	Rectal; suppository	0.213	mg
Butylated hydroxyanisole	Vaginal; suppository	1	mg
Butylated hydroxytoluene	Topical; lotion	0.02	%
Butylated hydroxytoluene	Topical; ointment	0.025	%
Butylated hydroxytoluene	Topical; cream, augmented	0.05	%
Butylated hydroxytoluene	Vaginal; emulsion, cream	0.05	%
Butylated hydroxytoluene	Topical; cream, emulsion, sustained release	0.1	%
Butylated hydroxytoluene	Topical; emulsion, cream	0.1	%
Butylated hydroxytoluene	Rectal; suppository	0.213	mg
Butylated hydroxytoluene	Topical; gel	2	%
Butylene glycol	Transdermal; patch, controlled release	2.03	mg
Butylene glycol	Transdermal; film, controlled release	8.12	mg
Butylparaben	Topical; lotion	0.15	%
Butylparaben	Topical; emulsion, cream	0.4	%
Calcium acetate	Topical; emulsion, cream	0.092	%
Calcium chloride	Topical; emulsion, cream	0.25	%
Calcium hydroxide	Topical; emulsion, cream	1.4	%
Caprylic/capric triglyceride	Topical; cream, emulsion, sustained release	10	%
Caprylic/capric triglyceride	Topical; emulsion, cream	10.8	%
Caprylic/capric/stearic triglyceride	Topical; ointment	70	%
Caramel	Topical; emulsion, cream	0.26	%
Carbomer 1342	Topical; cream, augmented	0.2	%
Carbomer 1342	Topical; cream, emulsion, sustained release	0.2	%
Carbomer 1342	Topical; lotion	0.2	%
Carbomer 1342	Topical; emulsion, lotion	0.3	%
Carbomer 1342	Transdermal; gel	1.5	%
Carbomer 1342	Transdermal; film, controlled release	24.3	mg
Carbomer 934	Topical; lotion	0.5	%
Carbomer 934	Topical; ointment	0.5	%
Carbomer 934	Topical; emulsion, cream	1	%

Ingredient	Dosage Form	Qty	Unit
Carbomer 934	Topical; gel	1.498	%
Carbomer 934	Vaginal; gel	2	%
Carbomer 934P	Topical; lotion	0.56	%
Carbomer 934P	Topical; cream, augmented	1	%
Carbomer 934P	Topical; cream, emulsion, sustained release	1	%
Carbomer 934P	Topical; emulsion, cream	1	%
Carbomer 934P	Topical; gel	2	%
Carbomer 934P	Vaginal; gel	2	%
Carbomer 940	Topical; emulsion, cream	0.6	%
Carbomer 940	Topical; cream, augmented	1	%
Carbomer 940	Transdermal; gel	1.2	%
Carbomer 940	Topical; ointment, augmented	2.25	%
Carbomer 940	Topical; gel	3.5	%
Carbomer 940	Topical; lotion	58	%
Carbomer 941	Topical; lotion	0.15	%
Carbomer 941	Topical; gel	0.2	%
Carbomer 974P	Topical; gel	0.8	%
Carbomer 980	Topical; gel	0.85	%
Carbomer 980	Topical; emulsion, cream	1.2	%
Carbomer 980	Transdermal; gel	7.5	%
Carbomer 981	Topical; gel	0.85	%
Carboxy vinyl copolymer	Topical; gel	30	%
Carboxymethylcellulose	Topical; patch	6.14	mg
Carboxymethylcellulose sodium	Topical; jelly	3.5	%
Carboxypolymethylene	Topical; lotion	0.3	%
Carboxypolymethylene	Topical; gel	1	%
Carrageenan	Topical; lotion	0.5	%
Carrageenan	Transdermal; film, controlled release	33	mg
Carrageenan salt	Topical; lotion	0.271	%
Castor oil	Topical; emulsion, cream	12.5	%
Castor oil	Topical; ointment	14.9	%
Cerasynt-SE	Topical; lotion	3	%
Cerasynt-SE	Rectal; suppository	35	mg
Ceresin	Topical; ointment	7.31	%
Ceteareth-12	Topical; emulsion, cream	5	%
Ceteareth-15	Topical; emulsion, cream	1.5	%
Ceteareth-30	Topical; cream, augmented	1	%
Ceteareth-30	Topical; lotion	2.3	%
Ceteareth-30	Topical; emulsion, cream	3	%
Cetearyl alcohol	Topical; ointment	1.2	%
Cetearyl alcohol	Topical; lotion	4	%
Cetearyl alcohol	Topical; emulsion, lotion	5	%
Cetearyl alcohol	Vaginal; cream, augmented	10	%

Ingredient	Dosage Form	Qty	Unit
Cetearyl alcohol	Topical; emulsion, cream	12	%
Cetearyl alcohol	Vaginal; emulsion, cream	12	%
Cetearyl alcohol/ceteareth-20	Topical; cream, augmented	4.72	%
Cetearyl alcohol/ceteareth-20	Topical; emulsion, cream	8	%
Cetearyl octanoate	Topical; emulsion, cream	3	%
Ceteth-10	Topical; lotion	2.5	%
Ceteth-2	Topical; lotion	0.8	%
Ceteth-2	Topical; emulsion, cream	2.5	%
Ceteth-20	Topical; emulsion, lotion	1	%
Ceteth-20	Topical; lotion	2	%
Ceteth-20	Topical; emulsion, cream	4.005	%
Ceteth-20	Topical; cream, augmented	6	%
Ceteth-23	Topical; emulsion, cream	2	%
Cetrimonium chloride	Topical; lotion	0.2	%
Cetyl alcohol	Topical; cream, augmented	4	%
Cetyl alcohol	Topical; cream, emulsion, sustained release	6	%
Cetyl alcohol	Topical; ointment	7	%
Cetyl alcohol	Topical; emulsion, cream	12	%
Cetyl alcohol	Vaginal; emulsion, cream	15	%
Cetyl alcohol	Topical; lotion	68.4	%
Cetyl esters	Topical; lotion	3	%
Cetyl esters	Vaginal; cream, augmented	3	%
Cetyl esters	Vaginal; emulsion, cream	3	%
Cetyl esters	Topical; emulsion, cream	10.3	%
Cetyl palmitate	Vaginal; emulsion, cream	3.3	%
Cetyl palmitate	Topical; emulsion, cream	9.45	%
Cetylpyridinium chloride	Iontophoresis; drug delivery system	1.2	mg
Cetylpyridinium chloride	Transdermal; drug delivery system	1.2	mg
Chemoderm 6401B	Topical; cream, emulsion, sustained release	0.1	%
Chlorocresol	Topical; cream, augmented	0.1	%
Chlorocresol	Topical; emulsion, cream	0.75	%
Chloroxylenol	Topical; emulsion, cream	0.15	%
Cholesterol	Vaginal; emulsion, cream	0.5	%
Cholesterol	Topical; emulsion, cream	1	%
Cholesterol	Topical; lotion	1.5	%
Cholesterol	Topical; ointment	5	%
Choleth	Vaginal; emulsion, cream	1	%
Citric acid	Topical; ointment	0.012	%
Citric acid	Iontophoresis; solution	0.02	%
Citric acid	Topical; cream, augmented	0.05	%
Citric acid	Topical; gel	0.05	%
Citric acid	Iontophoresis; patch, controlled release	0.2	mg
Citric acid	Topical; patch, controlled release	0.2	mg

Ingredient	Dosage Form	Qty	Unit
Citric acid	Topical; lotion	0.85	%
Citric acid	Iontophoresis; drug delivery system	1.4	mg
Citric acid	Transdermal; drug delivery system	1.4	mg
Citric acid	Topical; emulsion, cream	5	%
Citric acid	Vaginal; sponge	7.5	mg
Citric acid monohydrate	Topical; emulsion, cream	0.05	%
Citric acid monohydrate	Topical; gel	0.1	%
Citric acid monohydrate	Vaginal; emulsion, cream	0.494	%
Citric acid, hydrous	Topical; emulsion, lotion	0.05	%
Citric acid, hydrous	Topical; emulsion, cream	0.1	%
Cocamide diethanolamine	Topical; emulsion, cream	4	%
Cocamide diethanolamine	Topical; sponge	20.2	mg
Cocoa butter	Topical; lotion	0.1	%
Cocoa butter	Rectal; suppository	2070.6	mg
Coconut oil	Topical; emulsion, cream	6	%
Coconut oil	Topical; ointment	25	%
Coconut oil, fractioned	Topical; ointment	0.02	%
Coconut oil/palm kernel oil glycerides, hydrogenated	Rectal; suppository	1734.9	mg
Coconut oil/palm kernel oil glycerides, hydrogenated	Vaginal; suppository	2375	mg
Collagen	Topical; gel	0.024	%
Crospovidone	Topical; lotion	0.185	%
Crospovidone	Vaginal; suppository	116.1	mg
Cyclomethicone	Topical; lotion	4	%
Cyclomethicone	Topical; cream, augmented	7.6	%
Cyclomethicone	Topical; emulsion, cream	13	%
Cyclomethicone/dimethicone copolyol	Topical; gel	2.3	%
D&C Yellow No. 10	Topical; gel	0.001	%
D&C Yellow No. 10	Rectal; suppository	0.11	mg
Daubert 1–5 pestr (matte) 164Z	Transdermal; film, controlled release	507.5	mg
Dehydroacetic acid	Topical; lotion	11.6	%
Dehymuls E	Topical; ointment	7.5	%
Denatonium benzoate	Topical; gel	0.0006	%
Dextrin	Topical; emulsion, cream	0.029	%
Diazolidinylurea	Topical; cream, emulsion, sustained release	0.2	%
Diazolidinylurea	Topical; emulsion, cream	0.3	%
Dichlorobenzyl alcohol	Topical; emulsion, cream	0.1	%
Diethanolamine	Topical; emulsion, cream	0.3	%
Diethylene glycol monoethyl ether	Transdermal; gel	5	%
Diethylene glycol monoethyl ether	Topical; gel	25	%
Diisopropanolamine	Topical; emulsion, cream	0.12	%
Diisopropanolamine	Topical; gel	0.2	%
Diisopropyl adipate	Topical; lotion	20	%
Dimethicone 350	Topical; emulsion, cream	1	%

Ingredient	Dosage Form	Qty	Unit
Dimethicone 360	Topical; emulsion, cream	5	%
Dimethicone 360	Transdermal; film, controlled release	564	mg
Dimethicone copolyol	Topical; gel	1	%
Dimethyl isosorbide	Topical; emulsion, cream	15	%
Dimethyl sulfoxide	Topical; dressing	16.5	mg
Dioctylphthalate	Transdermal; film, controlled release	600.12	mg
Dipropylene glycol	Transdermal; patch, controlled release	0.218	mg
Dipropylene glycol	Transdermal; film, controlled release	12	mg
Disodium laureth sulfosuccinate	Topical; gel	0.04	%
Docusate sodium	Topical; gel	3	%
Duro-Tak 80–1196	Transdermal; film, controlled release	172	mg
Duro-Tak 87–2194	Transdermal; film, controlled release	208.28	mg
Duro-Tak 87–2287	Transdermal; film, controlled release	121.1	mg
Duro-Tak 87–2287	Percutaneous; patch, controlled release	165	cm
Duro-Tak 87–2296	Transdermal; patch, controlled release	43	mg
Duro-Tak 87–2888	Transdermal; patch	175.9	mg
Edamine	Topical; emulsion, cream	0.18	%
Edetate calcium disodium	Ureteral; solution	0.01	%
Edetate calcium disodium	Urethral; solution	0.01	%
Edetate disodium	Topical; ointment	0.0065	%
Edetate disodium	Topical; cream, emulsion, sustained release	0.05	%
Edetate disodium	Vaginal; emulsion, cream	0.05	%
Edetate disodium	Vaginal; gel	0.05	%
Edetate disodium	Transdermal; gel	0.06	%
Edetate disodium	Iontophoresis; patch, controlled release	0.1	mg
Edetate disodium	Topical; cream, augmented	0.1	%
Edetate disodium	Topical; lotion	0.1	%
Edetate disodium	Topical; patch, controlled release	0.1	mg
Edetate disodium	Topical; gel	0.17	%
Edetate disodium	Topical; emulsion, cream	1	%
Edetate sodium	Topical; lotion	0.05	%
Edetic acid	Topical; lotion	0.11	%
Edetic acid	Rectal; suppository	1.7	mg
Essence bouquet 9200	Topical; lotion	0.2	%
Ethyl acetate	Transdermal; film, controlled release	36138	mg
Ethyl oleate	Transdermal; film, controlled release	8.64	mg
Ethylcellulose	Topical; patch	2.53	mg
Ethylcellulose	Transdermal; film, controlled release	80.4	mg
Ethylene vinyl acetate copolymer	Transdermal; film, controlled release	735	mg
Ethylene vinylacetate copolymer, 28% vinylacetate	Vaginal; sponge	1677	mg
Ethylene vinylacetate copolymer, 9% vinylacetate	Vaginal; sponge	197	mg
Ethylenediamine dihydrochloride	Topical; emulsion, cream	0.25	%
Ethylene-propylene copolymer	Transdermal; film, controlled release	31.67	mg

Ingredient	Dosage Form	Qty	Unit
Fat, hard	Rectal; suppository	1920	mg
Fatty Acid pentaerythriol ester	Topical; ointment	1	%
FD&C Green No. 3	Rectal; suppository	0.015	mg
FD&C Red No. 4	Topical; lotion	0.0007	%
FD&C Red No. 40	Topical; sponge	50	mg
FD&C Yellow No. 10	Topical; lotion	0.0008	%
FD&C Yellow No. 5	Topical; emulsion, cream	0.004	%
FD&C Yellow No. 5	Vaginal; emulsion, cream	0.004	%
FD&C Yellow No. 6	Topical; gel	0.0013	%
FD&C Yellow No. 6	Topical; lotion	0.0016	%
Ferric oxide	Topical; lotion	0.15	%
Formaldehyde	Topical; emulsion, cream	0.27	%
Formaldehyde solution	Topical; emulsion, cream	0.27	%
Fragrance 6.007	Topical; lotion	0.2	%
Fragrance 9128-Y	Topical; emulsion, cream	0.07	%
Fragrance 93498G	Topical; lotion	0.0069	%
Fragrance chemoderm 6401-B	Topical; cream, augmented	0.25	%
Fragrance chemoderm 6411	Topical; emulsion, cream	0.1	%
Fragrance CS-28197	Topical; emulsion, cream	0.1	%
Fragrance givaudan ESS 9090/1 C	Topical; sponge	1.01	mg
Fragrance NJ-1085	Topical; lotion	0.1	%
Fragrance pera derm D	Topical; lotion	0.12	%
Fragrance RBD-9819	Topical; lotion	0.084	%
Fragrance RBD-9819	Topical; emulsion, cream	0.125	%
Fragrance ungerer N5195	Topical; lotion	8.1	%
Gluconolactone	Topical; sponge	2500	mg
DL-Glutamic acid	Vaginal; emulsion, cream	0.1	%
Glycerin	Topical; cream, emulsion, sustained release	2	%
Glycerin	Topical; cream, augmented	4	%
Glycerin	Vaginal; emulsion, cream	5	%
Glycerin	Vaginal; gel	14.51	%
Glycerin	Topical; emulsion, cream	20	%
Glycerin	Topical; gel	20	%
Glycerin	Transdermal; gel	25	%
Glycerin	Topical; lotion	50	%
Glycerin	Rectal; suppository	128	mg
Glycerin	Iontophoresis; patch, controlled release	168.1	mg
Glycerin	Topical; patch, controlled release	168.1	mg
Glycerin	Vaginal; suppository	227.9	mg
Glycerin	Transdermal; film, controlled release	306.2	mg
Glyceryl citrate	Topical; emulsion, cream	0.05	%
Glyceryl isostearate	Topical; emulsion, cream	2	%
Glyceryl isostearate	Vaginal; emulsion, cream	2.7	%

Ingredient	Dosage Form	Qty	Unit
Glyceryl laurate	Transdermal; film, controlled release	0.36	mg
Glyceryl oleate	Topical; cream, augmented	3.5	%
Glyceryl oleate	Transdermal; film, controlled release	18.8	mg
Glyceryl oleate/propylene glycol	Topical; cream, augmented	3	%
Glyceryl oleate/propylene glycol	Topical; emulsion, cream	3	%
Glyceryl oleate/propylene glycol	Topical; ointment	10	%
Glyceryl palmitate	Topical; emulsion, cream	18	%
Glyceryl stearate	Topical; ointment	5	%
Glyceryl stearate	Topical; lotion	11.5	%
Glyceryl stearate	Vaginal; emulsion, cream	17	%
Glyceryl stearate	Topical; emulsion, cream	20	%
Glyceryl stearate	Rectal; suppository	32.3	mg
Glyceryl stearate–laureth-23	Topical; emulsion, cream	0.7	%
Glyceryl stearate SE	Topical; lotion	0.5	%
Glyceryl stearate SE	Topical; emulsion, cream	7	%
Glyceryl stearate/PEG stearate	Rectal; suppository	36.85	mg
Glyceryl stearate/PEG-100 stearate	Topical; cream, augmented	7.08	%
Glyceryl stearate/PEG-100 stearate	Topical; lotion	7.1	%
Glyceryl stearate/PEG-100 stearate	Topical; emulsion, cream	7.5	%
Glyceryl stearate/PEG-40 stearate	Rectal; suppository	35	mg
Glycol stearate	Topical; emulsion, cream	1	%
Hair conditioner (18N195–1M)	Topical; lotion	78.8	%
Herbacol	Topical; sponge	964	mg
Hexylene glycol	Topical; gel	2	%
Hexylene glycol	Topical; emulsion, cream	12	%
Hexylene glycol	Topical; ointment	12	%
Hyaluronate sodium	Topical; gel	2.5	%
Hydrochloric acid	Topical; emulsion, cream	0.34	%
Hydrogenated palm/palm kernel oil PEG-6 esters	Topical; emulsion, cream	5	%
Hydroxyethyl cellulose	Topical; lotion	0.8	%
Hydroxyethyl cellulose	Topical; gel	1.25	%
Hydroxyethyl cellulose	Topical; sponge	9.09	mg
Hydroxyethyl cellulose	Transdermal; film, controlled release	20	mg
Hydroxyoctacosanyl hydroxystearate	Topical; cream, augmented	5	%
Hydroxypropyl cellulose	Topical; lotion	0.54	%
Hydroxypropyl cellulose	Topical; lotion, augmented	0.54	%
Hydroxypropyl cellulose	Topical; patch	1.26	mg
Hydroxypropyl cellulose	Topical; gel	4	%
Hydroxypropyl cellulose	Transdermal; film, controlled release	19	mg
Hydroxypropyl methylcellulose 2208	Vaginal; emulsion, cream	0.3	%
Imidurea	Topical; emulsion, lotion	0.14	%
Imidurea	Topical; lotion	0.2	%
Imidurea	Topical; emulsion, cream	0.4	%

Ingredient	Dosage Form	Qty	Unit
Irish moss extract	Topical; lotion	0.3	%
Isopropyl alcohol	Topical; gel	20	%
Isopropyl alcohol	Topical; lotion, augmented	30	%
Isopropyl alcohol	Topical; sponge	56.1	mL
Isopropyl alcohol	Topical; lotion	99.57	%
Isopropyl isostearate	Topical; cream, emulsion, sustained release	3	%
Isopropyl isostearate	Topical; emulsion, cream	3	%
Isopropyl myristate	Transdermal; gel	0.86	%
Isopropyl myristate	Topical; emulsion, lotion	1	%
Isopropyl myristate	Topical; lotion	2	%
Isopropyl myristate	Vaginal; emulsion, cream	5	%
Isopropyl myristate	Topical; emulsion, cream	10	%
Isopropyl myristate	Topical; gel	10	%
Isopropyl myristate	Topical; ointment	35	%
Isopropyl palmitate	Topical; cream, emulsion, sustained release	1.8	%
Isopropyl palmitate	Topical; lotion	3.9	%
Isopropyl palmitate	Topical; emulsion, cream	5.5	%
Isopropyl palmitate	Transdermal; film, controlled release	187.5	mg
Isostearic acid	Topical; emulsion, cream	2.5	%
Isostearyl alcohol	Topical; emulsion, cream	3	%
Isostearyl alcohol	Topical; lotion	25	%
Kathon CG	Topical; cream, emulsion, sustained release	0.05	%
Kathon CG	Topical; emulsion, cream	0.05	%
Kathon CG II	Topical; emulsion, cream	0.05	%
Lactic acid	Vaginal; emulsion, cream	0.81	%
Lactic acid	Topical; emulsion, cream	1	%
Lactic acid	Topical; lotion	5.7	%
Lactic acid	Topical; gel	6.07	%
Lactose	Vaginal; emulsion, cream	3	%
Lactose	Transdermal; ointment	18.9	%
Lactose	Transdermal; film, controlled release	675	mg
Lanolin	Topical; emulsion, cream	2	%
Lanolin	Topical; ointment	2	%
Lanolin	Vaginal; emulsion, cream	2	%
Lanolin	Topical; lotion	2.5	%
Lanolin alcohol – mineral oil	Topical; emulsion, cream	5	%
Lanolin alcohol – mineral oil	Topical; lotion	11	%
Lanolin alcohols	Topical; ointment	3.01	%
Lanolin alcohols	Topical; emulsion, cream	6	%
Lanolin, anhydrous	Vaginal; emulsion, cream	0.2	%
Lanolin, anhydrous	Topical; emulsion, cream	2	%
Lanolin, anhydrous	Transdermal; ointment	35	%
Lanolin, hydrogenated	Topical; ointment	10	%

Ingredient	Dosage Form	Qty	Unit
Laureth-4	Topical; emulsion, cream	1.1	%
Laureth-4	Topical; lotion	3	%
Lauric diethanolamide	Topical; lotion	1.7	%
Lauric myristic diethanolamide	Topical; lotion	0.54	%
Lecithin	Topical; gel	1	%
Lecithin	Vaginal; emulsion, cream	1	%
Lecithin	Rectal; suppository	6.5	mg
Lecithin	Transdermal; film, controlled release	9.86	mg
Lecithin, soybean	Vaginal; emulsion, cream	0.33	%
Lemon oil	Topical; gel	1	%
Light mineral oil	Topical; lotion	16	%
Light mineral oil	Topical; emulsion, cream	20	%
Light mineral oil	Topical; ointment	23	%
Light mineral oil	Topical; cream, augmented	25	%
Light mineral oil	Transdermal; film, controlled release	162	mg
DL-Limonene	Topical; lotion	10	%
Lipocol SC-15	Topical; emulsion, cream	1	%
Magnesium aluminum silicate	Topical; emulsion, cream	1.5	%
Magnesium aluminum silicate	Topical; lotion	1.5	%
Magnesium aluminum silicate	Vaginal; ointment	5	%
Magnesium aluminum silicate hydrate	Topical; emulsion, cream	1.5	%
Magnesium aluminum silicate hydrate	Topical; cream, augmented	3	%
Magnesium aluminum silicate hydrate	Vaginal; ointment	5.39	%
Magnesium stearate	Topical; emulsion, cream	0.0008	%
Magnesium stearate	Vaginal; sponge	0.85	mg
Maprofix	Topical; emulsion, cream	2	%
Medical adhesive modified S-15	Transdermal; film, controlled release	164	mg
Medical antiform A-F emulsion	Topical; emulsion, cream	0.1	%
Meglumine	Ureteral; solution	7.238	%
Menthol	Topical; lotion	0.05	%
Methoxypolyoxyethylene glycol 350	Topical; gel	20	%
Methyl alcohol	Transdermal; film, controlled release	4015	mg
Methyl gluceth-10	Topical; cream, augmented	5	%
Methyl gluceth-20	Topical; emulsion, cream	5	%
Methyl gluceth-20 sesquistearate	Topical; emulsion, cream	3.5	%
Methyl glucose sesquistearate	Topical; emulsion, cream	3.5	%
Methyl laurate	Transdermal; film, controlled release	17.6	mg
Methyl salicylate	Topical; gel	1	%
Methyl stearate	Topical; emulsion, cream	1	%
Methyl stearate	Vaginal; emulsion, cream	1	%
Methylcellulose	Topical; emulsion, cream	1.3	%
Methylcellulose	Topical; lotion	1.5	%
Methylparaben	Vaginal; gel	0.08	%

Ingredient	Dosage Form	Qty	Unit
Methylparaben	Iontophoresis; solution	0.1	%
Methylparaben	Topical; emulsion, lotion	0.17	%
Methylparaben	Urethral; injection	0.18	%
Methylparaben	Topical; cream, augmented	0.2	%
Methylparaben	Topical; cream, emulsion, sustained release	0.2	%
Methylparaben	Topical; ointment	0.2	%
Methylparaben	Vaginal; emulsion, cream	0.2	%
Methylparaben	Topical; gel	0.3	%
Methylparaben	Topical; patch	0.35	mg
Methylparaben	Topical; lotion	15	%
Methylparaben	Topical; emulsion, cream	18	%
Methylparaben	Topical; jelly	70	%
Microcrystalline wax	Vaginal; emulsion, cream	0.45	%
Microcrystalline wax	Topical; ointment	30	%
Mineral oil	Transdermal; patch, controlled release	1.52	mg
Mineral oil	Vaginal; gel	4.725	%
Mineral oil	Transdermal; film, controlled release	11.8	mg
Mineral oil	Vaginal; emulsion, cream	15	%
Mineral oil	Topical; lotion	19.4796	%
Mineral oil	Topical; emulsion, lotion	20	%
Mineral oil	Topical; cream, emulsion, sustained release	23.63	%
Mineral oil	Topical; emulsion, cream	40	%
Mineral oil	Topical; cream, augmented	50.618	%
Mineral oil	Topical; ointment	95	%
Myristyl alcohol	Topical; lotion	1	%
Myristyl alcohol	Topical; emulsion, cream	3	%
Myristyl lactate	Topical; lotion	92.8	%
N-3-chloroallyl-methenamine chloride	Topical; emulsion, cream	0.1	%
Niacinamide	Topical; gel	1.25	%
Nonoxynol-15	Topical; sponge	50.5	mg
Octadecene-1/maleic acid copolymer	Topical; lotion	2	%
Octoxynol-9	Topical; gel	0.012	%
Octyl hydroxystearate	Topical; emulsion, cream	12	%
Octyldodecanol	Topical; lotion	3.3	%
Octyldodecanol	Topical; gel	10	%
Octyldodecanol	Topical; emulsion, cream	12	%
Octyldodecanol	Vaginal; cream, augmented	13.5	%
Octyldodecanol	Vaginal; emulsion, cream	13.5	%
Octyldodecanol	Transdermal; film, controlled release	253.4	mg
Oleic acid	Transdermal; patch, controlled release	5.51	mg
Oleic acid	Transdermal; film, controlled release	22	mg
Oleyl alcohol	Topical; ointment	5	%
Oleyl alcohol	Topical; emulsion, cream	10	%

Ingredient	Dosage Form	Qty	Unit
Oleyl oleate	Topical; ointment	2.55	%
Palm oil, hydrogenated	Vaginal; gel	1.125	%
Paraffin	Topical; emulsion, cream	4.5	%
Paraffin	Topical; ointment	68.995	%
Paraffin, white soft	Topical; emulsion, cream	15	%
Peanut oil	Topical; emulsion, cream	3	%
Peanut oil	Vaginal; emulsion, cream	9	%
PEG 6–32 stearate/glycol stearate	Topical; emulsion, cream	19.6	%
PEG 6–32 stearate/glycol stearate	Vaginal; emulsion, cream	19.6	%
PEG-22 methyl ether/dodecyl glycol copolymer	Topical; cream, augmented	5	%
PEG-25 propylene glycol stearate	Topical; emulsion, cream	2.5	%
PEG-45/dodecyl glycol copolymer	Topical; cream, augmented	3	%
Peglicol-5-oleate	Vaginal; emulsion, cream	3	%
Peglicol-5-oleate	Topical; emulsion, cream	3.05	%
Pegoxol 7 stearate	Vaginal; emulsion, cream	20	%
Pegoxol 7 stearate	Topical; emulsion, cream	22	%
Pentadecalactone	Transdermal; gel	40	%
Pentaerythritol cocoate	Topical; ointment	1	%
Perfume GD 5604	Topical; emulsion, cream	0.12	%
Perfume TANA 90/42 SCBA	Topical; lotion	0.075	%
Petrolatum	Topical; lotion	2.5	%
Petrolatum	Topical; emulsion, cream	16.43	%
Petrolatum	Topical; ointment	99.98	%
Petrolatum, white	Topical; lotion	15	%
Petrolatum, white	Topical; cream, augmented	26	%
Petrolatum, white	Transdermal; ointment	29	%
Petrolatum, white	Topical; emulsion, cream	58.2	%
Petrolatum, white	Topical; ointment, augmented	81.936	%
Petrolatum, white	Vaginal; ointment	88.49	%
Petrolatum, white	Topical; ointment	99.98	%
Petroleum distillates	Topical; emulsion, cream	6	%
Phenonip	Iontophoresis; patch, controlled release	0.23	mg
Phenonip	Topical; patch, controlled release	0.23	mg
Phenoxyethanol	Topical; cream, augmented	0.5	%
Phenoxyethanol	Topical; emulsion, cream	0.5	%
Phenoxyethanol	Topical; gel	0.7	%
Phenoxyethanol	Topical; lotion	0.7	%
Phenylmercuric acetate	Topical; emulsion, cream	0.01	%
Phenylmercuric acetate	Vaginal; emulsion, cream	0.01	%
Phospholipon 90G	Vaginal; emulsion, cream	1	%
Phosphoric acid	Topical; ointment	0.004	%
Phosphoric acid	Topical; lotion, augmented	0.012	%
Phosphoric acid	Topical; lotion	0.1	%

Ingredient	Dosage Form	Qty	Unit
Phosphoric acid	Topical; emulsion, cream	0.5	%
Phosphoric acid	Vaginal; emulsion, cream	0.8	%
Pine needle oil	Topical; lotion	0.25	%
Plastibase-50 W	Topical; ointment	99.95	%
Polacrilin	Iontophoresis; drug delivery system	1.1	mg
Polacrilin	Transdermal; drug delivery system	1.1	mg
Poloxamer 124	Topical; gel	0.2	%
Poloxamer 182	Topical; gel	0.2	%
Poloxamer 188	Topical; emulsion, cream	0.0126	%
Poloxamer 188	Topical; gel	5.5	%
Poloxamer 407	Topical; emulsion, cream	1	%
Poloxamer 407	Topical; gel	15.5	%
Polycarbophil	Vaginal; gel	2.25	%
Polycarbophil	Topical; patch	3.54	mg
Polyester	Transdermal; film, controlled release	24	mg
Polyester – fluoro chemical releasing agent	Transdermal; film, controlled release	393	mg
Polyester fluorocarbon diacrylate	Transdermal; film, controlled release	566	mg
Polyester polyamine copolymer	Transdermal; film, controlled release	6.6668	mg
Polyethylene	Topical; ointment	9	%
Polyethylene	Topical; gel	26	%
Polyethylene	Transdermal; film, controlled release	85	mg
Polyethylene	Vaginal; suppository	3321.2	mg
Polyethylene glycol 1000	Topical; emulsion, cream	7.2	%
Polyethylene glycol 1000	Rectal; suppository	1625000	mg
Polyethylene glycol 1450	Urethral; suppository	9.75	mg
Polyethylene glycol 1500	Topical; ointment	5	%
Polyethylene glycol 1540	Topical; ointment	38	%
Polyethylene glycol 200	Topical; ointment	39	%
Polyethylene glycol 300	Topical; ointment	57	%
Polyethylene glycol 3350	Topical; ointment	40	%
Polyethylene glycol 3350	Rectal; suppository	1425.96	mg
Polyethylene glycol 400	Topical; emulsion, cream	7.5	%
Polyethylene glycol 400	Topical; lotion	12	%
Polyethylene glycol 400	Topical; gel	45	%
Polyethylene glycol 400	Topical; ointment	65	%
Polyethylene glycol 4000	Vaginal; emulsion, cream	0.5	%
Polyethylene glycol 4000	Topical; ointment	84	%
Polyethylene glycol 4000	Rectal; suppository	1269	mg
Polyethylene glycol 540	Topical; ointment	76.5	%
Polyethylene glycol 6000	Topical; ointment	1	%
Polyethylene glycol 6000	Rectal; suppository	128	mg
Polyethylene glycol 8000	Topical; emulsion, cream	11	%
Polyethylene glycol 8000	Rectal; suppository	52	mg

Ingredient	Dosage Form	Qty	Unit
Polyglyceryl-3 oleate	Vaginal; emulsion, cream	2.7	%
Polyglyceryl-4 oleate	Vaginal; emulsion, cream	2.71	%
Polyisobutylene	Transdermal; patch, controlled release	10.5	mg
Polyisobutylene	Transdermal; film, controlled release	119	mg
Polyisobutylene 1200,000	Transdermal; film, controlled release	69	mg
Polyisobutylene 35,000	Transdermal; film, controlled release	86	mg
Polyoxyethylene alcohols	Topical; emulsion, cream	9	%
Polyoxyethylene fatty acid esters	Topical; emulsion, cream	1.9	%
Polyoxyl 100 glyceryl stearate	Vaginal; emulsion, cream	2	%
Polyoxyl 100 glyceryl stearate	Topical; emulsion, cream	5	%
Polyoxyl 100 stearate	Topical; lotion	1	%
Polyoxyl 100 stearate	Topical; emulsion, cream	2.1	%
Polyoxyl 2 stearate	Topical; emulsion, cream	1	%
Polyoxyl 20 cetostearyl ether	Topical; emulsion, cream	10	%
Polyoxyl 4 dilaurate	Topical; lotion	2	%
Polyoxyl 40 hydrogenated castor oil	Topical; emulsion, cream	1	%
Polyoxyl 40 stearate	Topical; lotion	5.1	%
Polyoxyl 40 stearate	Topical; emulsion, cream	8.8	%
Polyoxyl 400 stearate	Topical; emulsion, cream	8	%
Polyoxyl 50 stearate	Topical; emulsion, cream	2	%
Polyoxyl 6 and polyoxyl 32 palmitostearate	Topical; emulsion, cream	20	%
Polyoxyl 6 isostearate	Topical; emulsion, lotion	2	%
Polyoxyl 60 hydrogenated castor oil	Topical; emulsion, cream	1.9	%
Polyoxyl 8 stearate	Topical; emulsion, cream	8	%
Polyoxyl glyceryl stearate	Topical; lotion	1.5	%
Polyoxyl glyceryl stearate	Topical; emulsion, cream	5	%
Polyoxyl palmitate	Vaginal; suppository	276	mg
Polyoxyl stearate	Topical; lotion	2	%
Polyoxyl stearate	Topical; emulsion, cream	20	%
Polypropylene	Transdermal; film, controlled release	13.5	mg
Polysorbate 20	Topical; emulsion, cream	0.8	%
Polysorbate 20	Topical; lotion	7.8	%
Polysorbate 40	Topical; gel	0.2	%
Polysorbate 40	Topical; lotion	3	%
Polysorbate 40	Topical; emulsion, cream	6	%
Polysorbate 60	Vaginal; cream, augmented	1.5	%
Polysorbate 60	Topical; lotion	5	%
Polysorbate 60	Vaginal; emulsion, cream	7.5	%
Polysorbate 60	Topical; emulsion, cream	8	%
Polysorbate 65	Topical; ointment	5	%
Polysorbate 80	Topical; ointment	0.1	%
Polysorbate 80	Vaginal; emulsion, cream	0.5	%
Polysorbate 80	Topical; emulsion, cream	5	%

Ingredient	Dosage Form	Qty	Unit
Polysorbate 80	Topical; gel	8.5	%
Polysorbate 80	Topical; lotion	9.4	%
Polysorbate 80	Vaginal; suppository	28	mg
Polysorbate 80	Rectal; suppository	72.15	mg
Polyvinyl acetate	Transdermal; patch, controlled release	3.99	mg
Polyvinyl acetate	Transdermal; film, controlled release	16	mg
Polyvinyl alcohol	Topical; lotion	2.5	%
Polyvinyl alcohol	Topical; patch	25.2	mg
Polyvinyl alcohol	Iontophoresis; drug delivery system	119	mg
Polyvinyl alcohol	Transdermal; drug delivery system	119	mg
Polyvinyl chloride-polyvinyl acetate copolymer	Transdermal; film, controlled release	899.88	mg
Potassium hydroxide	Topical; emulsion, cream	0.5	%
Potassium hydroxide	Vaginal; emulsion, cream	0.5	%
Potassium sorbate	Topical; lotion	0.2	%
Potassium sorbate	Topical; emulsion, cream	2.7	%
Povidone hydrogel	Iontophoresis; patch, controlled release	506.5	mg
Povidone hydrogel	Topical; patch, controlled release	506.5	mg
Povidone K29–32	Transdermal; film, controlled release	7.266	mg
Povidone/eicosene copolymer	Topical; lotion	1	%
PPG-12/SMDI copolymer	Topical; emulsion, cream	10	%
PPG-12/SMDI copolymer	Topical; gel	10	%
PPG-15 stearyl ether	Topical; gel	2	%
PPG-15 stearyl ether	Topical; ointment	15	%
PPG-20 methyl glucose ether distearate	Topical; gel	4.75	%
PPG-26 oleate	Topical; emulsion, cream	4	%
Promalgen type G	Topical; lotion	1.5	%
Promulgen D	Topical; lotion	3.5	%
Promulgen G	Topical; lotion	2.16	%
Propyl gallate	Topical; ointment	0.015	%
Propyl gallate	Topical; gel	0.05	%
Propylene carbonate	Topical; ointment	5	%
Propylene glycol	Topical; patch	0.44	mg
Propylene glycol	Vaginal; gel	3	%
Propylene glycol	Topical; cream, augmented	8	%
Propylene glycol	Vaginal; emulsion, cream	20	%
Propylene glycol	Transdermal; gel	25	%
Propylene glycol	Topical; lotion, augmented	30	%
Propylene glycol	Topical; ointment	38	%
Propylene glycol	Topical; emulsion, lotion	47.5	%
Propylene glycol	Topical; lotion	50.9	%
Propylene glycol	Transdermal; film, controlled release	58.13	mg
Propylene glycol	Topical; ointment, augmented	65	%
Propylene glycol	Topical; emulsion, cream	71.08	%

Ingredient	Dosage Form	Qty	Unit
Propylene glycol	Topical; gel	98.09	%
Propylene glycol	Vaginal; suppository	252	mg
Propylene glycol diacetate	Topical; emulsion, cream	10	%
Propylene glycol dicaprylate	Topical; emulsion, cream	10	%
Propylene glycol monostearate	Topical; ointment, augmented	2	%
Propylene glycol monostearate	Topical; lotion	4.69	%
Propylene glycol monostearate	Vaginal; emulsion, cream	7	%
Propylene glycol monostearate	Topical; ointment	8	%
Propylene glycol monostearate	Topical; emulsion, cream	9.3	%
Propylene glycol palmitostearate	Topical; ointment	5	%
Propylparaben	Topical; patch	0.02	mg
Propylparaben	Urethral; injection	0.02	%
Propylparaben	Vaginal; gel	0.02	%
Propylparaben	Topical; cream, augmented	0.032	%
Propylparaben	Topical; emulsion, lotion	0.06	%
Propylparaben	Topical; gel	0.08	%
Propylparaben	Topical; cream, emulsion, sustained release	0.1	%
Propylparaben	Vaginal; emulsion, cream	0.1	%
Propylparaben	Topical; ointment	0.2	%
Propylparaben	Topical; emulsion, cream	1	%
Propylparaben	Topical; lotion	10	%
Propylparaben	Topical; jelly	30	%
Protein hydrolysate	Topical; lotion	0.39	%
Quaternium-15	Topical; emulsion, cream	0.02	%
Quaternium-15	Topical; cream, augmented	0.1	%
Quaternium-15	Topical; lotion	0.2	%
RA-2397	Transdermal; film, controlled release	142.2	mg
RA-3011	Transdermal; film, controlled release	142.2	mg
Saccharin	Topical; ointment	0.5	%
Safflower oil	Topical; lotion	3	%
Scotchpak 1109	Transdermal; film, controlled release	115.71	mg
Scotchpak 9739 backing film PET/EVA	Transdermal; patch	211.8	mg
SD alcohol 40–2	Topical; gel	97.5	%
Silicon	Topical; emulsion, cream	0.4	%
SILICON	Topical; lotion	92.5	%
Silicon dioxide	Topical; gel	0.25	%
Silicon dioxide	Vaginal; emulsion, cream	1	%
Silicon dioxide, colloidal	Vaginal; emulsion, cream	1.01	%
Silicon dioxide, colloidal	Rectal; suppository	14	mg
Silicon dioxide, colloidal	Transdermal; film, controlled release	49	mg
Silicone	Vaginal; drug delivery system	8.7	mg
Silicone	Transdermal; film, controlled release	353.51	mg
Silicone adhesive 4102	Percutaneous; patch, controlled release	165	cms

Ingredient	Dosage Form	Qty	Unit
Silicone adhesive 4102	Transdermal; film, controlled release	228.23	mg
Silicone emulsion	Topical; lotion	0.5	%
Silicone/polyester film strip	Transdermal; patch	485.2	mg
Silicone/polyester film strip	Transdermal; film, controlled release	873	mg
Simethicone	Topical; lotion	0.5	%
Simethicone	Topical; emulsion, cream	1	%
Simethicone emulsion	Topical; emulsion, cream	0.2	%
Sodium acetate, anhydrous	Topical; emulsion, cream	0.02	%
Sodium benzoate	Topical; emulsion, cream	0.2	%
Sodium benzoate	Topical; patch	0.44	mg
Sodium bisulfite	Iontophoresis; solution	0.055	%
Sodium bisulfite	Topical; lotion	0.22	%
Sodium bisulfite	Topical; emulsion, cream	0.3	%
Sodium cetearyl sulfate	Topical; emulsion, cream	1	%
Sodium chloride	Topical; lotion	0.27	%
Sodium chloride	Topical; emulsion, cream	0.5	%
Sodium chloride	Iontophoresis; drug delivery system	0.6	mg
Sodium chloride	Iontophoresis; solution	0.6	%
Sodium chloride	Transdermal; drug delivery system	0.6	mg
Sodium chloride	Iontophoresis; patch, controlled release	3.1	mg
Sodium chloride	Topical; patch, controlled release	3.1	mg
Sodium chloride	Rectal; suppository	52.5	mg
Sodium citrate	Topical; emulsion, lotion	0.08	%
Sodium citrate	Topical; emulsion, cream	0.319	%
Sodium citrate	Iontophoresis; drug delivery system	2.2	mg
Sodium citrate	Transdermal; drug delivery system	2.2	mg
Sodium citrate	Vaginal; sponge	7.6	mg
Sodium citrate, anhydrous	Topical; emulsion, cream	0.28	%
Sodium hydroxide	Topical; jelly	0.0134	%
Sodium hydroxide	Topical; emulsion, lotion	0.022	%
Sodium hydroxide	Topical; ointment, augmented	0.106	%
Sodium hydroxide	Vaginal; emulsion, cream	0.1881	%
Sodium hydroxide	Vaginal; gel	0.25	%
Sodium hydroxide	Topical; emulsion, cream	0.52	%
Sodium hydroxide	Transdermal; film, controlled release	0.85	mg
Sodium hydroxide	Topical; lotion	2.6	%
Sodium hydroxide	Topical; cream, augmented	2.72	%
Sodium hydroxide	Topical; cream, emulsion, sustained release	2.72	%
Sodium hydroxide	Iontophoresis; drug delivery system	4.2	mg
Sodium hydroxide	Transdermal; drug delivery system	4.2	mg
Sodium hydroxide	Transdermal; gel	4.72	%
Sodium hydroxide	Topical; gel	10	%
Sodium lactate	Topical; gel	0.77	%

Ingredient	Dosage Form	Qty	Unit
Sodium laureth-5 sulfate	Topical; emulsion, cream	1	%
Sodium lauroyl sarcosinate	Topical; lotion	7.5	%
Sodium lauryl sulfate	Vaginal; emulsion, cream	0.333	%
Sodium lauryl sulfate	Topical; lotion	0.5	%
Sodium lauryl sulfate	Topical; ointment	1	%
Sodium lauryl sulfate	Topical; emulsion, cream	2.5	%
Sodium metabisulfite	Topical; emulsion, cream	0.03	%
Sodium metabisulfite	Iontophoresis; solution	0.05	%
Sodium metabisulfite	Topical; cream, augmented	0.2	%
Sodium metabisulfite	Iontophoresis; patch, controlled release	0.5	mg
Sodium metabisulfite	Topical; patch, controlled release	0.5	mg
Sodium metabisulfite	Vaginal; sponge	1.5	mg
Sodium phosphate	Topical; ointment	0.15	%
Sodium phosphate, dibasic	Topical; emulsion, cream	0.2	%
Sodium phosphate, dibasic, anhydrous	Topical; ointment	0.026	%
Sodium phosphate, dibasic, anhydrous	Topical; lotion	0.1	%
Sodium phosphate, dibasic, anhydrous	Topical; emulsion, cream	0.36	%
Sodium phosphate, dibasic, dihydrate	Topical; emulsion, cream	0.25	%
Sodium phosphate, dibasic, heptahydrate	Topical; ointment	0.15	%
Sodium phosphate, dibasic, heptahydrate	Topical; emulsion, cream	0.39	%
Sodium phosphate, dibasic, heptahydrate	Topical; lotion	1.59	%
Sodium phosphate, dibasic, heptahydrate	Urethral; injection	2	%
Sodium phosphate, monobasic	Topical; lotion, augmented	0.2	%
Sodium phosphate, monobasic	Topical; emulsion, cream	0.265	%
Sodium phosphate, monobasic	Topical; lotion	0.3	%
Sodium phosphate, monobasic	Iontophoresis; patch, controlled release	14.2	mg
Sodium phosphate, monobasic	Topical; patch, controlled release	14.2	mg
Sodium phosphate, monobasic, anhydrous	Topical; emulsion, cream	0.5	%
Sodium phosphate, monobasic, anhydrous	Topical; lotion	0.6	%
Sodium phosphate, monobasic, monohydrate	Topical; lotion, augmented	0.15	%
Sodium phosphate, monobasic, monohydrate	Topical; lotion	0.2	%
Sodium phosphate, monobasic, monohydrate	Topical; emulsion, cream	0.3	%
Sodium pyrrolidone carboxylate	Topical; lotion	5.2	%
Sodium sulfite	Topical; emulsion, cream	0.2	%
Sodium sulfosuccinated undecyclenic monoalkylolamide	Topical; lotion	0.1	%
Sodium thiosulfate	Topical; cream, augmented	0.1	%
Sodium thiosulfate	Topical; cream, emulsion, sustained release	0.1	%
Sorbic acid	Vaginal; gel	0.09	%
Sorbic acid	Topical; ointment	0.1	%
Sorbic acid	Topical; gel	0.175	%
Sorbic acid	Topical; lotion	0.2	%
Sorbic acid	Topical; emulsion, cream	2.7	%
Sorbic acid	Vaginal; sponge	6	mg

Ingredient	Dosage Form	Qty	Unit
Sorbitan monooleate	Topical; cream, augmented	0.2	%
Sorbitan monooleate	Topical; cream, emulsion, sustained release	0.2	%
Sorbitan monooleate	Topical; emulsion, cream	3.5	%
Sorbitan monooleate	Topical; lotion	7	%
Sorbitan monooleate	Rectal; suppository	22	mg
Sorbitan monopalmitate	Topical; lotion	1	%
Sorbitan monopalmitate	Topical; emulsion, cream	2	%
Sorbitan monopalmitate	Topical; patch	10.5	mg
Sorbitan monostearate	Vaginal; cream, augmented	2	%
Sorbitan monostearate	Topical; lotion	2.5	%
Sorbitan monostearate	Vaginal; emulsion, cream	5	%
Sorbitan monostearate	Topical; emulsion, cream	8	%
Sorbitan sesquioleate	Topical; ointment	2	%
Sorbitol	Topical; emulsion, cream	67.52	%
Sorbitol solution	Topical; ointment	1.5	%
Sorbitol solution	Topical; lotion	5	%
Sorbitol solution	Topical; cream, augmented	15	%
Sorbitol solution	Topical; emulsion, cream	25	%
Sorbitol solution	Vaginal; emulsion, cream	36.8	%
Soybean oil	Topical; lotion	50.2	%
Spermaceti	Vaginal; emulsion, cream	3	%
Spermaceti	Topical; emulsion, cream	11	%
Squalane	Topical; emulsion, cream	6	%
Stearalkonium chloride	Topical; lotion	3.15	%
Stearamidoethyl diethylamine	Topical; emulsion, cream	0.6	%
Stearamidoethyl diethylamine	Vaginal; emulsion, cream	2.5	%
Steareth-100	Topical; emulsion, cream	0.35	%
Steareth-100	Topical; ointment	0.6	%
Steareth-2	Topical; lotion	0.4	%
Steareth-2	Topical; cream, emulsion, sustained release	0.85	%
Steareth-2	Topical; emulsion, cream	4.5	%
Steareth-2	Topical; ointment	5	%
Steareth-20	Topical; cream, emulsion, sustained release	4.15	%
Steareth-21	Topical; cream, emulsion, sustained release	2.5	%
Steareth-21	Topical; emulsion, cream	3	%
Steareth-21	Topical; lotion	3	%
Stearic acid	Topical; cream, augmented	3	%
Stearic acid	Topical; cream, emulsion, sustained release	4	%
Stearic acid	Vaginal; emulsion, cream	14	%
Stearic acid	Topical; ointment	15	%
Stearic acid	Topical; lotion	20	%
Stearic acid	Topical; emulsion, cream	22.6	%
Stearoxytrimethylsilane	Topical; cream, augmented	1	%

Ingredient	Dosage Form	Qty	Unit
Steartrimonium hydrolyzed animal collagen	Topical; lotion	0.5	%
Stearyl alcohol	Topical; cream, emulsion, sustained release	3	%
Stearyl alcohol	Topical; cream, augmented	4	%
Stearyl alcohol	Topical; ointment	8	%
Stearyl alcohol	Topical; lotion	12	%
Stearyl alcohol	Topical; emulsion, cream	30	%
Stearyl alcohol	Vaginal; emulsion, cream	42.5	%
Stearyl citrate	Topical; ointment	0.75	%
Sucrose	Topical; ointment	20	%
Sucrose distearate	Topical; emulsion, cream	5	%
Talc	Topical; lotion	7.28	%
Talc	Topical; ointment	8.27	%
Tallow glycerides	Topical; emulsion, cream	2.78	%
DL-Tartaric acid	Rectal; suppository	21.5	mg
DL-Tartaric acid	Vaginal; suppository	32.3	mg
T-butylhydroquinone	Vaginal; emulsion, cream	0.02	%
Tenox	Topical; emulsion, cream	0.025	%
Tenox	Topical; ointment	0.025	%
Tenox-2	Topical; ointment	0.025	%
Thimerosal	Topical; emulsion, cream	0.005	%
Thimerosal	Topical; ointment	0.04	%
Titanium dioxide	Topical; emulsion, cream	2	%
Titanium dioxide	Topical; ointment	5	%
Tocopherol	Topical; ointment	0.002	%
Triacetin	Transdermal; patch	22.1	mg
Triglycerides, medium chain	Topical; gel	1	%
Triglycerides, medium chain	Topical; cream, augmented	1.37	%
Triglycerides, medium chain	Topical; cream, emulsion, sustained release	1.37	%
Triglycerides, medium chain	Topical; emulsion, cream	15	%
Trihydroxystearin	Topical; ointment	3	%
Trilaneth-4 phosphate	Topical; ointment	1.9	%
Trilaureth-4 phosphate	Topical; ointment	4.7	%
Trisodium citrate dihydrate	Topical; lotion	0.32	%
Trolamine	Transdermal; gel	0.35	%
Trolamine	Vaginal; emulsion, cream	0.75	%
Trolamine	Topical; emulsion, cream	1	%
Trolamine	Topical; gel	1	%
Trolamine	Topical; lotion	31.7	%
Trolamine lauryl sulfate	Topical; emulsion, cream	0.13	%
Tromethamine	Urethral; solution	0.121	%
Tromethamine	Transdermal; gel	0.5	%
Tromethamine	Topical; gel	0.8	%
Union 76 AMSCO-RES 6038	Transdermal; film, controlled release	5.7	mg

Ingredient	Dosage Form	Qty	Unit
Urea	Vaginal; emulsion, cream	0.64	%
Vegetable oil	Topical; emulsion, cream	3.5	%
Vegetable oil glyceride, hydrogenated	Rectal; suppository	870	mg
Vegetable oil, hydrogenated	Topical; emulsion, cream	72	%
Vegetable oil, hydrogenated	Vaginal; emulsion, cream	72	%
Vegetable oil, hydrogenated	Rectal; suppository	2026.5	mg
Vegetable oil, hydrogenated	Vaginal; suppository	2400	mg
Viscarin	Topical; lotion	1	%
Viscose/cotton	Transdermal; film, controlled release	84	mg
Wax, dehydag	Topical; emulsion, cream	8.5	%
Wax, emulsifying	Topical; ointment	1.5	%
Wax, emulsifying	Topical; lotion	4	%
Wax, emulsifying	Topical; emulsion, cream	24.8	%
Wax, white	Vaginal; emulsion, cream	2	%
Wax, white	Topical; emulsion, cream	6	%
Wax, white	Topical; ointment, augmented	6.75	%
Wax, white	Topical; ointment	7.3	%
Wax, white	Topical; cream, augmented	10	%
Wax, white	Rectal; suppository	265	mg
Wecobee FS	Vaginal; suppository	1700	mg
White ceresin wax	Vaginal; emulsion, cream	7	%
Xanthan gum	Topical; lotion	0.18	%
Xanthan gum	Topical; cream, augmented	0.215	%
Xanthan gum	Topical; cream, emulsion, sustained release	0.3	%
Xanthan gum	Topical; emulsion, cream	0.75	%
Zinc acetate	Topical; lotion	1.2	%
Zinc oxide	Rectal; suppository	375	mg

Part II

Manufacturing Formulations

Aceclofenac Gel Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg Tablets (g)
1.5	1	Aceclofenac	1.5
9.9	2	Miglyol® 812 (Dynamit-Nobel)	9.9
4.9	3	Lutrol E 400	4.9
64.0	4	Deionized water	64.0
19.7	5	Lutrol F 127	19.7

Manufacturing Directions

1. Mix item 1 with water and cool to approximately 5°C.
2. Add slowly Lutrol F 127 and continue stirring until it is dissolved.
3. Maintain cool until the air bubbles escape. A milky, firm gel is obtained.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
80.00	1	Acetaminophen (micronized)	80.00
836.80	2	Hard fat (Suppocire AM®)	836.80
3.20	3	Sorbitan monostearate (Crill-3)	3.20

Manufacturing Directions

1. Fill weight is 920 mg/suppository. The molten suppository mass must be stirred throughout the storage period and during manufacturing and filling to avoid sedimentation of the active drug.
2. Load items 2 and 3 into the fat-melting vessel and heat to 50°C ± 3°C.
3. Transfer the molten mass to a mixer through filter sieves.
4. Set the temperature at 45°C ± 2°C.
5. Load item 1 into the mixer containing molten item 2.
6. Carefully mix the powder with molten item 2 for 20 minutes at 10 rpm, at a temperature of 45°C ± 2°C, and at a vacuum of 0.4 to 0.5 bar, then homogenize for 10 minutes at low speed.
7. Continue mixing at 10 rpm.
8. Heat the storage vessel and set the temperature at 45°C ± 2°C.
9. Transfer the molten mass from the mixer to the storage vessel.
10. Hold the mass at 45°C ± 2°C, with continuous mixing at low speed.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
125.00	1	Acetaminophen micronized, 5% excess	131.25
785.54	2	Suppocire AM	785.54
3.21	3	Crill-3	3.21

Manufacturing Directions

1. Load item 2 in the fat-melting vessel and heat to 60°C.
2. Transfer about one-third of step 1 to a Becomix vessel through filter sieves. Set the temperature to 60°C.
3. Add item 3 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 60°C under vacuum of 0.4 to 0.6 bar to dissolve.
4. Cool down to 50°C to 55°C.
5. Load item 1 in step 4 and mix at 10 rpm and homogenize at speed I for 10 minutes maintaining the temperature of 50°C to 55°C under vacuum as above to make a smooth slurry.
6. Transfer balance quantity of item 2 from step 1 into step 5 through filter sieve, set the temperature at 50°C and speed at 10 rpm, homogenize at speed II and under vacuum for 10 minutes.
7. Transfer into storage vessel and set temperature at 45°C.
8. Fill 920 mg in a suppository mold.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
150.00	1	Acetaminophen (fine powder), excess	150.00
20.00	2	Aerosil® 200	20.00
1.290.00	3	Lutrol E 1500	1.290.00
554.00	4	Lutrol E 4000	554.00

Manufacturing Directions

1. Melt the mixture of items 1 and 2 in a mixture of items 3 and 4.
2. Fill the molten mass in suppository molds.
3. Average weight is 2 g.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
500.00	1	Acetaminophen (fine powder)	500.00
100.00	2	Lutrol E 400	100.00
600.00	3	Lutrol E 1500	600.00
800.00	4	Lutrol E 4000	800.00

Manufacturing Directions

1. Fill weight is 2.09 g. Melt items 2 through 4 and add and dispense item 1.
2. Fill the molten mass in suppository molds.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
250.00	1	Acetaminophen micronized, 5% excess	252.50
1137.50	2	Suppocire AM	1137.50

Manufacturing directions

1. Load item 2 in the fat-melting vessel and heat to 60°C.
2. Transfer step 1 to a Becomix vessel through filter sieves; set the temperature to 60°C.
3. Cool down to 50°C to 55°C and apply vacuum 0.4 to 0.6 bar.
4. Load item 1 and mix at 10 rpm and homogenize at speed I for 10 minutes, maintaining the temperature of 50°C to 55°C under vacuum as above to make a smooth slurry.
5. Transfer into storage vessel and set temperature at 45°C.
6. Fill 1390 mg in a suppository mold.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
500.00	1	Acetaminophen micronized, 5% excess	525.00
1137.50	2	Suppocire AM	1137.50

Manufacturing Directions

1. Load item 2 in the fat-melting vessel and heat to 60°C.
2. Transfer step 1 to a Becomix vessel through filter sieves. Set the temperature to 60°C.
3. Cool down to 50°C to 55°C and apply vacuum 0.4 to 0.6 bar.
4. Load item 1 and mix at 10 rpm and homogenize at speed I for 10 minutes maintaining the temperature of 50°C to 55°C under vacuum as above to make a smooth slurry.
5. Transfer into storage vessel and set temperature at 45°C.
6. Fill 1390 mg in a suppository mold.

Acetylsalicylic Acid Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
100.00	1	Acetylsalicylic acid	100.00
400.00	2	Suppocire AM	400.00

Manufacturing Directions

1. Heat item 2 to 50°C.
2. Allow to cool to 40°C and add item 1 while stirring with a turbine mixer.
3. Continue mixing and cooling and pour into molds at 35°C that were previously chilled to 0° to 5°C. Remove suppositories from molds after 7 minutes.
4. Fill to appropriate weight for strength desired.

Acne Cover Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
37.00	1	Glyceryl stearate S/E	37.00
46.00	2	Mineral oil/Lanolin alcohol (liquid base CB3939)	46.00
9.00	3	Polawax GP2000	9.00
18.00	4	Stearic acid	18.00
QS	5	Deionized water	QS
36.00	6	Propylene glycol	36.00
2.00	7	Carboxymethylcellulose (CMC-7HF)	2.00
9.00	8	Magnesium aluminum silicate (regular) Veegum®	9.00
9.00	9	Triethanolamine (99%)	9.00
120.00	10	Titanium dioxide	120.00
QS	11	Iron oxides	QS
50.00	12	Actives	50.00
QS	13	Perfume, preservative	QS

Manufacturing Directions

1. Disperse CMC in propylene glycol and triethanolamine and add warm water (60–65°C) while stirring, until the gum is hydrated.
2. Add Veegum and stir until hydrated.
3. Heat oil phase to 60°C to 65°C.
4. Add water phase to oil phase while stirring.
5. Add pigments and stir to cool, adding the actives at 30°C.
6. Homogenize using suitable equipment.
7. Fill. (*Note*: Active ingredients may be added as required to this base formula.)

Acne Treatment Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Polychol 10 (Laneth-10)	20.00
5.00	2	Lanolin alcohols (Super Hartolan)	5.00
55.00	3	Cetyl alcohol C90	55.00
60.00	4	Polawax, NF	60.00
14.00	5	Sulfur	14.00
QS	6	Deionized water	QS
40.00	7	Veegum (regular)	40.00
20.00	8	Propylene glycol	20.00
20.00	9	Resorcinol	20.00
QS	10	Perfume, preservative	QS

Manufacturing Directions

1. Hydrate Veegum in water.
2. Add rest of the water-phase ingredients and heat to 70°C.
3. Heat oil phase to 70°C.
4. Disperse sulfur in the oil phase.
5. Add oil phase to water phase while stirring.
6. Stir to cool. Fill.

Acyclovir Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Acyclovir: Use acyclovir micronized	52.00
5.20	2	Acyclovir: Use acyclovir micronized	52.00
1.63	3	Polyoxyl 20 cetostearyl ether (cetomacrogol 1000)	16.35
20.40	4	Propylene glycol	204.00
17.00	5	Propylene glycol	170.00
9.65	6	Petrolatum (white soft paraffin)	96.50
6.50	7	Cetostearyl alcohol	65.00
3.50	8	Mineral oil (liquid paraffin)	35.00
36.50	9	Purified water	365.00

Manufacturing Directions

1. Oil phase
   a. Load items 5 to 7 in fat-melting vessel and melt at 70°C. Maintain temperature at 70°C ± 2°C.
2. Aqueous phase
   a. Heat item 8 in mixer at 90°C. Cool down to 70°C. Add item 2 in item 8 at 70°C and stir to dissolve.
   b. Add item 4 to mixer (step 2b) and mix. Maintain temperature at 70°C ± 2°C.
3. Cream phase
   a. Add oil phase through stainless steel filter to aqueous phase in mixer while mixing at 10 to 12 rpm, manual mode, and temperature 70°C ± 2°C.
   b. Homogenize at low speed with mixing 10 to 12 rpm, vacuum 0.4 to 0.6 bar, temperature 70°C ± 2°C for 10 minutes.
   c. Cool down to 50°C with mixing.
4. Drug phase
   a. Heat 169 g of item 3 at 50°C in water bath.
   b. Disperse item 1 in item 3 (step 4a) with the help of homogenizer. Homogenize two times with homogenizer (gap setting 1) to make smooth dispersion. Dispersion should be smooth with no gritty particles.
   c. Add the drug phase from step 4b to cream base at step 3.3 in mixer.
   d. Rinse the homogenizer and the container with 35 g of item 3 (50°C) and add the rinsing to cream base in mixer.
5. Final mixing
   a. Homogenize at high speed for 15 minutes at a temperature of 45°C with continuous mixing at 10 to 12 rpm.
   b. Cool down to 25°C to 30°C with continuous mixing.
   c. Unload in stainless steel drum lined with polythene bag.

Acyclovir Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.000	1	Acyclovir micronized (4% excess)	52.00
28.000	2	Polyethylene glycol 3350	280.00
41.800	3	Polyethylene glycol 400	418.00
25.000	4	Propylene glycol	250.00

Manufacturing Directions

1. Oil phase
   a. Heat items 2 and 3 to 70°C ± 2°C in mixer to melt. Cool down to 45°C with mixing.
2. Drug dispersion
   a. Disperse item 1 in 200 g of item 4 at 50°C in a water bath with the help of homogenizer. The drug dispersion should be smooth with no gritty particles.
   b. Add the drug dispersion to mixer at step 1.
   c. Rinse the container with 50 g of item 4 at 50°C and add the rinsing to mixer.
3. Final mixing
   a. Homogenize at high speed with mixing under vacuum 0.4 to 0.6 bar at 45°C ± 2°C for 30 minutes.
   b. Cool down to 25° to 30°C with continuous mixing.
   c. Unload in stainless steel drum lined with polythene bag.

Adapalene Cream

Adapalene cream, 0.1%, contains adapalene, 0.1%, in an aqueous cream emulsion consisting of carbomer 934P, cyclomethicone, edetate disodium, glycerin, methyl glucose sesquistearate, methyl paraben, PEG-20 methyl glucose sesquistearate, phenoxyethanol, propyl paraben, purified water, squalane, and trolamine.

Alclometasone Dipropionate Cream and Ointment

Each gram of cream contains 0.5 mg of alclometasone dipropionate in a hydrophilic, emollient cream base of propylene glycol, white petrolatum, cetearyl alcohol, glyceryl stearate, PEG-100 stearate, ceteth-20, monobasic sodium phosphate, chlorocresol, phosphoric acid, and purified water. Each gram of ointment contains 0.5 mg of alclometasone dipropionate in an ointment base of hexylene glycol, white wax, propylene glycol stearate, and white petrolatum.

Aloe Vera Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
4.0	1	Aloe vera extract 200X	4.0
50.0	2	Propylene glycol	50.0
QS	3	Preservative	QS
736.0	4	Water	736.0
11.0	5	Cremophor RH 40	11.0
QS	6	Perfume	QS
200.0	7	Lutrol F 127	200.0

Manufacturing Directions

1. Prepare solutions items 1 to 4 and items 5 and 6 separately and add second to first mixture.
2. Cool this mixture to <10°C (or heat to 70–80°C) and dissolve item 7. Maintain the temperature until the air bubbles escape and the appearance is clear. Viscosity should be approximately 60 Pa, pH approximately 5.5 (20–25°C) in the storage vessel.
3. Mix for 2 minutes. Store in a clean storage vessel.

Alum Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
4.00	1	Cetostearyl alcohol	40.00
5.00	2	Octyldodecanol	50.00
4.00	3	Lanolin alcohol	40.00
2.00	4	Ethoxylated castor oil	20.00
2.00	5	White petrolatum	20.00
6.50	6	Alum (aluminum potassium sulfate, 12 H_20)	65.00
2.50	7	Cetylpyridinium ammonium chloride	25.00
95.00	8	Water purified	740.00

Manufacturing Directions

1. Cetostearyl alcohol, ethoxylated castor oil, lanolin alcohol, octyldodecanol, and white petrolatum weighed and mixed in the ratio defined above are heated to 60°C.
2. Alum and item 7 are dissolved in water at room temperature and then the solution is heated to 62°C.
3. Both phases are combined in an ointment mixer and homogenized by stirring.
4. While stirring, the cream is cooled to approximately 30°C and its weight is supplemented with purified water.
5. The cream is again homogenized by stirring and then filled into an electrolyte-resistant storage bottle.

6-Aminonicotinamide Ointment

Manufacturing Directions

1. 6-Aminonicotinamide, 0.1 g, is dissolved in 3.6 mL of 0.2 N HCl and 6.3 mL water.
2. The solution thus obtained is admixed with commercially available USP grade hydrophilic ointment (90 g) to a uniform consistency.
3. The ointment thus prepared is stored preferably in opaque jars at room temperature.

6-Aminonicotinic Acid Methyl Ester Ointment

Manufacturing Directions

6-Aminonicotinic acid methyl ester, 1 g, is dissolved in anhydrous ethanol (9 mL) and the solution is admixed with white petrolatum USP grade (54 g) and liquid petrolatum USP grade (36 g) to a uniform consistency. This ointment also may be stored in opaque jars at room temperature.

6-Aminonicotinic Acid Ointment

Manufacturing Directions

6-Aminonicotinic acid, 1 g, is dissolved in 7 mL of 1N HCl and 2 mL of water. The solution is admixed with USP grade hydrophilic ointment (90 g) to a uniform consistency. The ointment thus prepared is also stored in opaque jars at room temperature.

Aminacrine Hydrochloride Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.10	1	Aminacrine hydrochloride	1.00
5.00 mg	2	Thymol	50.00 mg
9.50	3	Glyceryl monostearate	95.00
3.20	4	Cetostearyl alcohol	32.00
1.90	5	Polyoxyl 40 stearate	19.00
10.00	6	Liquid paraffin	100.00
0.45	7	Cetrimide	4.50
QS	8	Isopropyl alcohol	1.30 L
QS	9	Perfume	QS
QS	10	Water purified	QS to 1 kg

Manufacturing Directions

1. Charge items 3 to 5 and half of item 6 into a suitable mixing vessel. Heat to 60°C and mix well.
2. Prepare slurry of item 1 in the balance of item 6 and add to step 1 slowly at 60°C under constant stirring.
3. Heat item 10 to 60°C and add to step 2 with stirring to form an emulsion.
4. Cool down to 45°C and add perfume. Continue to mix to cool down to room temperature.
5. Fill in appropriate containers.

Amoxicillin Lotion

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.00	1	Ethoxylated cetyl stearyl alcohol	70.00
0.75	2	Cetyl alcohol	7.50
5.00	3	Isopropyl myristate	50.00
0.10	4	Butylated hydroxyanisole	1.00
0.25	5	Polyoxyl 40 stearate	2.50
71.80	6	Water purified	718.00
3.00	7	Propylene glycol	30.00
10.00	8	Acetone	100.00
0.10	9	Dioctyl sodium sulfosuccinate	1.00
2.00	10	Amoxicillin	20.00

Ampicillin Lotion

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.00	1	Ethoxylated cetyl stearyl alcohol	70.00
0.75	2	Cetyl alcohol	7.50
5.00	3	Isopropyl myristate	50.00
0.10	4	Butylated hydroxyanisole	1.00
0.25	5	Polyoxyl 40 stearate	2.50
71.80	6	Water purified	718.00
3.00	7	Propylene glycol	30.00
10.00	8	Acetone	100.00
0.10	9	Dioctyl sodium sulfosuccinate	1.00
2.00	10	Ampicillin	20.00

Analgesic Clear Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
25.00	1	Hydroxypropyl cellulose	25.00
QS	2	Deionized water	QS to 1 kg
400.00	3	Ethanol DEB 100	400.00
100.00	4	Menthol	100.00
150.00	5	Methyl salicylate	150.00
25.00	6	DEA-oleath-3-phosphate	25.00

Manufacturing Directions

1. Hydrate hydroxypropyl cellulose in water at 60°C to 65° C.
2. Stir to cool.
3. Add ethanol.
4. Add remaining ingredients and stir until homogeneous.

Analgesic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
130.00	1	Methyl salicylate	130.00
60.00	2	Menthol	60.00
20.00	3	Eucalyptus oil	20.00
5.00	4	Lanolin	5.00
1.00	5	Chloroxylenol	1.00
150.00	6	Glyceryl stearate and PEG-100 stearate	150.00
73.00	7	Cetearyl alcohol	73.00
70.00	8	Glyceryl stearate	70.00
QS	9	Deionized water	QS to 1 kg
QS	10	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 30°C.

Analgesic Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Methyl salicylate	150.00
70.00	2	Menthol	70.00
10.00	3	Lanolin oil	10.00
30.00	4	PEG-40 stearate	30.00
20.00	5	Glyceryl stearate	20.00
QS	6	Deionized water	QS
1.50	7	Carbopol® 980	1.50
10.00	8	Potassium hydroxide (10% aqueous solution)	10.00
QS	9	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases (except potassium hydroxide) separately to 65°C to 70°C.
2. Add water phase to oil phase while stirring.
3. Add potassium hydroxide solution to neutralize.
4. Stir to cool.
5. Fill at 30°C.

Anthralin Cream

Anthralin cream, 1% USP, is a smooth, yellow cream acid, sodium hydroxide, and purified water. For topical containing 1% anthralin USP in an aqueous cream base dermatological use only.

Antiacne Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
422.00	1	Witch hazel (distilled, 14% alcohol)	422.00
5.00	2	Salicylic acid	5.00
5.00	3	Aloe vera gel	5.00
10.00	4	Sorbitol	10.00
500.00	5	Polyglycerylmethacrylate	500.00
10.00	6	Propylene glycol	10.00
0.80	7	Methyl paraben	0.80
0.20	8	Propyl paraben	0.20

Manufacturing Directions

1. Premix items 1 to 4.
2. Add item 5 with low-shear mixing until homogeneous.
3. Mix together items 6 to 8 and add them to the formulation.

Antifungal Foot Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Dichlorobenzyl alcohol (Myacide SF)	5.00
5.00	2	Allantoin	5.00
200.00	3	Cornstarch	200.00
790.00	4	Talc	790.00

Manufacturing Directions

Mix all ingredients using geometric dilution technique.

Antifungal Topical Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
39.00	1	Urea[a]	390.00
0.15	2	Carbopol 940	1.50
5.94	3	Petrolatum	59.40
12.06	4	Mineral oil	120.60
1.875	5	Glyceryl stearate	187.50
0.626	6	Cetyl alcohol	6.26
3.00	7	Propylene glycol	30.00
0.05	8	Xanthan gum	0.50
0.15	9	Trolamine	1.50
1.00–5.00	10	Antifungal compound[a]	10.00–50.00

[a]Adjust quantity of urea for the quantity of antifungal compound; this formula is for 1% level of antifungal added.

Antiseptic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Polawax GP200	50.00
10.00	2	Lanolin	10.00
150.00	3	Mineral oil (70 cS)	150.00
70.00	4	Cetearyl alcohol	70.00
30.00	5	Dimethicone	30.00
QS	6	Deionized water	QS to 1 kg
5.00	7	Cetrimonium bromide	5.00
0.50	8	Chlorhexidine gluconate	0.50
QS	9	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases to 65°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Fill.

Antiseptic Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
30.00	1	Cetearyl alcohol and ceteareth-20	30.00
50.00	2	Mineral oil (70 cS)	50.00
2.00	3	Lanolin alcohol	2.00
QS	4	Deionized water	QS to 1 kg
5.00	5	Cetrimonium bromide (as 40% cetrimide solution BP)	5.00
20.00	6	Glycerin	20.00
QS	7	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Fill at 30°C.

Antiseptic Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
30.00	1	Cetearyl alcohol and ceteareth-20	30.00
45.00	2	Mineral oil (70 cS)	45.00
25.00	3	Stearyl alcohol	25.00
10.00	4	Lanolin	10.00
5.00	5	Polysorbate 60	5.00
15.00	6	Laneth-15	15.00
QS	7	Deionized water	QS to 1 kg
5.00	8	Cetrimonium bromide (as 40% cetrimide solution BP)	5.00
20.00	9	Glycerin	20.00
QS	10	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Fill at 30°C.

Arginine and Oleoresin Capsicum Cream

Active ingredients: L-arginine and oleoresin capsicum. Other ingredients: water, choline chloride, sodium chloride, magnesium chloride, white oil, glyceryl stearate SE, squalane, cetyl alcohol, propylene glycol stearate SE, wheat germ oil, glyceryl stearate, isopropyl myristate, stearyl stearate, polysorbate-60, propylene glycol, oleic acid, tocopheryl acetate, collagen, sorbitan stearate, vitamins A and D, triethanolamine, aloe vera extract, imidazolidinyl urea, oleoresin capsicum, methyl paraben, propyl paraben, BHA.

Arginine Cream

Active ingredient: L-arginine. Other ingredients: water, choline chloride, sodium chloride, magnesium chloride, white oil, glyceryl stearate SE, squalane, cetyl alcohol, propylene glycol stearate SE, wheat germ oil, glyceryl stearate, isopropyl myristate, stearyl stearate, polysorbate-60, propylene glycol, oleic acid, tocopheryl acetate, collagen, sorbitan stearate, vitamins A and D, triethanolamine, aloe vera extract, imidazolidinyl urea, methyl paraben, propyl paraben, BHA.

Arginine–Aspartate Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.50	1	Cetostearyl alcohol	35.00
40.00	2	Squalane	400.00
3.00	3	Beeswax	30.00
5.00	4	Reduced lanolin	50.00
0.30	5	Ethyl *p*-oxybenzoate	3.00
2.00	6	Polyoxyethylene (20 mol) sorbitan monopalmitate	20.00
2.00	7	Monoglyceride stearate	20.00
0.50	8	Sodium *N*-stearoyl glutamate	5.00
1.00	9	2-Hydroxy-4-methoxy benzophenone	10.00
2.00	10	Retinol acetate	20.00
0.05	11	Evening primrose oil	0.50
0.03	12	Perfume	0.30
0.01	13	L-Arginine-L-aspartate	0.10
5.00	14	1,3-Butylene glycol	50.00
5.00	15	Polyethylene glycol 1500	50.00
QS	16	Water purified	QS to 1 kg

Manufacturing Directions

1. Charge items 1 to 12 in a heating vessel and dissolve and mix.
2. In another vessel, prepare a solution of items 13 to 16 heated to 75°C with stirring.
3. Add step 2 into step 1 and homogenize to reduce the size of emulsified particles.
4. Cool rapidly to produce a cream.

Atropine Opthalmic Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Atropine sulfate	10.00
5.00	2	Liquid paraffin	50.00
5.00	3	Cetostearyl alcohol	50.00
5.00	4	Hard paraffin	50.00
84.00	5	Soft paraffin	840.00

Manufacturing Directions

1. Load items 2 to 5 in a melting vessel. Heat to 145°C and keep it at this temperature for 45 minutes.
2. Allow to cool to room temperature.
3. In a separate vessel, dissolve item 1 in 200 mL of water for injection and add to step 1 under aseptic conditions.
4. Fill and sterilize in tubes (gamma radiation).

Azelaic Acid Cream and Gel

Azelaic acid cream, 20%, contains azelaic acid, a naturally occurring saturated dicarboxylic acid. Each gram contains azelaic acid (0.2 g, 20% w/w). Inactive ingredients: cetearyl octanoate, glycerin, glyceryl stearate, cetearyl alcohol, cetyl palmitate, cocoglycerides, PEG-5 glyceryl stearate, propylene glycol, and purified water. Benzoic acid is present as a preservative. Azelaic acid in a gel form is manufactured by the following method: Benzoic acid and EDTA are dissolved in usual concentrations in 60 to 70 parts of water. Then a mixture of 1 part midchain triglycerides and 1.5 parts polysorbate 80 is added and homogenized while being stirred (preemulsion). One part lecithin is introduced into twelve parts propylene glycol. The solution that is produced is stirred into the preemulsion and homogenized. After 1 part polyacrylic acid is added, 15 parts azelaic acid are added. Sodium hydroxide is used to neutralize the carbomer to form the gel.

Baby Cream, Benzalkonium Chloride, and Zinc Oxide

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.002 mL	1	Benzalkonium chloride solution	2.30 mL
85.00 mg	2	Zinc oxide (powder)	85.00
100.00 mg	3	Polawax (emulsifying, nonionic wax)	100.00
16.00 mg	4	Alcohol cetostearyl	16.00
4.00 mg	5	Lanolin (acetylated/anhydrous, regular)	4.00
80.00 mg	6	Glycerin (96%)	80.00
10.00 mg	7	Oil (neutral, vegetable triglycerides mixture; Miglyol)	10.00
0.50 mg	8	Propyl paraben (Aseptoform(tm) P)	0.50
1.00 mg	9	Methyl paraben (Aseptoform(tm) M)	1.00
0.80 mL	10	Purified water	QS to 800.00 mL
0.24 mg	11	Perfume (Diabolo 110.388/B)	0.24

Manufacturing Directions

Avoid mixing air into emulsion. Emulsify under vacuum to minimize air entrapment. Use jacketed tank with vacuum with high-speed agitator (adjustable, slow-speed, anchor type with Teflon sweep blades).

1. If necessary, mill zinc oxide in a Fitz mill or similar device (impact forward, maximum speed), fitted with a 250-μm screen.
2. Repeat 3 times.
3. Heat 800 mL of water to 75°C in a steam-jacketed mixing tank and dissolve methyl paraben.
4. Maintain temperature at 75°C.
5. Disperse milled zinc oxide in solution of previous step.
6. Maintain temperature at 75°C.
7. Dissolve benzalkonium chloride and glycerin in solution and maintain temperature at 75°C.
8. In a separate steam-jacketed tank, add Polawax, cetostearyl alcohol, acetylated lanolin, oil, and propyl paraben. Carefully melt at 70°C.
9. Adjust the turbomixer of the steam-jacketed tank containing the aqueous phase to maximum speed, keeping the temperature at 75°C.
10. Slowly add the oil phase to the aqueous phase.
11. Generate as much vacuum as possible and maintain it for the rest of the process.
12. Circulate cold water to allow for a very slow temperature decrease (down to 60°C).
13. Stop the turbomixer and set the anchor-type agitator at minimum speed until 40°C to 45°C is reached.
14. The temperature decrease must be very slow.
15. Break the vacuum and add perfume to cream with anchor-type agitator set at slow speed.
16. Continue to mix until the perfume is completely dispersed.

Baby Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L
50.00	1	Alcohol (ethanol; natural cosmetic grade)	50.00 g
50.00	2	Propylene glycol	50.00 g
0.80	3	Ethoxylated nonyl phenol	0.80 g
0.005	4	FD&C Red Dye No. 40	5.70 mg
0.41	5	FD&C blue dye No. 1	0.41 g
0.70	6	FD&C yellow dye No. 5	0.70 g
0.40	7	Perfume essence (Nelandia)	0.40 g
QS	8	Hydrochloric acid (reagent-grade bottles)	~0.01 g
QS	9	Purified water	QS to 1.00 L

Manufacturing Directions

Use 316 or more resistant-grade stainless steel tank.

1. Charge approximately 800 mL of purified water in main mixing tank.
2. Add alcohol and propylene glycol and mix for 5 minutes.
3. Separately dissolve each dye in sufficient water to obtain 0.5% dye solutions.
4. Add color solutions to main tank and mix.
5. Rinse containers with small portions of purified water and add rinsings.
6. Dissolve perfume essence in ethoxylated nonyl phenol.
7. Add solution from previous step to main tank and mix for 5 minutes.
8. Determine pH of solution and adjust if necessary with 5% hydrochloric acid solution.
9. Mix well. ph should be 5.7 to 5.9.
10. QS to 1 L with purified water.

Baby Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Alcohol	50.0
50.00	2	Propylene glycol	50.0
0.80	3	Ethoxylated nonyl phenol	0.80
0.57	4	Dye red FD&C No. 40	0.57
0.41	5	Dye blue FD&C No. 1	0.41
0.70	6	Dye yellow FD&C No. 5	0.70
0.40	7	Perfume essence nelandia	0.40
QS	8	Acid hydrochloric reagent grade bottles	~0.012
QS	9	Water purified	QS to 1 L

Manufacturing Directions

1. Use 316 or more resistant grade stainless steel tank.
2. Charge approximately 800 mL of purified water in main mixing tank.
3. Add alcohol and propylene glycol and mix for 5 minutes. Separately dissolve each dye in sufficient water to obtain 0.5% dye solutions.
4. Add color solutions to main tank and mix. Rinse containers with small portions of purified water and add rinsings.
5. Dissolve perfume essence nelandia in ethoxylated nonyl phenol.
6. Add solution from step above to main tank and mix for 5 minutes.
7. Determine pH of solution and adjust if necessary with 5% hydrochloric acid solution.
8. Mix well (pH 5.7–5.9). QS to 1 L with purified water.

Baby Shampoo

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg
250.00	1	Sodium alkyl ether sulfate/sulfonate	250.00 g
30.00	2	Monateric CAB surfactant	30.00 g
30.00	3	Cocamide DEA surfactant (Synotol CN 90)	30.00 g
1.00	4	Methyl paraben	1.00 g
0.52	5	Anhydrous citric acid	0.52 g
0.003	6	FD&C yellow dye No. 6	3.50 mg
0.01	7	FD&C yellow dye No. 5	15.00 mg
4.00	8	Ethoxylated nonyl phenol	4.00 g
3.00	9	Perfume I	3.00 g
1.00	10	Perfume II	1.00 g
8.50	11	Sodium chloride	8.50 g
QS	12	Purified water	QS to 1.00 kg

Manufacturing Directions

Use 315 or more resistant-grade stainless steel tank.

1. Add approximately 270 g of purified water to the main mixing tank.
2. With slow agitation add cocamide DEA surfactant.
3. Add and dissolve methyl paraben and mix for approximately 10 minutes.
4. Add the following ingredients to tank: sodium alkyl sulfate/sodium alkyl ether sulfate/sulfonate, monateric CAB surfactant, and approximately 280 g of purified water.
5. Mix for 15 minutes until complete solution is obtained.
6. With constant stirring, slowly add citric acid (10% solution) until a pH of 6.9 to 7.1 is maintained constantly for 5 minutes after the last addition of the citric acid solution.
7. Separately dissolve FD&C yellow dyes No. 6 and 5 (if used) in sufficient purified water.
8. Add dye solution from step above to main tank and mix.
9. Rinse containers with a small portion of purified water and add rinsings.
10. Separately mix ethoxylated nonyl phenol with perfumes (perfume available from Firmenich; Plainsboro, NJ) and add to main mixing tank.
11. Rinse container with purified water and add rinsing.
12. Mix until completely dissolved.
13. Slowly add in small portions sodium chloride to adjust the viscosity to between 1500 and 3500 cps.
14. Mix for 15 minutes.
15. If necessary, QS to 1 kg with purified water.

Bacitracin Zinc and Polymyxin B Sulfate Opthalmic Ointment

The bacitracin zinc and polymyxin B sulfate ophthalmic ointment USP is a sterile antimicrobial ointment formulated for ophthalmic use. Bacitracin zinc is the zinc salt of bacitracin, a mixture of related cyclic polypeptides (mainly bacitracin A) produced by the growth of an organism of the licheniformis group of *Bacillus subtilis* var Tracy. It has a potency of not less than 40 bacitracin units per milligram. Polymyxin B sulfate is the sulfate salt of polymyxin B1 and B2, which are produced by the growth of *Bacillus polymyxa* (Prazmowski) Migula (family Bacillaceae). It has a potency of not less than 6000 polymyxin B units per milligram, calculated on an anhydrous basis. Each gram contains the following actives: Bacitracin zinc equal to 500 bacitracin units and polymyxin B sulfate equal to 10,000 polymyxin B units. Inactives: white petrolatum and mineral oil.

Base Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.0	1	Cetyl stearyl alcohol	70.00
1.5	2	Cremophor A 6	15.00
1.5	3	Cremophor A 25	15.00
12.0	4	Liquid paraffin	120.00
0.2	5	Paraben(s)	2.00
67.8–69.7	6	Water	678–697
8.0	7	Propylene glycol	80.00
0.1–2.0	8	Active ingredient	1–2.00

Manufacturing Directions

1. Heat a mixture of items 1 to 5 and the water separately to approximately 80°C.
2. With rigorous stirring, add the water to the obtained solution.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with aqueous solution, and continue to stir during cooling to room temperature.
4. This white basic cream can be readily used for active ingredients soluble in 1, 2-propylene glycol.

Base Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.50	1	Propylene glycol	25.00
2.50	2	Triacetin	25.00
57.00	3	Mineral oil	570.00
35.00	4	Microcrystalline wax	350.00
3.00	5	Propylene glycol stearate	30.00
0.05	6	Citric acid	0.50

Manufacturing Directions

1. The mineral oil, microcrystalline wax, and propylene glycol stearate are melted together by heating to 75° to 85°C and mixed, thus creating the oleaginous phase.
2. The citric acid, if used, is dissolved in the triacetin by stirring and using heat is necessary.
3. If used optionally, the propylene glycol is added to the triacetin and mixed.
4. After cooling the oleaginous phase to approximately 55°C, the triacetin solution is added to the oleaginous phase while mixing. Mixing should be of sufficient intensity to disperse the triacetin finely and uniformly.
5. Mixing is continued while cooling the ointment to 30°C or lower.

Base Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
10.00	1	Triacetin	100.00
30.00	2	Lanolin alcohol and petrolatum (Amerchol CAB)	300.00
1.00	3	Cholesterol	10.00
59.00	4	White petrolatum	590.00

Manufacturing Directions

1. Amerchol CAB, white petrolatum, and cholesterol are melted together by heating to 75°C to 85°C and are mixed to form the oleaginous phase.
2. After cooling the oleaginous phase to approximately 45°C, the triacetin is added to the oleaginous phase while mixing. Mixing should be of sufficient intensity to disperse the triacetin finely and uniformly.
3. Mixing is continued while cooling the ointment to 30°C or lower.

Base Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Triacetin	50.00
25.00	2	Dimethicone (1000 cS)	250.00
61.50	3	White petrolatum	615.00
5.00	4	Microcrystalline wax	50.00
1.00	5	Cholesterol	10.00
2.50	6	Sucrose distearate	25.00

Manufacturing Directions

1. To make the oleaginous phase, white petrolatum, sucrose distearate, cholesterol, and microcrystalline wax are melted at 75°C to 85°C.
2. Dimethicone is added and mixed. After cooling the oleaginous phase to approximately 55°C, the triacetin is added to the oleaginous phase while mixing. Mixing should be of sufficient intensity to disperse the triacetin finely and uniformly.
3. Mixing is continued while cooling the ointment to 30°C or lower.

Base Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Liquid paraffin	50.00
10.00	2	White paraffin	100.00
30.00	3	Glycerin	300.00
8.00	4	Cetostearyl alcohol	80.00
0.30	5	Methyl paraben	3.00
3.60	6	Polyoxyethylene sorbitan monostearate	36.00
2.00	7	Glyceryl monostearate	20.00
QS	8	Water purified	QS to 1 kg

Manufacturing Directions

1. Preparation of water phase
   a. Charge purified water, polysorbate 60, and glycerin with agitation to a melting kettle.
   b. Heat the contents to 61°C to 65°C.
   c. Add methyl paraben and mix the composition to dissolve while maintaining temperature.
2. Preparation of oil phase
   a. In a suitable vessel, charge liquid paraffin, cetostearyl alcohol, white petrolatum, glycerol monostearate, and white beeswax and mix continuously while heating to 71°C to 75°C.
3. Mixing of phases
   a. The mixture of step 2 is transferred to step 1 kettle with the water phase maintained less than 300 mbar vacuum.
   b. With mixing and keeping the temperature at 61°C to 65°C, draw the oil phase into the water phase.
   c. Mix for 15 minutes with agitation and vacuum at 300 mbar and 61°C to 65°C.
   d. While mixing and under vacuum, allow the mixture to cool gradually to room temperature.
4. Fill in appropriate container.

Becaplermin Gel (0.01%)

The gel contains becaplermin, a recombinant human platelet-derived growth factor for topical administration. Becaplermin is produced by recombinant DNA technology by insertion of the gene for the B chain of platelet-derived growth factor into the yeast *Saccharomyces cerevisiae*. Becaplermin has a molecular weight of approximately 25 kDa and is a homodimer composed of two identical polypeptide chains that are bound together by disulfide bonds. The gel is a nonsterile, low-bioburden, preserved, sodium carboxymethylcellulose-based topical gel containing the active ingredient becaplermin and the following inactive ingredients: sodium chloride, sodium acetate trihydrate, glacial acetic acid, water for injection, and methyl paraben, propyl paraben, and M-cresol as preservatives and L-lysine hydrochloride as a stabilizer. Each gram of gel contains 100 g of becaplermin.

Benzalkonium Chloride and Zinc Oxide Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.0023 mL	1	Benzalkonium chloride solution	2.3 mL
85.0	2	Zinc oxide USP powder	85.0
100.0	3	Wax emulsifying nonionic (Polawax®)	100.0
16.0	4	Alcohol cetostearyl	16.0
4.0	5	Lanolin acetylated/anhydrous USP regular	4.0
80.0	6	Glycerin USP (96%)	80.0
10.0	7	Oil-neutral vegetable triglycerides mixture Miglyol	10.0
0.5	8	Propyl paraben NF (Aseptoform P)	0.5
1.0	9	Methyl paraben NF (Aseptoform M)	1.0
0.80 mL	10	Purified water	QS to 800.0 mL
0.24	11	Perfume diabolo 110.388/B	0.24g

Manufacturing Directions

1. Avoid mixing air into emulsion. Emulsify under vacuum to minimize air entrapment. Use jacketed tank with vacuum with high-speed agitator and an adjustable slow-speed anchor type with Teflon sweep blades.
2. If necessary, mill zinc oxide in a Fitz mill or similar impact-forward, maximum-speed mill, fitted with a 250-μ aperture screen. Repeat 3 times. Heat 800 mL of water to 75°C in a steam-jacketed mixing tank and dissolve methyl paraben.
3. Maintain temperature at 75°C. Disperse milled zinc oxide in solution of step above. Maintain temperature at 75°C.
4. Dissolve benzalkonium chloride and glycerin in solution. Maintain temperature at 75°C.
5. In a separate steam-jacketed tank, add Polawax, cetostearyl alcohol, acetylated lanolin, oil-neutral vegetable triglycerides mixture, and propyl paraben and carefully melt at 70°C.
6. Adjust the turbomixer of the steam-jacketed tank containing the aqueous phase to maximum speed, keeping the temperature at 75°C. Slowly add the oil phase into the aqueous phase. Generate as much vacuum as possible and maintain it for the rest of the process.
7. Circulate cold water to allow for a very slow temperature decrease (down to 60°C). Stop turbomixer and put the anchor-type agitator at minimum speed until 40°C to 45°C is reached. The temperature decrease must be very slow.
8. Break the vacuum and add perfume to cream with anchor-type agitator at slow speed.
9. Continue to mix until the perfume is completely dispersed.

Benzalkonium Chloride Contraceptive Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PEG-6, PEG-32, and glycol stearate (Tefose® 63)	50.00
30.00	2	Apricot kernel oil PEG-6 esters (Labrafil® M 1944 CS)	30.00
816.00	3	Deionized water	816.00
80.00	4	Hydroxyethyl cellulose	80.00
24.00	5	Benzalkonium chloride (50 wt% in water)	24.00

Manufacturing Directions

1. Mix items 3 and 4 at room temperature.
2. Heat to 75°C and add items 1 and 2 while stirring.
3. Cool with gentle stirring to 30°C, then add item 5 and stir.

Benzocaine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
180.00	1	Trilaneth-4 phosphate and glyceryl stearate and PEG-2 stearate	180.00
20.00	2	Hydrogenated palm/Kernel oil PEG-6 esters	20.00
80.00	3	Mineral oil	80.00
0.30	4	Sodium methyl paraben	0.30
0.70	5	Sorbic acid	0.70
646.70	6	Deionized water	646.70
10.00	7	Benzocaine	10.00
10.00	8	Butamben	10.00
2.00	9	Menthol	2.00
0.30	10	Resorcinol	0.30
50.00	11	Ethoxydiglycol	50.00

Manufacturing Directions

1. Dissolve items 7 to 10 in item 11.
2. Mix and heat items 1to 6 to 75°C. Allow to cool slowly with constant stirring. At 35°C, add this to mixture above.
3. Homogenize if necessary.

Benzoyl Peroxide and Alpha-Bisabolol Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
2.00	1	Alpha-bisabolol, natural (BASF)	2.00
60.00	2	Propylene glycol	60.00
100.00	3	Triethanolamine	100.00
30.00	4	Cremophor RH 40	30.00
30.00	5	Kollidon 30	30.00
408.00	6	Water	408.00
10.00	7	Carbopol 940	10.00
400.00	8	Water	400.00
50.00	9	Benzoyl peroxide	50.00

Manufacturing Directions

1. Prepare suspension of items 7 and 8, then let swell for 1 hour.
2. Add this suspension to the well-stirred solution of items 1 to 5.
3. Add item 9 to create a colorless transparent gel.

Benzoyl Peroxide Antiacne Microemulsion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
470.00	1	Ethoxydiglycol (Transcutol®)	470.00
250.00	2	PEG-8 caprylic/Capric glycerides (Labrasol®)	250.00
150.00	3	Dipelargonate propylene glycol (DPPG)	150.00
80.00	4	Benzoyl peroxide	80.00
50.00	5	Propylene glycol laurate (Lauroglycol®)	50.00

Manufacturing Directions

1. Mix items 1 to 3.
2. Dissolve item 4 in this mixture with mixing for 1.5 to 2.0 hours.
3. Add item 5 to mixture and mix until uniform emulsion is obtained.

Benzoyl Peroxide Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
460.50	1	Deionized water	460.50
5.00	2	Carbomer 940	5.00
10.00	3	Hydroxypropylmethylcellulose, medium viscosity	10.00
137.50	4	Deionized water	137.50
70.00	5	Purified bentonite (Polargel NF)	70.00
2.00	6	Methyl paraben	2.00
1.00	7	Propyl paraben	1.00
20.00	8	Glyceryl stearate	20.00
60.00	9	Propylene glycol	60.00
20.00	10	Polyethylene glycol 600	20.00
20.00	11	Myristyl propionate	20.00
50.00	12	Dimethicone	50.00
70.00	13	Purified bentonite (Polargel NF)	70.00
10.00	14	Titanium dioxide	10.00
100.00	15	Benzoyl peroxide 70%	100.00

Manufacturing Directions

1. Sift carbomer 940 into vortex in water; when completely dispersed, sift in item 3.
2. Add parabens with stirring and heat (to 80°C at least) until dissolved.
3. Add glyceryl stearate.
4. Blend items 10 to 13 in propylene glycol in order and mix well. With the addition of Polargel, allow 15 minutes of mixing to complete hydration.
5. Blend propylene glycol portion into the first part. Finally, add benzoyl peroxide and titanium dioxide to the mixture and mill.

Benzoyl Peroxide Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
2.50	1	Acrylates/C10-30 alkyl acrylate crosspolymer	2.50
4.00	2	Carbopol 980	4.00
QS	3	Deionized water	QS to 1 kg
40.00	4	Isopropyl myristate	40.00
10.00	5	Cetyl alcohol	10.00
20.00	6	Glyceryl stearate	20.00
50.00	7	Sodium hydroxide 0.5 *M*	50.00
15.00	8	Deionized water	15.00
50.00	9	Benzoyl peroxide	50.00
50.00	10	PEG-600	50.00
QS	11	Perfume, preservative	QS

Manufacturing Directions

1. Hydrate Carbopol and pemulen in warm water, 60°C. When fully hydrated, heat to 70°C.
2. Heat oil phase to 70°C. Add water phase to oil phase while stirring.
3. Add sodium hydroxide and continue stirring. Combine benzoyl peroxide, PEG-600, and water (item 8) and add to the emulsion.
4. At 35°C, homogenize with caution, using suitable equipment.

Benzoyl Peroxide Lotion

The cleansing lotions contain benzoyl peroxide, 4% and 8% respectively, in a lathering vehicle containing purified water, cetyl alcohol, citric acid, dimethyl isosorbide, docusate sodium, hydroxypropylmethylcellulose, laureth-12, magnesium aluminum silicate, propylene glycol, sodium hydroxide, sodium lauryl sulfoacetate, and sodium octoxynol-2 ethane sulfonate.

Benzoyl Peroxide Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Purified bentonite (Polargel NF)	40.00
10.00	2	Hydroxypropylmethylcellulose	10.00
522.20	3	Water	522.20
190.00	4	Water	190.00
2.00	5	Methyl paraben	2.00
2.00	6	Propyl paraben	2.00
20.00	7	Glyceryl stearate	20.00
60.00	8	Propylene glycol	60.00
20.00	9	Myristyl propionate	20.00
5.00	10	Dimethicone	5.00
QS	11	Iron oxides	QS
10.00	12	Titanium dioxide	10.00
100.00	13	Benzoyl peroxide 77%	100.00

Manufacturing Directions

1. Sift the Polargel NF into water with rapid mixing. Allow to hydrate for 15 minutes.
2. Pass through coarse sieve, add item 2, and mix until all lumps are removed.
3. Add parabens to the water with stirring and heat to 90°C to dissolve parabens.
4. Add items 4 to 10 and mix well and then add these to the item 2 part. Mix well again. Finally, add items 11 to 13 and mix.
5. Mill it and fill.

Betamethasone and Cinchocaine Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
1.00	1	Betamethasone valerate	1.00
1.00	2	Cinchocaine hydrochloride	1.00
1798.00	3	Witepsol W 45®	1798.00

Manufacturing Directions

1. Charge item 3 in the fat-melting vessel and heat to 55°C; transfer molten mass to Becomix through stainless steel sieve. Set the temperature at 50°C.
2. Add items 1 and 2, mix well at 50°C, and mix for 20 minutes.
3. Homogenize at 0.6 bar vacuum and 50°C.
4. Transfer to storage at 40°C.
5. Fill suppository mold.

Betamethasone and Neomycin Gel Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
1.30	1	Betamethasone valerate	0.13
6.50	2	Neomycin sulfate	0.65
150.00	3	Lutrol E 400	15.00
100.00	4	Miglyol 812	10.00
200.00	5	Lutrol F 127	20.00
QS	6	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve betamethasone valerate in a mixture of Lutrol E 400 and Miglyol 812.
2. Dissolve Lutrol F 127 and neomycin sulfate in water at 5°C to 10°C.
3. Mix both solutions.
4. Maintain cool temperature until the air bubbles disappear. A milky-white soft gel cream is obtained.

Betamethasone and Salicylic Acid Lotion

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.10	1	Betamethasone dipropionate micronized, 5% excess[a]	1.05
1.90	2	Salicylic acid	19.00
0.032	3	Disodium edetate	0.32
0.55	4	Hydroxypropylmethylcellulose	5.50
0.55	5	Sodium hydroxide	5.50
40.00	6	Isopropyl alcohol	400.00
QS	7	Water purified	QS to 1 kg

[a]Adjust quantity of the basis of assay.

Manufacturing Directions

1. Charge about half of item 7 into a suitable vessel and slowly add item 4 with vigorous mixing.
2. Use item 7 to rinse the container for item 4 and add rinsings to the mixing vessel.
3. In 10% of the amount of item 6, add and dissolve item 1 in a separate vessel and then add an additional 20% of item 6 and mix well until completely dissolved.
4. Add 10% of item 7 in a separate vessel and add and dissolve item 5 into it.
5. Add 10% of item 7 in a separate vessel and add and dissolve item 3 into it.
6. Add 20% of item 7 in a separate vessel and add and dissolve item 2 into it.
7. Add 50% of item 6 to step 4 and mix slowly for 15 minutes. Add to this vessel step 3 and step 5 and mix vigorously.
8. Use item 7 to rinse all vessels and add rinsings.
9. Check pH to 4.8 to 5.3 and adjust if necessary.
10. Add step 1 to this and mix.
11. Fill in appropriate containers.

Betamethasone Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
70.00	1	Cetyl stearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
12.00	4	Liquid paraffin	12.00
2.00	5	Paraben(s)	2.00
697.00	6	Water	697.00
80.00	7	Propylene glycol	80.00
1.00	8	Betamethasone	1.00

Manufacturing Directions

1. Heat the mixture of items 1 to 5 and item 6 separately to approximately 80°C.
2. Add together with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved.
4. Mix with above mixture and continue to stir to cool to room temperature to produce white cream.

Betamethasone Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
70.00	1	Cetyl stearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
12.00	4	Liquid paraffin	120.00
2.00	5	Paraben(s)	2.00
697.00	6	Water	697.00
80.00	7	Propylene glycol	80.00
1.00	8	Betamethasone	1.00

Manufacturing Directions

1. Heat a mixture of items 1 to 5 and item 6 separately to approximately 80°C.
2. Add together with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with above mixture, and continue to stir to cool to room temperature. This creates a white cream.

Betamethasone Dipropionate Cream, Lotion, and Ointment

Each gram of cream, 0.05%, contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a hydrophilic emollient cream consisting of purified water USP, mineral oil USP, white petrolatum USP, ceteareth-30, cetearyl alcohol 70/30 (7.2%), sodium phosphate monobasic monohydrate R, and phosphoric acid NF, with chlorocresol and propylene glycol USP as preservatives. It may also contain sodium hydroxide R to adjust pH to approximately 5. Each gram of lotion, 0.05%, w/w contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a lotion base of isopropyl alcohol USP (39.25%) and purified water USP and is slightly thickened with carbomer 974P; the pH is adjusted to approximately 4.7 with sodium hydroxide R. Each gram of lotion, 0.05%, contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in a lotion base of purified water USP, isopropyl alcohol USP (30%), hydroxypropyl cellulose NF, propylene glycol USP, and sodium phosphate monobasic monohydrate R, with phosphoric acid NF used to adjust the pH to 4.5. Each gram of ointment, 0.05%, contains 0.643 mg betamethasone dipropionate USP (equivalent to 0.5 mg betamethasone) in an ointment base of mineral oil USP and white petrolatum USP.

Betamethasone Dipropionate Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.064	1	Betamethasone dipropionate	0.64
2.50	2	Propylene glycol stearate	25.00
3.50	3	Triacetin	35.00
0.05	4	Citric acid	0.50
35.00	5	Microcrystalline wax	350.00
58.88	6	Mineral oil	588.80

Manufacturing Directions

1. Betamethasone dipropionate and citric acid are dissolved in the triacetin with mixing and heat to 35°C if needed.
2. Microcrystalline wax, propylene glycol stearate, and mineral oil are melted together by heating to 75° to 85°C while stirring to make the oleaginous phase.
3. After cooling the oleaginous phase to approximately 55°C, the triacetin solution is added while mixing to make a homogenous dispersion. Mixing should be of sufficient intensity to disperse the triacetin solution finely and uniformly.
4. Mixing is continued while cooling at room temperature.

Betamethasone Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
1.00	1	Betamethasone valerate	1.00
100.00	2	Ethanol (96%)	100.00
200.00	3	Propylene glycol	200.00
220.00	4	Lutrol F 127	220.00
QS	5	Water QS	470.00

Manufacturing Directions

1. Prepare a solution of items 1 to 3 at room temperature and a solution of items 4 and 5 at approximately 6°C (or at >70°C).
2. Mix both solutions.
3. Maintain the temperature until the air bubbles disappear.
4. A certain amount of propylene glycol could be substituted by water. The obtained gel is clear and colorless.

Betamethasone Opthalmic Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Betamethasone sulfate	10.00
5.00	2	Liquid paraffin	50.00
5.00	3	Cetostearyl alcohol	50.00
5.00	4	Hard paraffin	50.00
84.00	5	Soft paraffin	840.00

Manufacturing Directions

1. Load items 2 to 5 in a melting vessel. Heat to 145°C and keep it at this temperature for 45 minutes.
2. Allow to cool to room temperature.
3. In a separate vessel, dissolve item 1 in 200 mL of water for injection and add to step 1 under aseptic condition.
4. Fill and sterilize in tubes.

Betamethasone Valerate and Cinchocaine Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Cinchocaine hydrochloride	5.00
1.00	2	Betamethasone valerate	1.00
75.00	3	Hydrogenated castor oil	75.00
400.00	4	Eutenol G (2-octyldodecanol)	400.00
75.00	5	PEG-400 monoricinoleate	75.00
0.08	6	Lavender oil	0.08
443.00	7	Castor oil	443.00

Manufacturing Directions

1. Charge items 3, 4, 5, and 7 in a melting vessel and heat to 85°C. Melt to a clear solution and cool down to 65°C. Transfer to Becomix.
2. Mix in Becomix at 65°CC under vacuum. Cool down to 50°C.
3. Add items 1 and 2 in a small portion of the melt from step 2 in a separate vessel and homogenize and then add to step 3.
4. Add item 6 at 30°C and mix for 10 minutes.
5. Transfer to storage vessel and fill.

Betamethasone Valerate Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.10	1	Betamethasone valerate (34% excess)	1.34
2.00	2	Polyoxyl 20 cetostearyl ether (Cetomacrogol 1000)	20.00
8.00	3	Cetostearyl alcohol	80.00
0.10	4	Methyl paraben	1.00
0.034	5	Propyl paraben	0.34
0.10	6	Chlorocresol	1.00
6.00	7	Mineral oil (liquid paraffin)	60.00
0.29	8	Monobasic sodium phosphate	2.90
17.80	9	Petrolatum (soft white paraffin)	178.00
66.00	10	Purified water	660.00

Manufacturing Directions

1. Heat item 10 to 90°C in a mixer.
2. Dissolve items 4 and 5 (parabens) to a clear solution by stirring.
3. Dissolve 3 g of item 2 in the parabens solution while stirring.
4. Dissolve items 6 and 8 in the parabens solution while stirring.
5. Set the mixer at a temperature of 65°C to 70°C and speed at 8 rpm. Use manual mode.
6. Load 17 g of items 2, 3, and 9 and 45 g of item 7 in a fat-melting vessel.
7. Heat to 70°C to 75°C while stirring. Maintain temperature at 65°C to 75°C.
8. Mix item 1 in 10 g of item 7 in a stainless steel container.
9. Homogenize for 10 minutes to make a smooth slurry.
10. Check the temperature of the aqueous phase in the mixer (should be 65–70°C).
11. Check the temperature of the fatty phase in the fat-melting vessel (should be 65–70°C).
12. Set the mixer speed 8 rpm and vacuum at 0.4 to 0.6 bar.
13. Transfer the fatty phase to the aqueous phase in mixer vessel through filter under vacuum, while mixing.
14. Start the homogenizer at high speed. Homogenize for 10 minutes.
15. Check and record the pH of cream (limit: 4.5–5.2 at 30°C).
16. Cool the temperature to 50°C while mixing. Release the vacuum.
17. Take out 400 g of the cream into the stainless steel vessel and set aside.
18. Add slurry from earlier step to the remaining cream base in mixer.
19. Rinse the container of slurry using 5 g of item 7 and transfer the rinsing to the mixer.
20. Homogenize for 10 minutes at high speed (mixer speed 8 rpm).
21. Load 400 g cream from step above to the mixer.
22. Set the mixer in manual mode at 8 rpm and a vacuum of 0.4 to 0.6 bar.
23. Homogenize at high speed with recirculation, temperature 25°C. Homogenize for 10 minutes with recirculation, stop the homogenizer, and continue mixing to produce a white, homogeneous cream of pH 4.5 to 5.2 at 30°C.

Betamethasone Valerate Foam

Each gram of foam contains 1.2 mg betamethasone valerate USP in a hydroalcoholic, thermolabile foam. The foam also contains cetyl alcohol, citric acid, ethanol (60.4%), polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol and is dispensed from an aluminum can pressurized with a hydrocarbon propellant (propane/butane).

Betamethasone Valerate Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.100	1	Betamethasone, USE: betamethasone valerate	1.300
84.870	2	Petrolatum (white soft paraffin)	848.700
15.000	3	Mineral oil (liquid paraffin)	150.000

Manufacturing Directions

1. Melt item 2 in a fat-melting vessel at 75°C. While mixing, do not overheat.
2. Maintain temperature of the molten mass in the melting vessel at 60°C to 65°C.
3. Start the steam on the mixer vessel and set the temperature at 60°C.
4. Transfer 160 g of the molten mass at 60°C to the mixer vessel. Retain the rest of the quantity in the fat-melting vessel.
5. Start mixing in the mixer vessel at medium speed with vacuum between 0.4 and 0.6 bar until obtaining an actual temperature of 40°C to 45°C.
6. Maintain the temperature of mixer vessel at 40°C to 45°C. Add item 1 to 80 g of item 3 and homogenize for 3 minutes, using homogenizer. Keep the slurry aside.
7. Rinse the homogenizer and container with 70 g of item 3. Transfer item 1 slurry from step above and the rinsing from previous step to the mixer vessel. Start mixing under vacuum 0.4 to 0.6 bar for 15 minutes. Temperature should be maintained at 40°C to 45°C.
8. Transfer the rest of the quantity of molten mass (temperature 60°C) into mixer vessel slowly, continuing to mix for 5 minutes after each addition. At the end of addition, mix a further 10 minutes under vacuum 0.4 to 0.6 bar.
9. Homogenize for 5 minutes at high speed under vacuum 0.4 to 0.6 bar.
10. Cool the ointment to 30°C to 35°C while stirring under a vacuum of 0.4 to 0.6 bar.

Betamethasone Valerate Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.100	1	Betamethasone USE betamethasone valerate with 10% excess	1.34
0.020	2	Vitamin E oily	0.20
79.34	3	White soft paraffin	793.40
3.00	4	Cetostearyl alcohol	20.00
2.50	5	Cetmacrogol 1000	25.00
15.00	6	Liquid paraffin	150.00

Manufacturing Directions

1. Melt item 3 in a fat-melting vessel at 60°C, add items 4 and 5, and mix until clear.
2. Transfer to Becomix at 60°C. Mix at 9 rpm under vacuum of 0.4 to 0.6 bar. Cool to 40°C to 45°C.
3. Add items 1, 2, and 6 to a stainless steel container and homogenize for 3 minutes. Transfer slurry to step 2.
4. Mix under vacuum at 40°C to 45°C.
5. Transfer to storage vessel and fill.

Bifonazole Cream (1%)

Formulation

I. Cetyl stearyl alcohol, 7.0 g, Cremophor A 6 (1)], 1.5 g, Cremophor A 25 (1), 1.5 g, liquid paraffin, 12.0 g, paraben(s), 0.2 g
II. Water, 68.8 g
III. Propylene glycol (1), 8 g, bifonazole, 1 g

Manufacturing Directions

Heat the mixture I and the water II separately to approximately 80°C. Add the water II to the obtained solution I with rigorous stirring. Heat III until the active ingredient is dissolved, mix with I/II, and continue to stir during cooling to room temperature.

This formulation could be used for other active ingredients too.

Bisacodyl Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
5.000	1	Bisacodyl (micronized)[a] 2% excess	5.10
447.500	2	Hard fat (Witepsol E 76®)	447.50
447.500	3	Hard fat (Witepsol W 45)	447.50

[a] 100% particles should be less than 70 m. Fill weight: 1800 mg/suppository

Manufacturing Directions

1. The molten suppository mass must be kept stirred throughout the storage period during manufacturing and during filling to avoid the sedimentation of active drug. The active ingredient causes skin irritation, which vanishes after sometime without having after effects. Avoid dust formation during processing. In particular, protect eyes and mucous membranes.
2. Load items 2 and 3 in the fat-melting vessel and heat to 50°C ± 3°C.
3. Transfer the molten mass to mixer through filter sieves. Set the temperature at 40°C ± 2°C. Load item 1 to the mixer containing the molten mass. Carefully mix the powder with the molten mass.
4. Set the mixer at temperature 40°C ± 2°C, speed 10 rpm (manual mode), and mix for 20 minutes. Set the mixer at temperature 40°C ± 2°C, speed 10 rpm (manual mode), vacuum 0.6 bar.
5. Homogenize at low speed while mixing for 10 minutes. Homogenize at high speed while mixing for 3 minutes.
6. Continue mixing of the mass under vacuum in mixer.
7. Heat the storage vessel, set the temperature at 40°C ± 2°C.
8. Transfer the molten mass from mixer to the storage vessel. Hold the mass at 40°C ± 2°C while mixing continuously at low speed.
9. Fill weight is 900 mg/suppository, but use a fill weight of 1.8 g for 10-mg suppositories.

Bisacodyl Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
10.00	1	Bisacodyl (micronized) 2% excess	10.02
895.00	2	Witepsol E 76	895.00
895.00	3	Witepsol W 45	895.00

Manufacturing Directions

1. Charge items 2 and 3 to a melting vessel, heat to 50°C, transfer to Becomix through filter sieve. Set temperature to 40°C.
2. Charge item 1 and mix carefully. Set temperature to 40°C, speed 10 rpm for 20 minutes.
3. Homogenize for 3 minutes. Continue mixing under vacuum.
4. Transfer to storage vessel and fill.

Biscarboxychromonyloxy Propanol Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
4.00	1	Disodium 1,3-bis(2-carboxychromonyloxy)propan-2-ol (micronized)	40.00
76.80	2	Yellow soft paraffin	768.00
9.60	3	Liquid paraffin	96.00
9.60	4	Lanolin acetylated (Modulan R)	96.00

Manufacturing Directions

1. The disodium salt of 1,3-bis(2-carboxychromon-5-yloxy) propan-2-ol is added slowly in small portions, with vigorous mixing, to a small portion of the preheated and sterilized components of the ointment base at 90°C.
2. When the addition is complete, mixing is continued for a further 15 minutes and then the concentrated dispersion is sterilized by heating at 150°C for 1 hour.
3. The concentrated dispersion is then added to a homogenizer heated at 80°C to 100°C and the remaining components of the ointment basis are added slowly with continuous blending.
4. When this addition is complete, the molten ointment is blended for a further 15 minutes and then cooled to a temperature of 58°C to 62°C.
5. The ointment is then filled in presterilized eye ointment tubes, which are crimped and allowed to cool to room temperature.

Bleaching and Antimicrobial Dentifrice

Manufacturing Directions

Weight percentage: hydrogen peroxide (50%), 10.00; carbamide peroxide, 14.00; sodium fluoride, 0.38; Pecogel S-2120 (VP/Dimethicolylacrylate is an inclusion complex polymer to retard the solubility of emulsified bleaching actives. It is obtained from Phoenix Chemical, Inc.), 0.50; hydroxyethyl cellulose 0.50, triethanolamine 0.30; water purified, 10.00; glycerin, 10.75; tetrafluoroethylene (Teflon), 50.58; sodium lauryl sulfate, 1.25; sodium saccharine, 0.18; sodium citrate, 0.20; citric acid, 0.20; triclosan, 0.06; flavor, 1.10.

Breast Care Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Polysorbate 60	20.00
70.00	2	Cetyl alcohol	70.00
60.00	3	Mineral oil 70cS	60.00
40.00	4	Glyceryl stearate	40.00
QS	5	Deionized water	QS
QS	6	Preservative	QS

Manufacturing Directions

1. Heat oil and water phases separately at 65°C to 70°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 20°C. Only food-grade materials should be used in this preparation. Do not use unapproved preservatives.

Budesonide Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.25	1	Budesonide	0.25
30.00	2	Polyoxy 40 stearate	30.00
80.00	3	Stearyl alcohol	80.00
150.00	4	Liquid paraffin	150.00
30.00	5	White soft paraffin	30.00
0.10	6	Ethylene diamine tetraacetate	0.10
3.00	7	Carbopol 934	3.00
0.67	8	Sodium hydroxide	0.67
0.70	9	Sodium methyl paraben	0.70
0.30	10	Sodium propyl paraben	0.30
QS	11	Water purified	685.00

Manufacturing Directions

1. Melt white soft paraffin, stearyl alcohol, and polyoxyl 40 stearate in the fat-melting vessel at 70°C to 75°C.
2. Heat the purified water in the manufacturing vessel to a temperature of 80°C to 90°C. Disperse Carbopol 934 in the heated water. Homogenize the dispersion to obtain clear gel.
3. Dissolve item 6, sodium methyl paraben, sodium propyl paraben, and sodium hydroxide in purified water. Transfer this solution to the clear gel from step 2 in the manufacturing vessel and homogenize well.
4. Transfer the fat phase (70–75°C) into the manufacturing vessel containing aqueous phase (70–75°C) while mixing. Homogenize under vacuum for few minutes.
5. Disperse budesonide with liquid paraffin in a stainless steel container at 40°C to 45°C and transfer this dispersion to the manufacturing vessel from step 4 at temperature 40°C to 45°C; mix and homogenize under vacuum to obtain a smooth, homogeneous cream and the stated amount of budesonide per 100 g.
6. Cool the cream to 25°C to 30°C while stirring continuously.

Budesonide Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.25	1	Budesonide	0.25
369.75	2	Liquid paraffin	369.75
450.00	3	Hard paraffin	450.00
150.00	4	White wax	150.00
30.00	5	Hydrogenated castor oil	30.00

Manufacturing Directions

1. Melt hard paraffin, white wax, and hydrogenated castor oil in the fat-melting vessel at 100°C and maintain this temperature for 20 minutes. Then transfer this melted mass to the manufacturing vessel preheated to 85°C through 0.150 mm. Cool to 33°C while stirring.
2. Disperse budesonide with liquid paraffin at 33°C; use homogenizer to get homogeneous suspension.
3. Transfer the dispersion from step 2 to the ointment base from step 1 in the manufacturing vessel while stirring. Homogenize well to obtain a homogeneous ointment containing the stated amount of budesonide per 100 g ointment.
4. Filling in the tube is performed in an aseptic area at 33°C.

Buprenorphine Hydrochloride Suppository

Manufacturing Directions

1. Propylene glycol, 10 g; polyethylene glycol 400, 10 g; polyethylene glycol 1000, 30 g; polyethylene glycol 6000, 50 g; buprenorphine hydrochloride, 43.2 mg.
2. After mixing propylene glycol and polyethylene glycol 400, buprenorphine hydrochloride was blended and dissolved and the mixture was blended with the separately heated and dissolved polyethylene glycol 1000 and 6000.
3. The combined mixture was charged into a container for suppository, cooled and solidified, and a suppository of buprenorphine hydrochloride was obtained (suppository weight 1.5 g/piece, each containing 0.6 mg of buprenorphine).

Burn Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
120.00	1	Glyceryl stearate SE (monthybase)	120.00
80.00	2	Octyldodecyl myristate (MOD)	80.00
20.00	3	Apricot kernel oil PEG-6 esters (Labrafil M 1944 CS)	20.00
0.50	4	Sodium methyl paraben	0.50
0.50	5	Sodium propyl paraben	0.50
0.50	6	Sorbic acid	0.50
767.50	7	Deionized water	767.50
10.00	8	Avocado oil	10.00
1.00	9	Fragrance	1.00

Manufacturing Directions

1. Mix and heat items 1 to 7 to 75°C. Cool slowly with stirring.
2. At 30°C, add item 8 and then item 9.

Burn Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
15.00	1	Magnesium aluminum silicate (Veegum)	15.00
568.00	2	Deionized water	568.00
30.00	3	Propylene glycol	30.00
2.00	4	Dimethicone emulsion	2.00
100.00	5	Mineral oil, light	100.00
170.00	6	Acetylated lanolin alcohol	170.00
50.00	7	Benzocaine USP	50.00
30.00	8	C-18-C36 acid	30.00
120.00	9	Glyceryl stearate and PEG-100 stearate	120.00
5.00	10	Polysorbate 60	5.00
QS	11	Preservatives	QS

Manufacturing Directions

1. Add item 1 to water slowly, agitating with extensive shear force until smooth.
2. Add items 3 and 4 to the mixture and heat to 75°C to 80°C. Mix and heat items 5 to 11, keeping item 7 suspended to 75°C to 80°C. Mix the two parts while cooling. Pour and fill at 40°C.

Butenafine Hydrochloride Cream

Butenafine cream, 1%, contains the synthetic antifungal agent butenafine hydrochloride. Each gram of cream, 1%, contains 10 mg of butenafine HCl in a white cream base of purified water USP, propylene glycol dicaprylate, glycerin USP, cetyl alcohol NF, glyceryl monostearate SE, white petrolatum USP, stearic acid NF, polyoxyethylene cetyl ether, benzyl alcohol NF, diethanolamine NF, and sodium benzoate NF.

Butesin Picrate and Metaphen Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
6.48	1	Lanolin anhydrous	6.48
0.219	2	Metaphen chloride powder	0.219
QS	3	Acetone	0.96
8.80	4	Sodium borate	8.80
2.48	5	Potassium chloride	2.48
QS	6	Water purified	253.70
115.00	7	Beeswax white	115.00
80.00	8	Wax ceresin white	80.00
510.00	9	Mineral oil	510.00
10.00	10	Butyl aminobenzoate (Butesin) picrate powder	10.00
13.31	11	2-Ethoxyethanol (Cellosolve)	13.31

Manufacturing Directions

1. Melt lanolin in vacuum flask and heat to 45°C to 60°C. Use sufficient acetone to completely dissolve metaphen chloride. Add metaphen solution to melted lanolin and mix thoroughly. Use vacuum to remove all acetone.
2. Dissolve borax and potassium chloride in the purified water at 85°C to 90°C.
3. Melt beeswax, ceresin wax, and mineral oil and strain into ointment mixing tub at 95°C.
4. Add prepared base (step 1) to melted oil–wax mixture (step 4).
5. Add borax–potassium chloride solution (step 2) to oil–wax mixture with constant stirring.
6. Mix for 1 hour.
7. Dissolve Butesin picrate in warm (50°C) cellosolve and filter. Hold solution at 50°C for use in following step.
8. Adjust temperature of mass from step 5 to 50°C (this temperature is important).
9. Add Butesin picrate solution (at 50°C) to mass (at 50°C), with constant stirring.
10. Mix for several hours. Circulate cold water in jacket overnight.
11. Mill to smooth ointment and fill suitable containers.

Butesin Picrate Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
249.40	1	Water purified	249.40
8.85	2	Sodium borate powder	8.85
2.47	3	Potassium chloride	2.47
1.00	4	Methyl paraben	1.00
1.00	5	Propyl paraben	1.00
6.65	6	Lanolin anhydrous	6.65
114.60	7	Beeswax white	114.60
79.82	8	Wax ceresin white	79.82
405.30	9	Oil mineral light	405.30
119.90	10	Oil-neutral vegetable triglycerides mixture: Miglyol 812; Neobee M-5	119.90
10.00	11	Butyl aminobenzoate picrate (butesin picrate), 11% excess	11.10

Manufacturing Directions

1. Charge purified water into a suitable steam tank and begin heating to 85°C to 90°C.
2. Add borax and potassium chloride and mix until dissolved (at 85–90°C).
3. Add parabens to above solution and mix for at least 15 minutes (at 85–90°C) or until dissolution.
4. Melt lanolin, beeswax, ceresin wax, and mineral oil into a suitable equipment. Heat mixture to 90°C to 95°C. Mix until uniform.
5. Filter the melted waxes from step 4 through a 74-m aperture SS screen into a suitable mixing tank.
6. Heat waxes to 90°C to 95°C while mixing slowly.
7. Filter approximately 6.3 mL of borax–potassium–paraben solution (at 85–90°C) from step 2 slowly through a 74-m aperture SS screen into the wax–oil mixture from step 5. *Caution:* Slow the addition of water solution if the product shows tendency to bubble over the side of the equipment.
8. While mixing, slowly pass the remaining borax–potassium–paraben solution (at 85–90°C) from step 2 through a 74-m aperture SS screen into the wax–oil mixture from step 5. See caution above.
9. If necessary, adjust batch temperature to 85°C to 90°C and maintain temperature of batch at 85°C to 90°C while mixing for 60 minutes (range 60–75 minutes).
10. Add Neobee M-5 oil to a clean suitable SS container and start heating to 72°C (70–74°C). Add and dissolve the butyl aminobenzoate picrate while mixing and maintaining temperature at 72°C (70–74°C).
11. Reduce main batch temperature to 70°C (68–72°C) while continuing mixing slowly.
12. Filter Neobee M-5 oil–butyl picrate solution at 72°C (70–74°C) through a 74-m aperture SS screen into the main batch, mixing and maintaining temperature at 70°C (68–72°C).
13. Continue mixing and maintain main batch temperature at 70°C (68–72°C) for 15 to 30 minutes.
14. While mixing slowly cool the main batch to 40°C to 45°C. Maintain 40°C to 45°C temperature and continue mixing for at least 10 minutes. *Note:* Use 35°C (30–40°C) water for cooling. Do not force cool with cold water.
15. Set cooling water to 20°C (range 18–25°C) and continue cooling batch to 25°C to 30°C while mixing. When batch reaches 25°C to 30°C, stop mixing. The product is ready for milling. *Note:* The cooling water temperature must not drop below 18°C.
16. Pump product to roller mill and mill at high speed to a smooth uniform consistency.
17. Collect product in suitable bulk containers.
18. Fill in suitable containers. Theoretical tube fill weight: 30 g, minimum 28.35 g. If product does not flow freely, heat the water in hopper jacket to a maximum of 40°C.

Butoconazole Nitrate Vaginal Cream

The butoconazole nitrate vaginal cream, 2%, contains butoconazole nitrate, 2%, in a cream of edetate disodium, glyceryl monoisostearate, methyl paraben, mineral oil, polyglyceryl-3 oleate, propylene glycol, propyl paraben, colloidal silicon dioxide, sorbitol solution, purified water, and microcrystalline wax. Another formulation contains inactive ingredients cetyl alcohol, glyceryl stearate and PEG-100 stearate, methyl paraben and propyl paraben (preservatives), mineral oil, polysorbate 60, propylene glycol, sorbitan monostearate, stearyl alcohol, and water (purified).

Calamine and Diphenhydramine Hydrochloride Lotion

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
8.00	1	Calamine	80.00
1.00	2	Diphenhydramine hydrochloride	10.00
0.10	3	Camphor	1.00
2.40	4	Alcohol	24.00
70.00	5	Water purified	700.00
2.70	6	Carboxymethylcellulose	27.00
7.00	7	Zinc oxide	70.00
2.00	8	Water purified	20.00
0.06	9	Ferric oxide yellow	0.60
1.00	10	Zinc oxide	10.00
1.00	11	Glycerin	10.00
1.50	12	Glycerin	15.00
0.12	13	Ferric oxide red	1.20
QS	14	Perfume	QS
QS	15	Water purified	QS to 1 kg

Manufacturing Directions

1. Hydrate item 6 in item 5 and disperse item 7 in the suspension.
2. Mix the ferric oxides in items 10 and 11, homogenize, and add to step 1.
3. Dissolve item 2 in item 15 at 75°C, dissolve camphor and perfume in alcohol, and add to step 2.
4. Add item 12 and blend well.
5. QS to volume with item 15.

Calamine and Pramoxine Hydrochloride Lotion

Active ingredients are calamine, 8%, and pramoxine hydrochloride, 1%. Inactive ingredients include caladryl lotion, alcohol USP, camphor, diazolidinyl urea, fragrance, hydroxypropylmethylcellulose, methyl paraben, oil of lavender, oil of rosemary, polysorbate 80, propylene glycol, propyl paraben, purified water, and xanthan gum.

Calamine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
80.00	1	Polawax GP200	80.00
10.00	2	Polysorbate 60	10.00
50.00	3	Caprylic/Capric triglyceride	50.00
QS	4	Deionized water	QS to 1 kg
100.00	5	Witch hazel distillate	100.00
50.00	6	Glycerin	50.00
20.00	7	Zinc oxide	20.00
20.00	8	Calamine	20.00
QS	9	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 65°C to 70°C.
2. Add water phase to oil phase while stirring.
3. Add zinc oxide and calamine under high shear. Stir to cool.

Calamine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Microcrystalline cellulose (Avicel RC-591)	20.00
100.00	2	Glycerin	100.00
1.80	3	Methyl paraben	1.80
0.20	4	Propyl paraben	0.20
100.00	5	Glyceryl stearate and PEG-100 stearate	100.00
25.00	6	Cetyl alcohol	25.00
50.00	7	Zinc oxide	50.00
50.00	8	Calamine	50.00
653.00	9	Distilled water	653.00

Manufacturing Directions

1. Mix item 2 with item 9 and heat to 75°C.
2. Add items 3 and 4. Mix until dissolved using a shearing mixer.
3. Maintain temperature at 75°C and gradually add item 1. Continue mixing at 75°C for 15 minutes or until item 1 is homogenously dispersed. Mix well.
4. When temperature drops to 60°C to 65°C, gradually add items 7 and 8. Mix well until powders are homogenously dispersed.
5. Pass through homogenizer if necessary. Adjust theoretical weight with warm distilled water and continue mixing until the cream congeals.

Calamine Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
78.30	1	Calamine	78.30
78.30	2	Zinc oxide	78.30
19.60	3	Glycerin	19.60
230.80	4	Deionized water	230.80
558.00	5	Calcium hydroxide solution	558.00
34.40	6	Purified bentonite (Polargel NF)	34.40
0.60	7	Carboxymethylcellulose	0.60

Manufacturing Directions

1. Prepare a saturated item 5 solution using 3 g of item 5 in 1000 mL purified water, mixing vigorously for 1 hour.
2. Decant the clear supernatant liquid for use in the formula.
3. Add the balance of water. Add item 6 and item 7 to the above solution with rapid mixing for 15 minutes.
4. In a separate vessel, blend items 1 and 2.
5. Add item 3 and mix until uniform. Begin adding the aqueous solution with mixing until it is blended into a lotion.

Calcipotriene Cream

Calcipotriene cream, 0.005%, contains calcipotriene monohydrate, a synthetic vitamin D_3 derivative, for topical dermatological use. The cream contains calcipotriene monohydrate equivalent to 50 g/g anhydrous calcipotriene in a cream base of cetearyl alcohol, ceteth-20, diazolidinyl urea, dichlorobenzyl alcohol, dibasic sodium phosphate, edetate disodium, glycerin, mineral oil, petrolatum, and water.

Calcipotriene Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00 mg	1	Calcipotriene	10.00 mg
1.00	2	Almond oil	10.00
40.00	3	Mineral oil	400.00
20.00	4	Self-emulsifying beeswax	200.00
QS	5	Water purified	QS to 1 kg

Manufacturing Directions

1. Add and dissolve item 1 in item 2.
2. Add to this solution item 3 and item 4.
3. Heat the mixture to liquefy at 70°C.
4. In a separate vessel, heat item 5 to 80°C and add to step 3.
5. Mix well and then homogenize.
6. Cool and fill.

Calcium Carbonate Ointment

Formulation

Calcium carbonate, 250 mg; magnesium hydroxide, 200 mg; aluminum hydroxide, 225 mg; dibucaine (1% in petrolatum), 100 mg; anhydrous lanolin, 28.35 g; hydrophilic ointment, 28.35 g; petrolatum, 10 g; water, 5 mL.

1. Calcium carbonate, magnesium hydroxide, and the aluminum hydroxide are substantially insoluble in water. To assist in the dispersion of these components in the base carrier material, a paste was formed therefrom by adding a little water at a time to form a relatively homogeneous dispersion thereof.
2. Dibucaine (1%), which is provided in a petrolatum base, was then added with mixing to obtain a smooth homogeneous mixture.
3. Anhydrous lanolin and hydrophilic ointment were then mixed to provide a homogeneous composition, which was blended with the dispersion of calcium carbonate, magnesium hydroxide, aluminum hydroxide, and dibucaine.
4. The entire composition was mixed thoroughly to ensure a homogeneous dispersion of all of the ingredients.
5. Calcium carbonate and magnesium hydroxide provide a relatively rapid neutralization of the area under treatment. Aluminum hydroxide, however, provides a slower, longer-lasting neutralization in addition to a mild astringent effect. The 1% dibucaine hydrochloride dispersed in petrolatum is used for its analgesic or anesthetic effect and the amount may be varied to increase or decrease the anesthetic effect depending on the condition being treated. Anhydrous lanolin and hydrophilic ointment are utilized to provide a base for the composition, which facilitates its application and retention in the area of treatment.

Camphor, Eucalyptus Oil, and Menthol Ointment

Camphor, eucalyptus oil, and menthol ointment contains camphor, 5.2%, eucalyptus oil, 1.2%, and menthol, 2.8%. Inactive ingredients are carbomer 954, cedar leaf oil, cetyl alcohol, cetyl palmitate, cyclomethicone copolyol, dimethicone copolyol, dimethicone, ethylene diamine tetraacetate, glycerin, imidazolidinyl urea, isopropyl palmitate, methyl paraben, nutmeg oil, PEG-100 stearate, propyl paraben, purified water, sodium hydroxide, stearic acid, stearyl alcohol, thymol, titanium dioxide, turpentine oil.

Carbamazepine Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Carbamazepine	10.00
50.00	2	Propylene glycol	500.00
5.00	3	Cetostearyl alcohol	50.00
1.00	4	Sodium lauryl sulfate	10.00
43.00	5	Water purified	430.00

Manufacturing Directions

1. An oil-in-water emulsion is prepared to form an elegant cream. Carbamazepine in pure powder form is dissolved in propylene glycol (e.g., up to approximately 95%). Alternatives for the aqueous phase include alcohol, such as ethanol or isopropanol, with a thickener added, for example, carbomer 934 or 940.
2. The oil phase preferably includes mineral oil, petrolatum, cetyl alcohol, or stearyl alcohol. Emulsifiers such as polysorbate 80, sorbitan monostearate, or others known in the art may be used. Buffering agents, antioxidants, and chelating agents may be added to improve the characteristics of the formulation.

Carbamazepine Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Carbamazepine	50.00
93.00	2	Propylene glycol	930.00
2.00	3	Carbopol 934	20.00
QS	4	Sodium hydroxide (to neutralize item 3)	QS

Carbamazepine Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.00	1	Carbamazepine	30.00
5.00	2	Mineral oil	50.00
92.00	3	Petrolatum	920.00

Manufacturing Directions

1. Micronize carbamazepine to provide particles with a size distribution primarily below 10 m.
2. Add item 1 to mineral oil to form a finely dispersed suspension Homogenize.
3. Add and mix item 3 and homogenize again.

Carbamide Peroxide Chewing Gum

Formulation

Gum base, 26.25 g; calcium carbonate, 3.75 g; sorbitol, 28.05 g; mannitol, 7.50 g; maltitol, 21.62 g; glycerin, 1.00 g; flavorant, 3.15 g; gum arabic, 1.16 g; titanium dioxide, 0.17 g; wax candellia, 0.03 g; sodium stearate/sodium palmitate 50%, each 3.00 g; tripolyphosphate sweetener, 0.82 g; Imwitor 370, 1.00 g; carbamide peroxide, 3.00 g.

Manufacturing Directions

1. The gum base is heated to sufficiently soften the base without adversely affecting the physical and chemical makeup of the base.
2. The molten gum base and the filler are then added to a mixing kettle.
3. The sugar alcohols, glycerin, flavor, high-intensity sweetener, and stain-removing agent carbamide peroxide added last with mixing to obtain a homogenous mixture.
4. The mixture is then discharged from the mixing kettle and rolled and scored into a desired piece size by conventional techniques.

2-Carbamoylpyrazinamide Ointment

Manufacturing Directions

1. 2-Carbamoylpyrazinamide, also known as 2, 3-pyrazinedicarboxamide, 1g, is dissolved in 5 mL of water and 4 mL of acetone.
2. The solution is admixed with USP grade hydrophilic ointment (90 g) to a uniform consistency.
3. The ointment thus prepared is also stored in opaque jars at room temperature.

Castor Oil Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
68.80	1	Castor oil	688.00
10.00	2	Hydrogenated castor oil	100.00
8.70	3	Balsam Peru oil	87.00
0.018	4	Trypsin	0.180
QS	5	Safflower oil	QS to 1 kg

Manufacturing Directions

This is an enzymatic wound debrider.

1. The aluminum/magnesium hydroxide stearate is dispersed in the castor oil.
2. The hydrogenated castor oil is added while mixing with a high-shear mixer.
3. Mixing is continued until a semisolid forms.
4. The remaining ingredients are then blended to the semisolid until homogeneous mixing appears.

Cefaclor and Benzoyl Peroxide Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.00	1	Cefaclor	30.00
5.00	2	Benzoyl peroxide	50.00
92.00	3	Gel carrier or vehicle	920.00
QS	4	Alcohol 70%	QS
QS	5	Citric acid for pH adjustment	QS

Manufacturing Directions

1. To a first container, add the benzoyl peroxide and the gel carrier or vehicle ingredients (approximately 5 g of benzoyl peroxide and approximately 89 g of gel carrier or vehicle).
2. To a second container, add powdered cefaclor (approximately 3 g of cefaclor) and dissolve in item 4 and add to step 1.
3. Adjust pH using citric acid.

Cefaclor and Benzoyl Peroxide Lotion

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.00	1	Ethoxylated cetyl stearyl alcohol	70.00
0.75	2	Cetyl alcohol	7.50
5.00	3	Isostearyl neopentanoate	50.00
0.10	4	Butylated hydroxyanisole	1.00
0.25	5	Polyoxyl 40 stearate	2.50
66.80	6	Water purified	668.00
3.00	7	Propylene glycol	30.00
5.00	8	Benzoyl peroxide micronized	50.00
10.00	9	Acetone	100.00
0.10	10	Dioctyl sodium sulfosuccinate	1.00
2.00	11	Cefaclor	20.00

Cetrimide Antiseptic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Cetearyl alcohol and cetrimonium bromide	50.00
75.00	2	White petroleum jelly	75.00
60.00	3	Mineral oil (70 cS)	60.00
QS	4	Deionized water	QS to 1 kg
QS	5	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 60°C to 65°C.
2. Add the water phase to the oil phase while stirring.
3. Stir to cool.

Cetrimonium Bromide Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Cetearyl alcohol and cetrimonium bromide	50.00
75.00	2	White petroleum jelly	75.00
60.00	3	Mineral oil 70 cS	60.00
QS	4	Deionized water	QS to 1 kg
QS	5	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 60°C to 65°C.
2. Add water phase to oil phase while stirring. Stir to cool.

Chloramphenicol Opthalmic Ointment

Each gram of ophthalmic ointment, 1%, contains 10 mg chloramphenicol in a special base of liquid petrolatum and polyethylene. It contains no preservatives. Another formulation contains active ingredient chloramphenicol, l1%.

Chlorhexidine and Cetrimonium Bromide Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Polawax GP200	50.00
10.00	2	Lanolin	10.00
150.00	3	Mineral oil 70 cS	150.00
70.00	4	Cetearyl alcohol	70.00
30.00	5	Dimethicone	30.00
QS	6	Deionized water	QS to 1 kg
5.00	7	Cetrimonium bromide	5.00
0.50	8	Chlorhexidine gluconate	0.50
QS	9	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil (items 1–5) and water (items 6–9) phases to 65°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool. Fill.

Chlorhexidine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Chlorhexidine diacetate	20.00
300.00	2	1,2-Propylene glycol pharma	300.00
220.00	3	Lutrol F 127	220.00
460.00	4	Water	460.00

Manufacturing Directions

1. Dissolve chlorhexidine diacetate in propylene glycol at >70°C, stir well, and slowly add Lutrol F 127 and water.
2. Maintain the temperature until the air bubbles escape. A clear, colorless gel is obtained.

Chlorpromazine Suppositories

Each suppository contains chlorpromazine (25 or 100 mg), glycerin, glyceryl monopalmitate, glyceryl monostearate, (10 mg/g) and preservative chlorobutanol (chloral derivative), 0.5% (5 mg/g), and inactives white petrolatum, mineral oil, polyoxyl 40 stearate, polyethylene glycol 300 and petrolatum and lanolin alcohol, hydrogenated coconut oil fatty acids, and hydrogenated palm kernel oil fatty acids.

Ciclopirox Cream, Lotion, and Gel

Cream, 0.77%, and lotion, 0.77%, are for topical use. Each gram of cream contains 7.70 mg ciclopirox (as ciclopirox olamine) in a water-miscible vanishing cream base consisting of purified water USP, cetyl alcohol NF, mineral oil USP, octyldodecanol NF, stearyl alcohol NF, cocamide DEA, polysorbate 60 NF, myristyl alcohol NF, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF (1%) as preservative. Each gram of lotion contains 7.70 mg ciclopirox (as ciclopirox olamine) in a water-miscible lotion base consisting of purified water USP, cocamide DEA, octyldodecanol NF, mineral oil USP, stearyl alcohol.

Ciclopirox Nail Varnish

NF, cetyl alcohol NF, polysorbate 60 NF, myristyl alcohol NF, sorbitan monostearate NF, lactic acid USP, and benzyl alcohol NF (1%) as preservative. Cream and lotion contain a synthetic, broad-spectrum antifungal agent ciclopirox (as ciclopirox olamine). Each gram of gel contains 7.70 mg ciclopirox in a gel consisting of purified water USP, isopropyl alcohol USP, octyldodecanol NF, dimethicone copolyol 190, carbomer 980, sodium hydroxide NF, and docusate sodium USP.

Ciclopirox Nail Varnish

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
57.50	1	Isopropyl alcohol	575.00
33.00	2	Ethyl acetate	330.00
3.80	3	Polyvinyl butyral	38.00
3.10	4	Cellulose nitrate	31.00
0.60	5	Dibutyl phthalate	6.00
2.00	6	Ciclopirox	20.00

Manufacturing Directions

1. All items are mixed to a uniform mixture. Pigments may be added to color the varnish.
2. A thixotropic paste is prepared by slowly stirring 10 parts of an organically modified montmorillonite (e.g., bentone 27) into 80 parts toluene and subsequently adding 8 parts wetting agent (e.g., anti-terra-U) and 2 parts methanol. A clear varnish is also prepared by dissolving 22 parts butanol-moist collodion cotton (e.g., type E 510) and 8 parts toluene sulfonamide resin (e.g., santolite MS 80) in a mixture of 3 parts dibutyl phthalate, 20 parts ethyl acetate, 10 parts butyl acetate, 7 parts ethyl alcohol, and 30 parts toluene; 40 parts DC ROT No. 7 calcium varnish (e.g., color pigment C 19021) and 60 parts dibutyl phthalate are also processed to give a color paste with a particle size of less than 1 m.
3. To prepare the pigmented nail varnish, 12 parts thixotropic paste and 0.8 parts antisettling agent (e.g., MPA 2000 X) are dispersed in 83.7 parts clear varnish, during which operation a temperature of at least 38°C is to be reached; 1 part 1-hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2-pyridone is then dissolved in the thixotropic clear varnish and 2.5 parts color paste was stirred in. The finished nail varnish is filtered through a 70-m sieve.

Ciprofloxacin Hydrochloride Opthalmic Ointment

The ciprofloxacin hydrochloride ophthalmic ointment consists of synthetic, sterile, multiple-dose antimicrobials for topical ophthalmic use. Each gram of ophthalmic ointment contains active ingredients ciprofloxacin HCl, 3.33 mg equivalent to 3-mg base. Inactive ingredients are mineral oil and white petrolatum.

Clindamycin Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Clindamycin USE clindamycin phosphate	11.90
0.15	2	Methyl paraben	1.50
0.20	3	Carbopol 941	2.00
15.00	4	Propylene glycol 400	50.00
5.00	5	Polyethylene glycol	50.00
QS	6	Sodium hydroxide 10% solution for pH adjustment	QS
QS	7	Water purified	QS to 1 kg

Manufacturing Directions

The viscosity of this composition is approximately 1000 cP.

1. Weigh approximately 90% of the purified water into a stainless steel kettle.
2. Add the propylene glycol 400 and polyethylene glycol. Stir with a propeller mixer.
3. At room temperature, add methyl paraben to step 1 with continued stirring. Mix until dissolved.
4. While continuing to mix, add clindamycin phosphate to step 2. Mix until dissolved.
5. While continuing to mix, add Carbopol 941 slowly to step above. Avoiding clumping.
6. Mix vigorously at room temperature until a uniform and lump-free dispersion is achieved.
7. While mixing, add sufficient sodium hydroxide, 10% solution, to achieve a pH of 5.3 to 5.7. Mix until uniform.
8. Add the remaining water to make 100% and mix until uniform. Please note that a commercial preparation contains an additional component, allantoin.

Clindamycin Lotion and Gel

The topical lotion contains clindamycin phosphate USP at a concentration equivalent to 10 mg clindamycin per milliliter. The lotion contains cetostearyl alcohol (2.5%), glycerin, glyceryl stearate SE (with potassium monostearate), isostearyl alcohol (2.5%), methyl paraben (0.3%), sodium lauroyl sarcosinate, stearic acid, and purified water. Topical gel contains clindamycin phosphate USP at a concentration equivalent to 10 mg clindamycin per gram. The gel contains allantoin, carbomer 934P, methyl paraben, polyethylene glycol 400, propylene glycol, sodium hydroxide, and purified water.

Clindamycin Phosphate Suppository

Manufacturing Directions

1. 29 kg of Witepsol H 32® hard fat NF base was melted in a manufacturing kettle by heating to and maintained at 40°C.
2. Using a preheated filter, 26.614 kg of the molten base was transferred to a second manufacturing vessel equipped with a homogenizing mixer.
3. 1.386 kg of clindamycin phosphate equivalent to 1.12 kg of clindamycin free base was added to the kettle and mixed and homogenized to obtain a uniform dispersion.
4. The drug dispersion was transferred to a jacketed kettle and transported to the form/fill/seal suppository machine.
5. While maintaining mixing and a temperature of 40°C, the drug dispersion was formed into 2.5-g suppositories using the automated form/fill/seal equipment. The final batch size is 11,200 units.

Clindamycin Phosphate Topical Gel

The topical gel also contains benzoyl peroxide for topical use. Each gram of topical gel contains, as dispensed, 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, sodium hydroxide, dioctyl sodium sulfosuccinate, and purified water.

Clindamycin Phosphate Vaginal Cream

Vaginal cream, 2%, is a semisolid white cream that contains 2% clindamycin phosphate USP at a concentration equivalent to 20 g clindamycin per gram. The pH of the cream is between 3 and 6. The cream also contains benzyl alcohol, cetostearyl alcohol, cetyl palmitate, mineral oil, polysorbate 60, propylene glycol, purified water, sorbitan monostearate, and stearic acid. Each applicatorful of 5 g of vaginal cream contains approximately 100 mg of clindamycin phosphate.

Clindamycin Phosphate Vaginal Suppository

Each 2.5-g suppository contains clindamycin phosphate equivalent to 100 mg clindamycin in a base consisting of a mixture of glycerides of saturated fatty acids.

Clobetasol Propionate Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.050	1	Clobetasol propionate (5% excess)	0.525
44.500	2	Propylene glycol	445.000
0.050	3	Sodium citrate	0.500
0.050	4	Citric acid	0.500
5.000	5	Glyceryl monostearate A/S	50.000
4.000	6	Cetostearyl alcohol	40.000
0.600	7	White wax (beeswax bleached)	6.000
0.075	8	Chlorocresol	0.750
1.000	9	Glyceryl monostearate SE	10.000
7.000	10	Propylene glycol	70.000
2.675	11	Propylene glycol	26.750
35.000	12	Purified water	350.000

Manufacturing Directions

1. Aqueous phase
   a. Heat item 12 to 90°C in mixer. Bring down the temperature to 60°C. Dissolve all ingredients to a clear solution. Maintain temperature at 60°C.
   b. Filter through a polyester cloth. Check the weight. Clean the manufacturing vessel with item 12. Adjust the weight with item 12, if required. Record the quantity of extra item 12.
   c. Transfer again to manufacturing vessel. Maintain temperature at 60°C.
2. Oil phase
   a. Melt items 5 to 9 in melting vessel at 70°C to 75°C while stirring. Cool to 60°C. Maintain temperature at 60°C.
3. Dispersed phase
   a. Transfer the oil phase to aqueous phase in the manufacturing vessel through mesh by vacuum while stirring at manual mode 10 rpm, temperature 60°C. Mix at 10 rpm for 10 minutes at 60°C. Homogenize at high speed under vacuum 0.4 bar for 5 minutes at temperature 60°C. Cool down the temperature to 50°C while mixing at 10 rpm.
4. Drug phase
   a. Mix item 1 in item 10 in a water bath at 50°C
   b. Cool to 30°C while mixing at 10 rpm, auto mode under vacuum 0.4 bar, mixing time 20 minutes until a clear solution is obtained. A homogenizer may be used.
   c. Add to dispersed phase at step 3.2. Rinse with item 11 and add to dispersed phase at step 3a. Mix and homogenize under vacuum 0.4 bar for 5 minutes, high speed, 10 rpm, temperature 50°C.
   d. Unload the cream in stainless steel drum and fill.

Clobetasol Propionate Cream, Ointment, and Gel

Cream contains clobetasol propionate 0.5 mg/g in a cream base of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG-100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water. Ointment contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, sorbitan sesquioleate, and white petrolatum. Gel contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, carbomer 934P, sodium hydroxide, and purified water.

Clobetasol Propionate Ointment Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.050	1	Clobetasol propionate (5% excess)	0.525
94.460	2	Petrolatum (white soft paraffin)	944.600
0.500	3	Sorbitan sesquioleate (Arlacel 83)	5.000
4.000	4	Propylene glycol	40.000
0.500	5	Propylene glycol	5.000

Manufacturing Directions

1. Melt items 2 and 3 in a fat-melting vessel at temperature 75°C while mixing.
2. Start heating mixer vessel to 75°C. Transfer molten items 2 and 3 to mixer through stainless steel mesh under vacuum 0.4 to 0.6 bar. Start mixer at 10 rpm manual mode.
3. Cool down to 50°C.
4. In a water bath (temperature 60°C), dissolve item 1 in item 4 using homogenizer for 5 minutes. Add this to mixer with stirring.
5. Rinse with item 5 and add to mixer at temperature 50°C.
6. Start homogenizer under vacuum 0.4 to 0.6 bar while stirring at 10 rpm high speed for 10 minutes.
7. Cool down the temperature to 30°C, 10 rpm, auto mode, vacuum 0.4 to 0.6 bar.
8. Transfer the ointment to a stainless steel container. Fill.

Clotrimazole and Betamethasone Cream and Lotion

Each gram of cream contains 10 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in a hydrophilic cream consisting of purified water, mineral oil, white petrolatum, cetearyl alcohol 70/30, ceteareth-30, propylene glycol, sodium phosphate monobasic monohydrate, and phosphoric acid, with benzyl alcohol as preservative. Each gram of lotion contains 10 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in a hydrophilic base of purified water, mineral oil, white petrolatum, cetearyl alcohol 70/30, ceteareth-30, propylene glycol, sodium phosphate monobasic monohydrate, and phosphoric acid, with benzyl alcohol as a preservative. Lotion may also contain sodium hydroxide.

Clotrimazole Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.00	1	Cetyl stearyl alcohol	70.00
1.50	2	Cremophor A6	15.00
1.50	3	Cremophor A25	15.00
12.00	4	Liquid paraffin	120.00
0.20	5	Methyl and propyl parabens	2.00
68.80	6	Water purified	688.00
8.00	7	Propylene glycol	80.00
1.00	8	Clotrimazole	1.00

Manufacturing Directions

1. Heat the mixture of items 1 to 5 and item 6 separately to approximately 80°C.
2. Add item 6 to the obtained solution step 1 mixture of items 1 to 5 with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with step 2, and continue to stir during cooling to room temperature.

Clotrimazole Lotion

Each gram of lotion contains 10 mg clotrimazole USP dispersed in an emulsion vehicle composed of benzyl alcohol NF (1%), cetearyl alcohol 70/30 (3.7%), cetyl esters wax NF, octyldodecanol NF, polysorbate 60 NF, sodium phosphate dibasic anhydrous R, sodium phosphate monobasic monohydrate USP, sorbitan monostearate NF, and purified water USP.

Clotrimazole Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Clotrimazole	40.00
50.00	2	White petrolatum	50.00
20.00	3	Mineral oil	60.00
24.00	4	Cetearyl alcohol	72.00
22.50	5	Ceteth-20	22.50
10.00	6	Benzyl alcohol	10.00
100.00	7	Propylene glycol	100.00
0.35	8	Sodium phosphate dibasic anhydrous	0.35
5.00	9	Sodium phosphate monobasic monohydrate	5.00
QS	10	Water purified	QS to 1 kg

Manufacturing Directions

1. Heat 75% of the water to 70°C in a suitable vessel. Add the monobasic sodium phosphate monohydrate, anhydrous dibasic sodium phosphate, propylene glycol, and benzyl alcohol to the vessel with agitation, maintaining the temperature at 70°C.
2. In a separate vessel, melt the petrolatum and heat to 70°C.
3. Add the mineral oil and mix. Add the cetearyl alcohol and 95% of the ceteth-20. Mix and maintain at 70°C.
4. Combine the contents of the two vessels with agitation, maintaining at 70°C.
5. Cool to 38°C with agitation.
6. In a separate vessel, dissolve the remaining ceteth-20 in the remaining water at 65°C with agitation.
7. Cool to room temperature and slurry the clotrimazole with vigorous agitation until smooth uniform slurry is obtained.
8. Add the slurry to the previous emulsion mixture and agitate while cooling to room temperature.

Clotrimazole Vaginal Cream

The vaginal cream's active ingredient is clotrimazole 2% (100 mg per applicator). The inactive ingredients are benzyl alcohol, cetearyl alcohol, cetyl esters wax, octyldodecanol, polysorbate 60, purified water, and sorbitan monostearate.

Clotrimazole Vaginal Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Clotrimazole	40.00
150.00	2	White petrolatum	150.00
60.00	3	Mineral oil	60.00
72.00	4	Cetearyl alcohol	72.00
22.50	5	Ceteth-20	22.50
10.00	6	Benzyl alcohol	10.00
100.00	7	Propylene glycol	100.00
0.35	8	Sodium phosphate dibasic anhydrous	0.35
5.00	9	Sodium phosphate monobasic monohydrate	5.00
QS	10	Water purified	QS to 1 kg

Manufacturing Directions

1. Heat 75% of the water to 70°C in a suitable vessel. Add the monobasic sodium phosphate monohydrate, anhydrous dibasic sodium phosphate, propylene glycol, and benzyl alcohol to the vessel with agitation, maintaining the temperature at 70°C.
2. In a separate vessel, melt the petrolatum and heat to 70°C.
3. Add the mineral oil and mix. Add the cetearyl alcohol and 95% of the ceteth-20. Mix and maintain at 70°C.
4. Combine the contents of the two vessels with agitation, maintaining at 70°C.
5. Cool to 38°C with agitation.
6. In a separate vessel, dissolve the remaining ceteth-20 in the remaining water at 65°C with agitation.
7. Cool to room temperature and slurry the clotrimazole with vigorous agitation until smooth uniform slurry is obtained.
8. Add the slurry to the previous emulsion mixture and agitate while cooling to room temperature.

Clotrimazole Vaginal Cream Inserts

Each clotrimazole vaginal insert contains 100 mg clotrimazole with inactive ingredients benzyl alcohol, cetostearyl alcohol, cetyl esters wax, octyldodecanol, polysorbate 60, purified water, and sorbitan monostearate. The inserts are made of cornstarch, lactose, magnesium stearate, and povidone.

Clotrimazole and Clindamycin Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Clotrimazole	20.00
4.00	2	Clindamycin base USE clindamycin hydrochloride	4.54
20.00	3	Sorbitan monostearate	20.00
30.00	4	Tween 60	30.00
130.46	5	Paraffin viscous	130.46
100.00	6	Cetyl stearyl alcohol	100.00
10.00	7	Benzyl alcohol	10.00
670.00	8	Water purified	670.00

Manufacturing Directions

1. One application unit is equivalent to 5 g. This comprises 100 mg clotrimazole and 20 mg clindamycin.
2. Add and dissolve items 1 and 2 in items 7 and 8 in a blender.
3. Add and dissolve remaining items in a separate blender and heat to 40°C.
4. Add into step 2 with vigorous mixing to form a cream base.

Clotrimazole and Clindamycin Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
100.00	1	Clotrimazole	100.00
20.00	2	Clindamycin base USE clindamycin hydrochloride	22.70
77.30	3	Calcium lactate pentahydrate	77.30
250.00	4	Gelatin	250.00
250.00	5	Water purified	250.00
1250.00	6	Glycerol	1250.00

Manufacturing Directions

1. Dissolve items 1 and 2 in item 5.
2. Heat item 4 in item 6 in a separate vessel and add item 3.
3. Mix well and add to step 1.
4. Fill suppository 2 g each.

Clotrimazole and Clindamycin Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 suppositories (g)
100.00	1	Clotrimazole	100.00
20.00	2	Clindamycin base USE clindamycin hydrochloride	22.70
77.30	3	Calcium lactate pentahydrate	77.30
1000.00	4	Macrogol 400	1000.00
800.00	5	Macrogol 6000	800.00
200.00	6	Lactic acid	200.00

Manufacturing Directions

1. Add and mix all ingredients.
2. Heat to 70°C and mix well.
3. Cool to 40°C and fill.

Coal Tar and Allantoin Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Lanolin alcohol	40.00
50.00	2	White petroleum jelly	50.00
120.00	3	Paraffin wax 140F	120.00
300.00	4	Mineral oil 70 cS	300.00
20.00	5	Coal tar	20.00
2.50	6	Allantoin	2.50
QS	7	Deionized water	QS to 1 kg
QS	8	Preservative	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Slowly add water phase in increments to the oil phase.
3. Allow each addition time to be fully incorporated.
4. Stir to cool. Fill just above melting point. Further homogenization may improve stability before filling.

Coal Tar and Allantoin Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
160.00	1	Stearic acid	16.00
60.00	2	Oleyl alcohol	6.00
20.00	3	Lanolin	2.00
20.00	4	Coal tar	2.00
6.00	5	Triethanolamine 99%	0.60
2.50	6	Allantoin	0.25
QS	7	Deionized water	QS to 1 kg
QS	8	Preservative	QS

Manufacturing Directions

1. Heat water (items 7 and 8) and oil phases (all other items) separately to 80°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 40°C. May homogenize.

Coal Tar Cream

The active ingredient in coal tar cream is 5% coal tar solution USP, equivalent to 0.8% coal tar. Inactive ingredients include acetylated lanolin alcohol, alcohol (4.7%), carbomer-934P, ceteth-2, ceteth-16, cetyl acetate, cetyl alcohol, D&C; red no. 28, fragrance, glyceryl tribehenate, laneth-16, lanolin alcohol, laureth-23, methyl gluceth-20, methylchloroisothiazolinone, methylisothiazolinone, mineral oil, octyldodecanol, oleth-16, petrolatum, potassium hydroxide, purified water, steareth-16, stearyl alcohol, titanium dioxide.

Collagenase Ointment

Collagenase ointment is a sterile enzymatic debriding ointment that contains 250 collagenase units per gram of white petrolatum USP. The enzyme collagenase is derived from the fermentation by *Clostridium histolyticum*. It possesses the unique ability to digest collagen in necrotic tissue exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blend to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17 (alpha)-dihydroequilin, together with smaller amounts of 17 (alpha)-estradiol, equilenin and 17 (alpha)-dihydroequilin as salts of their sulfate esters.

Conjugated Estrogens Vaginal Cream

Each gram of conjugated estrogens vaginal cream contains 0.625 mg conjugated estrogens USP in a nonliquefying base containing cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil. It is applied intravaginally.

Cyanocobalamin Gel

Cyanocobalamin gel for intranasal administration is a solution of cyanocobalamin USP (vitamin B_{12}) for administration as a metered gel to the nasal mucosa. Each bottle of gel contains 2.3 mL of a 500 µg/0.1 mL gel solution of cyanocobalamin with methylcellulose, sodium citrate, citric acid, glycerin, and benzalkonium chloride in purified water. The gel solution has a pH between 4.5 and 5.5. After initial priming, each metered gel delivers an average of 500 µg of cyanocobalamin and the 2.3 mL of gel contained in the bottle will deliver eight doses.

DBcAMP Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.00	1	DBcAMP	35.10
68.49	2	Polyethylene glycol 400	684.90
28.00	3	Polyethylene glycol 4000	280.00

Manufacturing Directions

1. In a glass-lined melting vessel, charge 90% of item 3 and item 2 and melt at 70°C to 80°C.
2. Transfer to a homogenizer and cool to 50°C.
3. Prepare a dispersion of item 1 in balance of item 3 in a separate vessel and add to step 2.
4. Rinse the container with item 2 and add rinsings.
5. Mix at 50°C. Cool and fill.

Desonide Cream, Ointment, and Lotion

Cream 0.05%, ointment 0.05%, and lotion 0.05% contain desonide. Each gram of cream contains 0.5 mg of desonide in a base of purified water, emulsifying wax, propylene glycol, stearic acid, isopropyl palmitate, synthetic beeswax, polysorbate 60, potassium sorbate, sorbic acid, propyl gallate, citric acid, and sodium hydroxide. Each gram of ointment contains 0.5 mg of desonide in a base of mineral oil and polyethylene. Each gram of lotion contains 0.5 mg of desonide in a base of sodium lauryl sulfate, light mineral oil, cetyl alcohol, stearyl alcohol, propylene glycol, methyl paraben, propyl paraben, sorbitan monostearate, glyceryl stearate SE, edetate sodium, and purified water and may contain citric acid or sodium hydroxide for pH adjustment.

Desoximetasone Emollient Cream, Gel, and Ointment

Desoximetasone emollient cream 0.25%, desoximetasone gel 0.05%, desoximetasone ointment 0.25%, and desoximetasone emollient cream 0.05% contain the active synthetic corticosteroid desoximetasone. Each gram of emollient cream 0.25% contains 2.5 mg desoximetasone in an emollient cream consisting of white petrolatum USP, purified water USP, isopropyl myristate NF, lanolin alcohols NF, mineral oil USP, cetostearyl alcohol NF, aluminum stearate, and magnesium stearate. Each gram of gel 0.05% contains 0.5 mg desoximetasone in a gel consisting of purified water USP, SD alcohol 40 (20% w/w), isopropyl myristate NF, carbomer 940, trolamine NF, edetate disodium USP, and docusate sodium USP. Each gram of ointment 0.25% contains 2.5 mg of desoximetasone in a base consisting of white petrolatum USP, propylene glycol USP, sorbitan sesquioleate, beeswax, fatty alcohol citrate, fatty acid pentaerythritol ester, aluminum stearate, citric acid, and butylated hydroxyanisole. Each gram of emollient cream 0.05% contains 0.5 mg desoximetasone in an emollient cream consisting of white petrolatum USP, purified water USP, isopropyl myristate NF, lanolin alcohols NF, mineral oil USP, cetostearyl alcohol NF, aluminum stearate, edetate disodium USP, lactic acid USP, and magnesium stearate.

Dexamethasone Sodium Phosphate Ointment

Sterile ophthalmic ointment dexamethasone sodium phosphate is a topical steroid ointment containing dexamethasone sodium phosphate equivalent to 0.5 mg (0.05%) dexamethasone phosphate in each gram. Inactive ingredients are white petrolatum and mineral oil.

Dexpanthenol Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Dexpanthenol	50.00
10.00	2	White soft paraffin	100.00
5.00	3	Cetostearyl alcohol	50.00
2.00	4	Lanolin anhydrous	20.00
10.00	5	Liquid paraffin	100.00
11.00	6	Propylene glycol	110.00
0.15	7	Methyl paraben	1.50
0.05	8	Propyl paraben	0.50
1.00	9	Tween 60	10.00
1.00	10	Simethicone M30	10.00
0.072	11	Lavender oil	0.072
0.028	12	Rose oil perfume	0.28
64.70	13	Water purified	647.00

Manufacturing Directions

1. Charge items 2 to 5 in a melting vessel and heat to 70°C.
2. Charge portion of item 13 (at 70°C), item 1, and item 9 and heat to 70°C and mix for 10 minutes.
3. In a separate container add and dissolve items 7 and 8 in item 6 at 70°C and add to step 2.
4. Add step 1 into step 3. Mix under vacuum and at 70°C for 20 minutes.
5. Cool to 35°C to 40°C and add item 10. Mix again under vacuum.
6. Add items 11 and 12 and mix (without vacuum) and cool down to 25°C.
7. Transfer to storage vessel and fill.

Dexpanthenol Gel Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Dexpanthenol (BASF)	50.00
100.00	2	Liquid paraffin	100.00
150.00	3	Lutrol E 400	150.00
180.00	4	Lutrol F 127	180.00
QS	5	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve dexpanthenol and Lutrol E 400 in water, add liquid paraffin, and stir, heating to 60°C to 70°C.
2. Slowly add Lutrol F 127 and stir until it is dissolved.
3. Cool to room temperature, stirring continuously until the air bubbles disappear.

Diclofenac Diethylamine Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Diclofenac diethylamine, 10% excess	11.00
1.20	2	Carbopol 934P	12.00
23.00	3	Isopropyl alcohol	230.00
5.00	4	Propylene glycol	50.00
2.50	5	Liquid paraffin	25.00
2.50	6	Cetiol LC	25.00
2.00	7	Cetomacrogol 1000	20.00
0.90	8	Diethylamine	9.00
0.028	9	Perfume	0.28
0.072	10	Perfume	0.72
68.00	11	Water purified	680.00

Manufacturing Directions

1. Charge 90% of item 11 in a mixing vessel, heat to 80°C, stir to produce vortex, and add item 2 to disperse after passing through 1-mm sieve. Mix for 5 minutes, avoiding foam.
2. Transfer step 1 into Becomix and maintain temperature at 70°C.
3. Charge items 5 to 7 in a separate vessel, melt at 70°C, transfer to step 2.
4. Mix at speed II under vacuum of 0.4 to 0.6 bar for 5 minutes at 10 rpm.
5. Cool down to 30°C.
6. Add and dissolve item 8 in item 11 separately and then add to step 5 and mix for 10 minutes.
7. Dissolve item 1 in items 3 and 4 separately and transfer to step 6 through a cloth filter. Mix for 20 minutes.
8. Homogenize at speed I for 5 minutes under vacuum at 10 rpm.
9. Add perfumes and mix for 5 minutes.
10. Fill in appropriate containers.

Diclofenac Diethylammonium Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
QS	1	Water purified	465.53
500.00	2	Alcohol 190 proof	500.00
2.00	3	Menthol	2.00
10.00	4	Diclofenac USE diclofenac diethylammonium	12.47
8.00	5	Carbopol 940	8.00
12.00	6	Trolamine	12.00

Manufacturing Directions

1. Place water purified and alcohol in a 316 grade stainless steel mixing tank.
2. Add menthol crystals to the alcohol–water mixture. Mix for 5 minutes or until completely dissolved.
3. Add diclofenac diethylammonium to the mixing tank. Mix for 10 minutes or until completely dissolved.
4. While mixing, sprinkle in carbomer. Continue mixing slowly at intervals for 1 to 2 hours or until carbomer swells completely in the hydroalcoholic solution.
5. Add trolamine and mix for 10 minutes or until gel forms.
6. Fill into suitable lined collapsible aluminum tube.

Diclofenac Sodium Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
12.50	1	Diclofenac sodium micronized, 1% excess	12.62
530.32	2	Suppocire CM	530.32
353.00	3	Suppocire AS2X	353.00
2.90	4	Crill 3	2.90
1.15	5	Aerosil 200	1.15

Manufacturing Directions

1. Load items 2 to 4 in the fat-melting vessel and heat to 55°C.
2. Transfer to a mixing vessel through filter sieves. Set the temperature to 50°C.
3. Add item 1 and 5 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 0.6 bar vacuum.
4. Cool down to 50°C to 55°C.
5. Transfer into storage vessel and set temperature at 50°C.
6. Fill 900 mg in a suppository mold.

Diclofenac Sodium Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
25.00	1	Diclofenac sodium micronized, 1% excess	25.25
522.70	2	Suppocire CM	522.70
348.00	3	Suppocire AS2X	348.00
2.90	4	Crill 3	2.90
1.15	5	Aerosil 200	1.15

Manufacturing Directions

1. Load items 2 to 4 in the fat-melting vessel and heat to 55°C.
2. Transfer to a Becomix vessel through filter sieves. Set the temperature to 50°C.
3. Add items 1 and 5 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 0.6 bar vacuum.
4. Cool down to 50°C to 55°C.
5. Transfer into storage vessel and set temperature at 50°C.
6. Fill 900 mg in a suppository mold.

Diclofenac Sodium Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
50.00	1	Diclofenac sodium micronized, 1% excess	50.50
1045.40	2	Suppocire CM	1045.40
696.00	3	Suppocire AS2X	696.00
5.80	4	Crill 3	5.80
2.30	5	Aerosil 200	2.30

Manufacturing Directions

1. Load items 2 to 4 in the fat-melting vessel and heat to 55°C.
2. Transfer to a mixing vessel through filter sieves. Set the temperature to 50°C.
3. Add items 1 and 5 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 0.6 bar vacuum.
4. Cool down to 50°C to 55°C.
5. Transfer into storage vessel and set temperature at 50°C.
6. Fill 1800 mg in a suppository mold.

Diclofenac Sodium Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
100.00	1	Diclofenac sodium micronized, 1% excess	101.00
1015.00	2	Suppocire CM	1015.00
675.00	3	Suppocire AS2X	675.00
6.00	4	Crill 3	6.00
2.50	5	Aerosil 200	2.50

Manufacturing Directions

1. Load items 2 to 4 in the fat-melting vessel and heat to 55°C.
2. Transfer to a mixing vessel through filter sieves. Set the temperature to 50°C.
3. Add items 1 and 5 to step 2. Mix at 10 rpm and homogenize at speed I for 15 minutes at 0.6 bar vacuum.
4. Cool down to 50°C to 55°C.
5. Transfer into storage vessel and set temperature at 50°C.
6. Fill 1800 mg in a suppository mold.

Dichlorobenzyl Alcohol Tooth Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	2,4-dichlorobenzyl alcohol (Myacid)	10.00
2.00	2	Sodium carboxymethylcellulose[a]	20.00
QS	3	Water purified	QS to 1 kg

[a]To obtain thicker gel, the quantity can be increased to 4.00.

Manufacturing Directions

1. Disperse item 2 in item 3 heated to 70°C.
2. Cool and add item and mix well.
3. Cool to 40°C and fill.

Dienestrol Vaginal Cream

The active ingredient in dienestrol vaginal cream is dienestrol 0.01%. It is compounded in a cream base suitable for intravaginal use only. The cream base is composed of glyceryl monostearate, peanut oil, glycerin, benzoic acid, glutamic acid, butylated hydroxyanisole, citric acid, sodium hydroxide, and water. The pH is approximately 4.3. Available in 2.75-oz (78-g) tubes with or without a measured dose applicator.

Diethylamine Salicylate Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
22.50	1	White soft paraffin	225.00
12.50	2	Glyceryl monostearate	125.00
5.00	3	Criss-3 (span 60)	50.00
0.10	4	Vitamin E oily	1.00
45.24	5	Water purified	452.40
0.71	6	Sodium phosphate monobasic	7.10
0.13	7	Sodium hydroxide pellets	1.30
0.10	8	Sodium disulfide pure	1.00
0.166	9	Sodium ethylene diamine tetraacetate	1.66
12.00	10	Diethylamine salicylate	120.00
0.12	11	Menthol	1.20
0.50	12	Chlorbutol	5.00
0.30	13	Lavender oil	3.00
0.40	14	Glycerin	4.00
0.20	15	Methyl paraben	2.00
0.12	16	Propyl paraben	1.20

Manufacturing Directions

1. Charge, one by one, items 1 to 4 to a melting vessel at 79°C to 75°C. Hold molten fat at 70°C with continuous stirring at low speed.
2. In a separate vessel, heat 90% of item 5 to 90°C, add, and dissolve parabens by stirring. Cool to 65°C to 70°C.
3. In a separate vessel, take the balance of item 5 and sodium hydroxide pellets and sodium phosphate monobasic and dissolve.
4. Transfer step 3 to the paraben solution and mix for 5 to 10 minutes at slow speed and at 65°C to 70°C.
5. Cool to 25°C. Check and adjust pH 6.8 to 7.2. Add items 8 to 10 and mix to dissolve at 50°C.
6. Filter solution through polyester cloth and keep aside at 50°C.
7. Set Becomix temperature to 70°C, 10 rpm, and vacuum 0.6 bar.
8. Transfer molten fat at 70°C after passing through a stainless steel filter to step above while mixing.
9. Homogenize at slow speed for 10 minutes. Temperature 65°C to 70°C.
10. Set Becomix to 50°C and transfer diethylamine salicylate solution to the cream at 50°C while stirring.
11. Continue mixing and add chlorbutol, menthol, lavender oil, and glycerin at 40°C. (Menthol and chlorbutol first dissolve in a separate container.)
12. Homogenize for 10 minutes under vacuum.
13. Cool to 25°C, transfer to storage vessel, fill.

Diflorasone Diacetate Cream and Ointment

Each gram of cream contains 0.5 mg diflorasone diacetate in a cream base. Each gram of cream contains 0.5 mg diflorasone diacetate in a hydrophilic vanishing cream base of propylene glycol, stearyl alcohol, cetyl alcohol, sorbitan monostearate, polysorbate 60, mineral oil, and purified water. Each gram of ointment contains 0.5 mg diflorasone diacetate in an ointment base. Emollient ointment contains diflorasone diacetate in an emollient occlusive base consisting of polyoxypropylene 15-stearyl ether, stearic acid, lanolin alcohol, and white petrolatum.

Dimethicone and Zinc Oxide Ointment

Active ingredients in dimethicone and zinc oxide ointment are dimethicone, 1%, and zinc oxide, 10%. Inactive ingredients include aloe extract, benzyl alcohol, cod liver oil (contains vitamins A and D), fragrance, glyceryl oleate, light mineral oil, ozokerite, paraffin, propylene glycol, sorbitol, synthetic beeswax, and water.

Dinoprostone Cervical Gel

Dinoprostone is the naturally occurring form of prostaglandin E_2 (PGE_2). The active constituent of gel is dinoprostone 0.5 mg/3 g (2.5 mL gel); other constituents are

colloidal silicon dioxide NF (240 mg/3 g) and triacetin USP (2760 mg/3 g).

Dinoprostone Vaginal Insert and Suppositories

Dinoprostone vaginal insert is a thin, flat polymeric slab that is rectangular with rounded corners, contained within the pouch of a knitted polyester retrieval system, an integral part of which is a long tape. Each slab is buff colored and semitransparent and contains 10 mg of dinoprostone. The hydrogel insert is contained within the pouch of an off-white knitted polyester retrieval system designed to aid retrieval at the end of the dosing interval. The finished product is a controlled-release formulation that has been found to release dinoprostone in vivo at a rate of approximately 0.3 mg/h. Each insert contains 10 mg of dinoprostone in 241 mg of a cross-linked polyethylene oxide/urethane polymer that is a semiopaque, beige-colored, flat rectangular slab measuring 29 mm × 9.5 mm × 0.8 mm in thickness. The insert and its retrieval system, made of polyester yarn, are nontoxic and when placed in a moist environment they absorb water, swell, and release dinoprostone. The insert contains 10 mg dinoprostone. The product is wound and enclosed in an aluminum sleeve that is contained in an aluminum–polyethylene pack. Vaginal suppositories are available. Each suppository contains 20 mg of dinoprostone in a mixture of glycerides of fatty acids.

Diphenhydramine Hydrochloride and Zinc Acetate Ointment

Diphenhydramine hydrochloride and zinc acetate ointment contain diphenhydramine hydrochloride 1% and zinc acetate 0.1%. The extra-strength formulation is diphenhydramine hydrochloride 2% and zinc acetate 0.1%. Inactive ingredients include cetyl alcohol, diazolidinyl urea, methyl paraben, polyethylene glycol monostearate 1000, propylene glycol, propyl paraben, and purified water.

Docosanol Lotion

Docosanol, 10%, is a cold sore/fever blister treatment. Inactive ingredients include benzyl alcohol, light mineral oil, propylene glycol, purified water, sucrose distearate, and sucrose stearate.

Econazole Nitrate and Benzoyl Peroxide Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
200.00	1	PEG-6 and PEG-32 and glyceryl stearate (Tefose 63)	200.00
30.00	2	Mineral oil	30.00
30.00	3	Apricot kernel oil PEG-6 esters (Labrafil M 1944)	30.00
0.50	4	Sorbic acid	0.50
0.50	5	Sodium methyl paraben	0.50
724.00	6	Deionized water	724.00
5.00	7	Benzoyl peroxide	5.00
10.00	8	Econazole nitrate	10.00

Manufacturing Directions

1. Mix and heat items 1 to 6 together and bring temperature to 75°C.
2. Allow to cool while stirring. Add items 7 and 8 at 30°C and mix well until uniform.

Econazole Nitrate and Benzoyl Peroxide Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PEG-6 stearate and cetech-20 and steareth-20 (Tefose 2000)	50.00
30.00	2	Mineral oil	30.00
20.00	3	Cetyl alcohol	20.00
0.70	4	Sodium methyl paraben	0.70
0.30	5	Sorbic acid	0.30
884.00	6	Deionized water	884.00
5.00	7	Benzoyl peroxide	5.00
10.00	8	Econazole nitrate	10.00

Manufacturing Directions

1. Mix and heat items 1 to 3 together and bring temperature to 75°C.
2. Allow to cool while stirring. Mix items 4 to 6 and add to above while stirring.
3. Cool with stirring. Add items 7 and 8 at 30°C while stirring.

Eflornithine Hydrochloride Cream

The cream contains 13.9% (139 mg/g) anhydrous eflornithine hydrochloride as eflornithine hydrochloride monohydrate (150 mg/g). Other ingredients include ceteareth-20, cetearyl alcohol, dimethicone, glyceryl stearate, methyl paraben, mineral oil, PEG-100 stearate, phenoxyethanol, propyl paraben, stearyl alcohol, and water.

Enzyme Extract Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
50.00	1	Fumed silica	500.00
18.50	2	Enzyme extract[a]	185.00
0.20	3	Methyl paraben	2.00
0.50	4	Propyl paraben	5.00
0.03	5	Bromopal	0.30
0.02	6	Fragrance	0.20
QS	7	Water purified	QS to 1 kg

[a]This is a generic formula to incorporate proteins, tissue components, or enzyme extracts (in powder form).

Erythromycin and Neomycin Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Erythromycin-base fine powder 10% excess (900 μg/mg potency)[a]	12.22
3.50	2	Neomycin-base USE neomycin sulfate (200 Waksman units/mg potency)[a]	5.00
100.00	3	Mineral oil light	100.00
QS	4	Petrolatum white	QS to 1 kg

[a]Adjust petrolatum weight to compensate for change in weight of erythromycin base and neomycin.

Manufacturing Directions

1. Heat petrolatum and mineral oil in a steam kettle to 115°C and maintain temperature for at least 3 hours.
2. Strain into mixing tank and cool to 40°C to 45°C.
3. Reserve portion of petrolatum–oil mixture for step 5.
4. Mix erythromycin and neomycin with 95 g of base and stir until thoroughly dispersed.
5. Run through a 200-mesh (74-m aperture) screen on Homoloid mill directly into main portion of petrolatum–oil mixture.
6. Rinse mill with reserved petrolatum–oil mixture from step 3.
7. Mix 2 hours before cooling. Cool slowly to avoid condensation.
8. Fill into suitable approved containers.

Erythromycin Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Erythromycin base	10.00
20.00	2	Lutrol E 400	200.00
20.00	3	Propylene glycol	200.00
20.00	4	Lutrol F 127	200.00
39.00	5	Water purified	390.00

Manufacturing Directions

1. Heat solution of items 1 to 3 to approximately 70°C.
2. Dissolve item 4, mix with item 5, and cool when the air bubbles escape.

Erythromycin Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Erythromycin powder 850 μg/mg, 10% excess[a]	12.94
100.00	2	Mineral oil light	100.00
QS	3	Petrolatum white	QS to 1 kg

[a]Adjust petrolatum weight to compensate for change in weight of erythromycin base calculated from its potency.

Manufacturing Directions

1. Heat petrolatum and mineral oil in a steam kettle to 115°C and maintain temperature for at least 3 hours.
2. Strain into mixing tank and cool to 40°C to 45°C.
3. Reserve portion of petrolatum–oil mixture for step 6.
4. Mix erythromycin with 78 g of base and stir until thoroughly dispersed.
5. Run through a 200-mesh (74-m aperture) screen on Homoloid mill directly into main portion of petrolatum–oil mixture.
6. Rinse mill with reserved petrolatum–oil mixture from step 3.
7. Mix 2 hours before cooling. Cool slowly to avoid condensation.
8. Fill into suitable approved containers.

Erythromycin Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
23.75	1	Isostearyl benzoate	237.50
23.85	2	Bis (2-ethylhexyl) maleate	238.50
10.00	3	Cyclomethicone	100.00
5.00	4	Stearyl alcohol	50.00
10.00	5	Starch	100.00
10.00	6	Microcrystalline cellulose	100.00
15.00	7	Ethylene/vinyl copolymer	150.00
0.10	8	Propyl paraben	1.00
0.10	9	Butylparaben	1.00
0.10	10	Fragrance	1.00
2.00	11	Erythromycin	21.00

Manufacturing Directions

1. Blend items 1 to 4 in a high-shear mixer.
2. Add balance ingredients and mix well.
3. Fill.

Estradiol and Norethindrone Acetate Transdermal System

The estradiol/norethindrone acetate transdermal system is an adhesive-based matrix transdermal patch designed to release both estradiol and norethindrone acetate, a progestational agent, continuously on application to intact skin. The patch is an alcohol-free, adhesive-based matrix transdermal drug delivery system comprising three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are a backing, an adhesive layer, and a protective liner. The adhesive matrix containing estradiol and norethindrone acetate is applied to a adhesive backing of polyester/ethylene vinyl acetate laminate film on one side and is protected on the other side by a transparent fluoropolymer-coated release liner. The transparent release liner must be removed before the system can be used. Each system is enclosed in a heat-sealed pouch. The active components of the system are estradiol USP and norethindrone acetate USP. The remaining components of the system are pharmacologically inactive: a silicone and acrylic-based multipolymeric adhesive, povidone USP, oleic acid NF, and dipropylene glycol.

Estradiol Transdermal System

Estradiol transdermal system is designed to deliver 17 (beta)-estradiol continuously and consistently for more than a 3-or 4-day interval on application to intact skin. Three strengths of Alora systems are available, having nominal in vivo delivery of 0.05, 0.075, and 0.1 mg estradiol per day through skin of average permeability (interindividual variation in skin permeability is approximately 20%). Alora systems have contact surface areas of 18, 27, and 36 cm^2 and contain 1.5, 2.3, and 3.0 mg of estradiol USP respectively. The composition of the systems per unit active surface area is identical. Estradiol USP 17 (beta)-estradiol is a white crystalline powder that is chemically described as estra-1,3,5(10)-triene-3,17(beta)-diol, has an empirical formula of $C_{18}H_{24}O_2$, and has a molecular weight of 272.37. The delivery system consists of three layers. Proceeding from the polyethylene backing film, the adhesive matrix drug reservoir that is in contact with the skin consists of estradiol USP and sorbitan monooleate dissolved in an acrylic adhesive matrix. The polyester overlapped release liner protects the adhesive matrix during storage and is removed before application of the system to the skin.

Manufacturing Directions

Estradiol-containing matrices are prepared by mixing acrylic adhesive (National Starch Durotac 1194), sorbitan monooleate (Arlacel 80), and estradiol at a ratio of 80-X/(20/X), where X is the proportion (wt%) of estradiol. The matrix contains 25 estradiol (8% estradiol was saturated) for optimal permeation.

Estradiol Vaginal Cream

Each gram of estradiol vaginal cream USP 0.01% contains 0.1 mg estradiol in a nonliquefying base containing purified water, propylene glycol, stearyl alcohol, white ceresin wax, mono- and diglycerides, hydroxypropylmethylcellulose, 2208 (4000 CPS; CPS refers to centipoise, a designation of viscosity) sodium lauryl sulfate, methyl paraben, edetate disodium, and tertiary butylhydroquinone. Tubes contain 1.5 oz (42.5 g), with a calibrated plastic applicator for delivery of 1, 2, 3, or 4 g. Each gram of estradiol vaginal cream USP 0.01% contains 0.1 mg estradiol in a nonliquefying base containing purified water, propylene glycol, stearyl alcohol, white ceresin wax, mono- and diglycerides, hydroxypropylmethylcellulose, 2208 (4000 CPS) sodium lauryl sulfate, methyl paraben, edetate disodium, and tertiary butylhydroquinone.

Estradiol Vaginal Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/10 kg (g)
7.00	1	Stearyl alcohol	700.00
4.00	2	Glyceryl monostearate (nonemulsifying)	400.00
7.00	3	Ceresin wax 160	700.00
0.02	4	Monotertiary butylhydroquinone	2.00
0.01	5	17-Beta-estradiol	1.00
10.00	6	Propylene glycol	1000.00
0.15	7	Methyl paraben	15.00
0.30	8	Hydroxypropylmethylcellulose 4000 CPS	30.00
0.05	9	Disodium edetate	5.00
0.30	10	Sodium lauryl sulfate	30.00
71.77	11	Water purified	7177.00

Manufacturing Directions

1. A nonaqueous phase premix is prepared by thoroughly mixing stearyl alcohol (700 g), glyceryl monostearate, non–self-emulsifying (400 g), white ceresin wax 160 (160 signifies the approximate melting point in degrees Fahrenheit, 700 g), and monotertiary butylhydroquinone (2 g) while heating to 75°C.
2. Mixing with heating is continued until all solids are dissolved and then 17-beta-estradiol (1 g dry weight) is added. The mixing is then continued until this phase is in the form of a clear solution, at which point it is held at 75°C for later use.
3. Propylene glycol (1000 g) and methyl paraben (15 g) are mixed together until all solids are dissolved. Hydroxypropylmethylcellulose 4000 CPS (CPS refers to centipoise, a designation of viscosity, 30 g) is added to and dispersed in the propylene glycol solution and this resulting mixture is then added to an aqueous solution of disodium edetate (5 g) and sodium lauryl sulfate (30 g) in 7117 g purified water. This mixture is heated and held at 75°C while being stirred to facilitate the formation of an oil-in-water emulsion.
4. The hot nonaqueous phase premix, prepared earlier, is then added to this hot aqueous phase slowly while mixing with an appropriate mixer. If the equipment used permits moisture loss, water may be added during this step to compensate for the loss.
5. The resultant hot emulsion is allowed to cool to 60°C, at which point it is thoroughly homogenized using a recirculating homogenizer, homomixer, or other suitable equipment to provide a particle size reduction to a range of 5 to 20 m for most particles.
6. The fluid emulsion, still at 60°C, is passed through a No. 100 to No. 200 stainless steel or nylon screen into a vessel equipped for slow stirring.
7. The emulsion is then cooled under vacuum while using slow sweep stirring until the temperature reaches 25°C.

Ethylenediamine Tetracetate Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Liquid paraffin	50.00
10.00	2	White paraffin	100.00
30.00	3	Glycerin	300.00
8.00	4	Cetostearyl alcohol	80.00
0.30	5	Methyl paraben	3.00
3.60	6	Polyoxyethylene sorbitan monostearate	36.00
2.00	7	Glyceryl monostearate	20.00
QS	8	Water purified	QS to 1 kg
1.00	9	Ethylene diamine tetraacetate	10.00

Manufacturing Directions

1. Water phase:
   a. Charge purified water, polysorbate 60, and glycerin with agitation in a melting kettle.
   b. Heat the contents to 61°C to 65°C.
   c. Add methyl paraben and mix the composition to dissolve while maintaining temperature.
2. Oil phase:
   a. In a suitable vessel, charge liquid paraffin, cetostearyl alcohol, white petrolatum, glycerol monostearate, and white beeswax and mix continuously while heating to 71°C to 75°C.
3. Mixing of phases:
   a. The mixture of step 2 is transferred to the step 1 kettle, with the water phase maintained at less than 300 mbar vacuum.
   b. Add EDTA and dissolve.
   c. With mixing and keeping the temperature at 61°C to 65°C, draw the oil phase into the water phase.
   d. Mix for 15 minutes with agitation and vacuum at 300 mbar and 61°C to 65°C.
   e. While mixing and under vacuum, allow the mixture to cool gradually to room temperature.
4. Fill in appropriate container.

Eucalyptus and Mint Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
160.00	1	Menthol	160.00
40.00	2	Eucalyptus	40.00
800.00	3	Anhydrous lanolin, USP	800.00

Manufacturing Directions

1. Mix lanolin until melted (approximately at 50°C), add remaining ingredients, and mix for 1 hour.
2. Fill hot.

Foot Freshener Cream

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
30.00	1	Alcohol and ceteareth-20 (Cosmowax® EM5483)	30.00
30.00	2	Isopropyl myristate (Crodamol® IPM)	30.00
5.00	3	Cetyl esters (Crodamol® SS)	5.00
20.00	4	Oleyl alcohol	20.00
5.00	5	Propylene glycol	5.00
5.00	6	Carbopol 980	5.00
QS	7	Deionized water	QS to 1 L
300.00	8	Ethanol (DEB100)	300.00
2.00	9	Triclosan (Irgasan® DP300)	2.00
0.50	10	Menthol	0.50
4.00	11	Triethanolamine 99 (to give pH 6 to 7)	~4.00

Manufacturing Directions

1. Preblend ethanol, Irgasan, and menthol and warm to 50°C.
2. Heat water and oil phases separately to 70°C.
3. Add the water phase to the oil phase while stirring.
4. Stir to cool, adding the preblend at 60°C. Adjust pH.

Foot Mousse

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
300.00	1	Ethanol (DEB100)	300.00
1.00	2	Menthol	1.00
QS	3	Deionized water	QS
20.00	4	Undecyleneamide DEA and diethanolamine	20.00
5.00	5	Cetrimonium bromide	5.00
10.00	6	PEG-75 and water	10.00
QS	7	Perfume, preservative, color	QS

Manufacturing Directions

1. Dissolve menthol in ethanol.
2. Add remaining ingredients.
3. Pack into mechanical mousse applicator.

Fluocinonide Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.05	1	Fluocinonide	0.50
7.00	2	Crotamiton	70.00
10.00	3	Liquid paraffin	100.00
1.00	4	Polyoxyethylene lauryl ether	10.00
20.00	5	Carboxyvinyl polymer	200.00
1.20	6	Disodium edetate	12.00
4.68	7	Triethanolamine	46.80
QS	8	Water purified	QS to 1 kg

Manufacturing Directions

1. Fluocinonide (50 mg) is dissolved in crotamiton (7 g) with warming and thereto is added liquid paraffin (10 g), propylene glycol (10 g), polyoxyethylene lauryl ether (1 g), a 4% aqueous solution of carboxyvinyl polymer (20 g), purified water (47 g), and a 1% aqueous solution of disodium edetate (1.2 g).
2. The mixture is heated until approximately 70°C to 80°C and then a 2% aqueous solution of triethanolamine (4.68 g) is added to it with stirring and further purified water is then added until the amount becomes 100 g.
3. The mixture is stirred well and then cooled to give a creamy preparation having a viscosity of 65,000 centipoises and a pH of 4.47.

Fluocinonide Cream, Ointment, and Gel

The cream contains fluocinonide 0.5 mg/g in a specially formulated cream base consisting of citric acid, 1,2,6-hexanetriol, polyethylene glycol 8000, propylene glycol, and stearyl alcohol. This white cream vehicle is greaseless, nonstaining, anhydrous, and completely water miscible. The base provides emollient and hydrophilic properties. In this formulation, the active ingredient is totally in solution. The cream contains fluocinonide 0.5 mg/g in a water-washable aqueous emollient base of cetyl alcohol, citric acid, mineral oil, polysorbate 60, propylene glycol, sorbitan monostearate, stearyl alcohol, and water (purified). Another strength of cream contains fluocinolone acetonide 0.25 mg/g in a water-washable aqueous base of butylated hydroxytoluene, cetyl alcohol, citric acid, edetate disodium, methyl paraben and propyl paraben (preservatives), mineral oil, polyoxyl 20 cetostearyl ether, propylene glycol, simethicone, stearyl alcohol, water (purified), and white wax. The gel contains fluocinonide 0.5 mg/g in a specially formulated gel base consisting of carbomer 940, edetate disodium, propyl gallate, propylene glycol, sodium hydroxide or hydrochloric acid (to adjust the pH), and water (purified). This clear, colorless thixotropic vehicle is greaseless, nonstaining, and completely water miscible. In this formulation, the active ingredient is totally in solution. The ointment contains fluocinonide 0.5 mg/g in a specially formulated ointment base consisting of glyceryl monostearate, white petrolatum, propylene carbonate, propylene glycol, and white wax. It provides the occlusive and emollient effects desirable in an ointment. In this formulation, the active ingredient is totally in solution. In another formulation, the ointment contains fluocinolone acetonide 0.25 mg/g in a white petroleum USP vehicle.

Fluorometholone Opthalmic Ointment

The fluorometholone ophthalmic ointment, 0.1%, contains active ingredients fluorometholone 0.1% and the preservative phenylmercuric acetate (0.0008%). Inactives are white petrolatum, mineral oil, and petrolatum and lanolin alcohol.

Fluorouracil Cream

Fluorouracil cream, 0.5%, contains fluorouracil for topical dermatologic use. Cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge®) composed of methyl methacrylate/glycol dimethacrylate crosspolymer and dimethicone. The cream formulation contains the following other inactive ingredients: carbomer 940, dimethicone, glycerin, methyl gluceth-20, methyl methacrylate/glycol dimethacrylate crosspolymer, methyl paraben, octyl hydroxy stearate, polyethylene glycol 400, polysorbate 80, propylene glycol, propyl paraben, purified water, sorbitan monooleate, stearic acid, and trolamine.

The 5% cream contains fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60, and parabens (methyl and propyl).

The 1% topical cream contains inactive ingredients benzyl alcohol, emulsifying wax, mineral oil, isopropyl myristate, sodium hydroxide, and purified water.

Flurandrenolide Lotion

Each milliliter of lotion contains 0.5 mg (1.145 mol) (0.05%) flurandrenolide in an oil-in-water emulsion base composed of glycerin, cetyl alcohol, stearic acid, glyceryl monostearate, mineral oil, polyoxyl 40 stearate, menthol, benzyl alcohol, and purified water.

Flurandrenolide Topical Film

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.10	1	Flurandrenolide	1.00
9.00	2	Polyvinyl alcohol	90.00
11.00	3	Polyvinylpyrrolidone (PVP)	110.00
9.00	4	Glycerin	90.00
10.00	5	Alcohol	100.00
2.00	6	Benzyl alcohol	20.00
3.00	7	Propylene glycol	30.00
0.02	8	Disodium edetate	0.20
0.10	9	Citric acid	1.00
QS	10	Water purified	QS to 1 kg

Manufacturing Directions

1. Add and dissolve flurandrenolide in propylene glycol, glycerin, and ethyl alcohol.
2. Dissolve all the remaining items (including some water) separately and add to step 1.
3. Mix thoroughly and make up the volume.
4. The formulation is spread manually or with an applicator. On evaporation of the solvents including water more than a period of 20 to 30 minutes, a continuous medicated adherent film of approximately 0.05- to 0.15-mm (average 0.08 mm) thickness is formed. After 18 to 24 hours or another desirable time span, the film is removed with water or is peeled.

Fluticasone Ointment

Fluticasone ointment, 0.005%, contains fluticasone propionate. Each gram of ointment contains fluticasone propionate 0.05 mg in a base of propylene glycol, sorbitan sesquioleate, microcrystalline wax, and liquid paraffin.

Fluticasone Propionate Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.05	1	Fluticasone propionate	0.05
87.00	2	Propylene glycol	87.00
21.00	3	Sorbitan sesquioleate	21.00
200.00	4	Liquid paraffin	200.00
180.00	5	Microcrystalline wax	180.00
481.95	6	White soft paraffin	481.95
30.00	7	Hard paraffin	30.00

Manufacturing Directions

1. Melt microcrystalline wax, hard paraffin, and sorbitan sesquioleate in a fat-melting vessel at 70°C to 75°C while mixing. Add liquid paraffin and mix well.
2. Transfer the mixture in step 1 to the manufacturing vessel through stainless steel filter. Mix and homogenize for 10 minutes under vacuum at 0.5 bar. Cool the mixture to 40°C to 45°C.
3. Disperse fluticasone propionate in propylene glycol, mix, and homogenize at a temperature of 40°C to 45°C.
4. Transfer the drug mixture from step 3 into the manufacturing vessel from step 2 while mixing. Mix and homogenize for 10 minutes under vacuum at 0.5 bar to obtain uniform homogeneous ointment to contain label amount of fluticasone propionate per gram.
5. Cool to a temperature of 25°C to 30°C with continuous stirring.
6. Fill the ointment into the tube.

Fluticasone Propionate Cream

Each gram of cream contains fluticasone propionate 0.5 mg in a base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as preservative.

Fluticasone Propionate Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.50	1	Fluticasone propionate	0.50
40.00	2	Propylene glycol	40.00
100.00	3	Liquid paraffin	100.00
70.70	4	Cetostearyl alcohol	70.70
40.00	5	Cetomacrogol 1000	40.00
50.00	6	Isopropyl myristate	50.00
4.80	7	Dibasic sodium phosphate	4.80
1.50	8	Citric acid monohydrate	1.50
2.50	9	Imidurea	2.50
690.00	10	Purified water	690.00

Manufacturing Directions

1. Melt cetostearyl alcohol and cetomacrogol 1000 in a fat-melting vessel at 70°C. Add liquid paraffin and isopropyl myristate and mix well. Hold the temperature between 60°C and 70°C.
2. Add purified water to the manufacturing vessel and heat to 70°C to 80°C.
3. Dissolve dibasic sodium phosphate, citric acid, and imidurea in purified water. Hold the temperature between 60°C and 70°C.
4. Transfer the fat phase of step 1 through a stainless steel filter to the manufacturing vessel while stirring at a temperature of 60°C to 70°C. Mix and homogenize for 10 minutes under vacuum at 0.5 bar. Cool the mixture to 40°C to 45°C.
5. Disperse fluticasone propionate in propylene glycol at a temperature of 40°C to 45°C.
6. Transfer the drug mixture of step 5 into step 4 to the manufacturing vessel while mixing. Mix and homogenize for 10 minutes under vacuum at 0.5 bar to obtain a uniform homogenous cream to contain labeled amount of drug per gram.
7. Cool the cream to a temperature of 25°C to 30°C with continuous stirring.
8. Transfer into stainless steel storage container with product identification label.

Folic Acid Suppository

Manufacturing Directions

1. Folic acid, 0.2%; allantoin, 0.5%; protein hydrolysate, 0.8%; lactose, 8.0%; lactic acid, 1.0%; magnesium sulfate, 1.0%; sodium chloride, 2.0%; polyoxyethylene glycol 1540, 66.5%; polyoxyethylene sorbitan monolaurate, 15.0%; polyoxyethylene sorbitan monostearate, 5%.
2. After mixing folic acid with an adequate amount of lactose, the remainder of lactose, magnesium sulfate, and sodium chloride are successively added while stirring.
3. Protein hydrolysate is immediately mixed to the powder mixture before preparing the suspension.
4. Simultaneously, after melting the polyoxyethylene glycol and polyoxyethylene glycol fatty acid esters and reaching a temperature of 60°C, lactic acid is mixed to the melt, the powder mixture is suspended in the liquid suppository base containing lactic acid, then the mass is homogenized in a colloid mill.
5. At a temperature of approximately 55°C, the mass is filled into cooled moulds.
6. The percentages given above refer to suppositories weighing 3.5 to 4.0 g each.

6-Formylaminonicotinamide Ointment and Lotion

Manufacturing Directions

1. Ointment: 6-Formylaminonicotinamide 0.1 g is dissolved in 5 mL of water and 4.9 mL of ethanol. The solution is admixed with hydrophilic ointment USP grade (90 g) to a uniform consistency. This ointment also may be stored in opaque jars at room temperature.
2. Lotion: 6-Aminonicotinamide 0.2 g is dissolved in 7.2 mL of 0.2 N HCl and the solution is admixed with 92.6 g of a water-in-oil lotion prepared from mineral oil, cottonseed oil, isopropyl palmitate, and water with a surfactant such as sorbitan sesquioleate. The ingredients in said water-in-oil lotion are present for example in 10:10:5:70:5 parts by weight respectively. The lotion thus prepared is stored in a plastic squeeze bottle.
3. Fill the cream into the tube.

Foscarnet Cream

Bill of Materials			
Scale (mg/100 g)	Item	Material Name	Qty/kg (mg)
3.00	1	Trisodium phosphonoformate hexahydrate (foscarnet sodium)	30.00
4.40	2	Polyoxyethylene fatty acid ester	44.00
2.00	3	Cetyl alcohol	20.00
2.00	4	Stearic acid	20.00
2.00	5	Liquid paraffin	20.00
2.00	6	Propylene glycol	20.00
1.50	7	Glycerin	15.00
0.07	8	Methyl paraben	0.70
0.03	9	Propyl paraben	0.30
QS	10	Water purified	QS to 1 kg

Gamma Benzene Hexachloride Lotion

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Gamma benzene hexachloride, 1% excess	10.10
2.00	2	Emulsifying wax	20.00
5.00	3	Xylene	50.00
0.50	4	Cetomacrogol 1000	5.00
10.00	5	Liquid paraffin	100.00
72.00	6	Water purified	720.00

Manufacturing Directions

1. Heat items 2, 4, and 5 to 95°C and pass through a stainless steel sieve.
2. Heat water to 65°C and add to step 1.
3. Dissolve item 1 in item 3 with stirring and add to step 2 at 35°C.
4. Adjust pH to 7.5 to 8.0 if necessary and mix for 2 hours.

Gentamicin Sulfate Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.100	1	Gentamycin USE gentamycin sulfate[a]	1.82
15.000	2	Petrolatum (white soft paraffin)	150.00
1.800	3	Polyoxyl 20 cetostearyl ether (cetomacrogol 1000)	18.00
7.200	4	Cetostearyl alcohol	72.00
0.100	5	Chlorocresol	1.00
6.000	6	Mineral oil (liquid paraffin)	60.00
0.300	7	Monobasic sodium phosphate	3.00
69.417	8	Purified water	694.17

[a]Considering the potency of the gentamicin sulfate is 700 μg/mg (anhydrous basis) with 15.0% water content. Quantity of gentamicin sulfate per batch will vary according to the actual potency. Required quantity should be calculated as below. Quantity of gentamicin sulfate required per batch is based on potency.

Manufacturing Directions

1. Fat phase: Load items 2 to 6 in a fat-melting vessel. Heat to 70°C. Stir to melt. Hold the molten fat at 70°C while stirring at low speed in the fat-melting vessel.
2. Aqueous phase: Set the mixer at temperature 70°C. Heat 608 g of item 8 to 70°C in mixer.
3. Cream preparation: Transfer the molten fat at 70°C from step 1 into mixer through a stainless steel filter while mixing at speed 10 rpm, vacuum 0.6 bar.
4. When the transfer is over, start the homogenizer at low speed. Homogenize for 10 minutes with recirculation. Temperature, 65°C to 70°C.
5. Stop the homogenizer, set the mixer at temperature 50°C, speed 10 rpm (manual mode), and vacuum 0.6 bar. Cool the cream to 50°C.
6. Drug phase: Dissolve items 7 and 1 in 86.17 g of item 8 in a stainless steel container while mixing with a stirrer. Hold the temperature at 50°C.
7. Transfer the drug solution from step 4 to the cream phase in mixer at 50°C while mixing.
8. Start the homogenizer at high speed, mixer speed 10 rpm. Mix and homogenize for 10 minutes under vacuum 0.6 bar.
9. While homogenization is in progress, set the temperature at 25°C so that the cream temperature shall not increase. Continue mixing at 10 rpm under vacuum 0.6 bar until the temperature reaches 25°C.
10. When the cream is cooled to 25°C, unload the cream in stainless steel container and fill.

Gentamicin Sulfate Ointment

Each gram of ointment contains gentamicin sulfate USP (equivalent to 3 mg gentamicin) in a base of white petrolatum, with methyl paraben (0.5 mg) and propyl paraben (0.1 mg) as preservatives. Active ingredients are gentamicin sulfate equivalent to 0.3% gentamicin base, prednisolone acetate 0.6%, and the preservative (chloral derivative) 0.5%. Inactives are white petrolatum, mineral oil, petrolatum and lanolin alcohol, and purified water.

Gentamicin Sulfate Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.100	1	Gentamycin sulfate (100% excess)	2.00
0.400	2	Cetostearyl alcohol	4.00
0.100	3	Polyoxyl 20 cetostearyl ether (cetomacrogol 1000)	1.00
1.500	4	Mineral oil (liquid paraffin)	15.00
1.000	5	Mineral oil (liquid paraffin)	10.00
96.600	6	Petrolatum (white soft paraffin)	966.00
0.200	7	Purified water	2.00

Manufacturing Directions

1. Melt items 2, 3, and 5 at 70°C in a small container using water bath. Put the melt under homogenizer (keep homogenizer warm to avoid losses caused by sticking).
2. Dissolve item 1 in item 7 and heat to 50°C in water bath. Add step 2 to step 1 and homogenize for 2 to 3 minutes using homogenizer. Maintain the temperature around 50°C.
3. Load item 6 in a fat-melting vessel while stirring at 70°C. Transfer the molten mass through filter to mixer and cool it down to 50°C. Note that the mixer should be warmed before the transfer starts to avoid sticking on the wall. Add step 2 to the step 3 while stirring. Maintain temperature at around 50°C.
4. Rinse the homogenizer with warm item 4 and transfer the rinsing to the mixer.
5. Mix and homogenize for 10 minutes at low speed, mixer speed 10 to 12 rpm, vacuum 0.4 to 0.6 bar, and temperature 50°C.
6. Cool the ointment to 30°C to 35°C with stirring under vacuum 0.4 to 0.6 bar.
7. Transfer the ointment to stainless steel drum and fill.

Glycerin Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
1800.00	1	Glycerin (glycerol)	1800.00
178.00	2	Sodium stearate	178.00
99.00	3	Purified water	99.00

Manufacturing Directions

1. The suppository mass is manufactured at a temperature of 120°C. Care must be taken to see that molten suppository mass does not accidentally spill on the person. The inside of the vessel should not be touched with a bare hand, as it is at a temperature of 120°C. Sodium stearate powder is light and fluffy. Avoid inhaling the dust.
2. Load item 1 into the mixer and heat to 120°C ± 2°C while stirring at low speed.
3. Load item 2 to the mixer containing item 1. Mix until complete solubilization occurs. Cool to 105°C ± 2°C.
4. Add item 3 slowly to the mixer containing mass while stirring. Mix for 20 minutes. Immediately transfer the hot mass to the heated storage vessel or heated vessel of suppository filling machine.
5. Check the temperature; it should be 105°C ± 2°C. Fill weight: 2077 mg/suppository.

Glycerin Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
900.00	1	Glycerin (glycerol) excess 0.06%	900.50
89.00	2	Sodium stearate	89.00
49.50	3	Purified water	49.50

Manufacturing Directions

See above; fill weight: 1039 mg/suppository.

Glycolic Acid Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.00	1	Polyoxyethylene (40) stearate	30.00
2.00	2	Polyoxyethylene (200 sorbitan monooleate	20.00
8.00	3	Glycerol monostearate	80.00
2.00	4	Lanolin	20.00
1.00	5	Mineral oil	10.00
49.00	6	Water purified	490.00
5.00	7	Propylene glycol	50.00
3.00	8	Sorbitol	30.00
1.00	9	Carbopol 940	10.00
10.00	10	Glycolic acid	100.00
16.00	11	Triisopropanolamine	160.00

Manufacturing Directions

1. Heat items 1 to 5 in a stainless steel container to 80°C.
2. In a separate container, heat items 6 to 9 to 80°C.
3. Add step 2 to step 1 with agitation.
4. After the mixture is congealed, add glycolic acid and triisopropanolamine.
5. Continue agitation until a uniform consistency is obtained. The pH of the cream is 3.8.

Gramicidin, Neomycin, Nystatin, and Triamcinolone Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.025	1	Gramicidin	0.025
10.00	2	Liquid paraffin	10.00
0.48	3	Neomycin sulfate	0.48
2.72	4	Nystatin micronized	2.72
1.00	5	Syncrowax	1.00
0.105	6	Triamcinolone acetonide micronized	0.105
86.72	7	White soft paraffin	86.72

Manufacturing Directions

1. Charge items 5 and 7 in a melting vessel and heat to 70°C to melt. Transfer to Becomix through stainless steel filters and cool to 40°C while mixing.
2. Add items 2 (half quantity) and 4 to a separate vessel and disperse using a spatula. Homogenize twice with fine-gap setting to make smooth dispersion and add this dispersion to step 1.
3. Charge items 1, 2 (balance quantity), 3, and 6 in a separate stainless steel vessel and homogenize to a smooth dispersion until here are no lumps.
4. Transfer to step 2.
5. Rinse homogenizer with liquid paraffin and add rinsings.
6. Homogenize the final mixture under a vacuum of 0.4 to 0.6 at 10 rpm and set temperature to 28°C to 30°C.
7. Mix till ointment is smooth, transfer to a stainless steel vessel, and fill.

Halobetasol Propionate Cream and Ointment

Each gram of cream contains 0.5 mg/g of halobetasol propionate in a cream base of cetyl alcohol, glycerin, isopropyl isostearate, isopropyl palmitate, steareth-21, diazolidinyl urea, methylchloroisothiazolinone, methylisothiazolinone, and water. Each gram of ointment contains 0.5 mg/g of halobetasol propionate in a base of aluminum stearate, beeswax, pentaerythritol cocoate, petrolatum, propylene glycol, sorbitan sesquioleate, and stearyl citrate.

Hemorrhoid Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Lanolin alcohol (Ivarlan 3310)	20.00
448.00	2	Petrolatum	448.00
450.00	3	Petrolatum amber	450.00
30.00	4	Shark liver oil	30.00
10.00	5	Live yeast cell derivative (Biodyne's TRF)	10.00
10.00	6	Deionized water	10.00
20.90	7	Lanolin	20.90
1.00	8	Thyme oil	1.00
0.10	9	Phenyl mercuric nitrate	0.10

Manufacturing Directions

1. Mix and heat items 1 to 4 to 70°C, cool to 50°C, and hold.
2. Separately combine items 5 to 7 and heat to 40°C and mix until homogenous dispersion is achieved; with rapid mixing add this mixture to previous mixture. Mix again and cool to 40°C. Add items 8 and 9.
3. Continue mixing while cooling to 35°C.

Heparin Gel Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.186	1	Heparin sodium	1.86
15.00	2	Lutrol E 400	150.00
10.00	3	Liquid paraffin	100.00
23.00	4	Lutrol F 127	230.00
QS	5	Water purified	QS to 1 kg

Manufacturing Directions

1. Dissolve heparin sodium in water. Add Lutrol E 400 and liquid paraffin.
2. Stir and cool to 6°C. Add Lutrol F 127 slowly and stir until it is dissolved.
3. Heat to room temperature when the air bubbles escape.

Hexachlorophene Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
45.80	1	Olive oil, low acidity	45.80
45.00	2	Diglycol stearate S	45.00
5.00	3	Cetyl alcohol	5.00
5.00	4	Lanolin anhydrous	5.00
5.00	5	Petrolatum white	5.00
1.03	6	Polysorbate 40	1.03
5.00	7	Hexachlorophene	5.00
0.10	8	Simethicone	0.10
50.00	9	Glycerin	50.00
1.00	10	Methyl paraben	1.00
10.00	11	Sodium borate	10.00
1.30	12	Sodium lauryl sulfate	1.30
1.76	13	Perfume	1.76
2.00	14	Menthol	2.00
14.02	15	Alcohol	14.02
QS	16	Water purified	779.0 mL

Manufacturing Directions

1. Strain olive oil through voile cloth or equivalent into a suitable stainless steel-jacketed tank.
2. Add diglycol stearate. While heating oil–stearate mix, add cetyl alcohol, lanolin, petrolatum, and polysorbate 40 with mixing. Mix until all are dissolved and temperature of mixture reaches 65°C to 70°C.
3. Add and dissolve hexachlorophene in the oil mix, then add and disperse the simethicone.
4. Start heating another jacketed tank as 820 mL of purified water is added to it. Add and dissolve glycerin, methyl paraben, and borax as purified water is added and as solution is heated to 65°C to 70°C.
5. Stop mixer, add sodium lauryl sulfate, and continue mixing under vacuum.
6. Reserve 4 mL of solution from step 5 in a separate container to rinse equipment in step 2.
7. While both solutions are at 65°C to 70°C, form the primary emulsion by pumping the aqueous solution from step 5 into the oil mixture from step 3 and QS to 200 mL with vigorous agitation.
8. Homogenize primary emulsion through a Troy Mill, or similar device, into the balance of aqueous solution, mixing continually under vacuum. Rinse pump, mill, tank, and lines with reserved solution from step 6. Note that the primary emulsion should be strained through voile cloth or equivalent before being run through the Troy mill.
9. Cool emulsion to 40°C to 50°C with agitation under vacuum.
10. Dissolve perfume and menthol in the alcohol and add.
11. Using purified water, QS to 1 liter.
12. Continue mixing and cooling to 25°C.
13. Fill.

Hydrocortisone Acetate and Pramoxine Hydrochloride Cream and Lotion

The cream contains hydrocortisone acetate, 1% or 2.5%, and pramoxine HCl, 1%, in a hydrophilic cream base containing stearic acid, cetyl alcohol, Aquaphor, isopropyl palmitate, polyoxyl-40 stearate, propylene glycol, potassium sorbate, sorbic acid, triethanolamine lauryl sulfate, and water. The lotion 2.5% contains hydrocortisone acetate, 2.5%, and pramoxine hydrochloride, 1%, in a hydrophilic lotion base containing stearic acid, cetyl alcohol, forlan-L, glycerin, triethanolamine, polyoxyl 40 stearate, diisopropyl adipate, povidone, silicone, potassium sorbate, sorbic acid, and purified water. Topical corticosteroids are anti-inflammatory and antipruritic agents. Other formulations include cream, which contains hydrocortisone acetate, 1% or 2.5%, and pramoxine HCl, 1%, in a hydrophilic base containing stearic acid, cetyl alcohol, Aquaphor, isopropyl palmitate, polyoxyl 40 stearate, propylene glycol, potassium sorbate, sorbic acid, triethanolamine lauryl sulfate, and water; lotion, which contains hydrocortisone acetate, 1% or 2.5%, and pramoxine HCl, 1%, in a base containing forlan-L, cetyl alcohol, stearic acid, diisopropyl adipate, polyoxyl 40 stearate, silicone, triethanolamine, glycerin, polyvinylpyrrolidone, potassium sorbate, sorbic acid, and water; ointment, which contains hydrocortisone acetate, 1% or 2.5%; and pramoxine HC1, 1%, in an emollient ointment base containing sorbitan sesquioleate, water, Aquaphor, and white petrolatum.

Hydrocortisone Acetate Suppositories

Each Anusol-HC 25-mg suppository contains 25 mg hydrocortisone acetate in a hydrogenated cocoglyceride base.

Hydrocortisone and Nitrofurazone Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.20	1	Nitrofurazone, 4% excess	2.08
1.00	2	Hydrocortisone acetate, 5% excess	10.50
7.20	3	Cetostearyl alcohol	72.00
1.80	4	Cetomacrogol 1000	18.00
6.00	5	Liquid paraffin	60.00
15.00	6	White soft paraffin	150.00
1.00	7	Propylene glycol	10.00
0.020	8	Chlorocresol	0.20
69.00	9	Water purified	690.00

Manufacturing Directions

1. Charge items 3, 4, 5 (90%), and 6 in a melting vessel after passing through stainless steel sieve and heat to melt.
2. In a separate vessel, heat two-thirds of item 9 to 50°C and dissolve item 8 in it. Add to step 1.
3. Add and mix item 1 with item 5 (balance) and add to step 2.
4. Dissolve item 2 in balance of item 9 and a portion of item 5 in a separate vessel and homogenize. Add to step 3 with stirring. Mix for several hours.
5. Fill.

Hydrocortisone Butyrate Cream and Ointment

The cream, ointment, and topical solution contain the topical corticosteroid hydrocortisone butyrate. Each gram of cream contains 1 mg hydrocortisone butyrate in a hydrophilic base consisting of cetostearyl alcohol, ceteth-20, mineral oil, white petrolatum, citric acid, sodium citrate, propyl paraben and butylparaben (preservatives), and purified water. Each gram of ointment contains 1 mg of hydrocortisone butyrate in a base consisting of mineral oil and polyethylene.

Hydrocortisone Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.000	1	Hydrocortisone, micronized (3% excess)	10.30
6.000	2	Propylene glycol	60.00
0.100	3	Chlorocresol	1.00
5.000	4	Mineral oil (liquid paraffin)	50.00
2.000	5	Polyoxyl 20 cetostearyl ether (cetomacrogol 1000)	20.00
8.000	6	Cetostearyl alcohol	80.00
18.000	7	Petrolatum (white soft paraffin)	180.00
0.290	8	Monobasic sodium phosphate	2.90
0.035	9	Propyl paraben	0.35
0.100	10	Methyl paraben	1.00
59.600	11	Purified water	596.00

Manufacturing Directions

1. Load 10 g of item 5 and items 4, 6, and 7 in a fat-melting vessel.
2. Heat to 70°C to 75°C while stirring. Cool down the temperature to 65°C.
3. Maintain temperature at 65°C to 70°C.
4. Heat item 11 to 90°C in mixer. Dissolve items 9 and 10 to a clear solution by stirring. Cool down the temperature to 65°C. Maintain temperature at 65°C to 70°C.
5. Add 10 g of item 5 and items 3 and 8 to the parabens solution to dissolve.
6. Mix for 10 to 15 minutes. Maintain temperature at 65°C to 70°C.
7. Transfer the oil phase to the aqueous phase in a mixer vessel through mesh by vacuum while stirring at manual mode, 10 rpm, temperature 60°C.
8. Homogenize at high speed, temperature 60°C, vacuum 0.4 bar, 10 minutes.
9. Cool down temperature to 45°C. Mix item 1 in 48 g of item 2 in a separate container at 45°C using homogenizer to make slurry.
10. Add to the dispersed phase while mixing at 10 rpm and temperature 45°C.
11. Rinse the container with 12 g of item 2 and add to the dispersed phase.
12. Mix and homogenize under vacuum 0.4 bar for 10 minutes, low speed, 10 rpm, temperature 45°C.
13. Cool down the temperature to 30°C while mixing at 10 rpm, auto mode, under vacuum 0.4 bar.

Hydrocortisone Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
70.00	1	Cetyl stearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
120.00	4	Liquid paraffin	120.00
2.00	5	Paraben	2.00
688.00	6	Water	688.00
80.00	7	Propylene glycol	80.00
10.00	8	Hydrocortisone	10.00

Manufacturing Directions

1. Heat the mixture of items 1 to 5 and the water separately to approximately 80°C.
2. Add the water to the obtained solution of items 1 to 5 with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with 1/2, and continue to stir during cooling to room temperature. White cream.

Hydrocortisone Cream

Bill of Materials			
Scale (mg/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Hydrocortisone, micronized	10.00
6.00	2	Propylene glycol	60.00
0.10	3	Chlorocresol	1.00
5.00	4	Liquid paraffin	5.00
2.00	5	Cetomacrogol 1000	20.00
8.00	6	Cetostearyl alcohol	80.00
18.00	7	Soft white paraffin	180.00
0.29	8	Sodium phosphate monobasic	2.90
0.035	9	Propyl paraben	0.35
0.10	10	Methyl paraben	1.00
59.60	11	Deionized water	596.00

Manufacturing Directions

1. Load items 4 to 7 in a fat-melting vessel (the oily phase; use only half of item 5) and heat to 70°C to 75°C while stirring.
2. Cool down temperature to 65°C and maintain within the range of 65°C to 70°C.
3. In a Becomix vessel, heat item 11 to 90°C.
4. Add and dissolve items 9 and 10 in step 3. Cool down to 65°C and maintain temperature between 65°C and 70°C.
5. Add item 3, balance of item 5, and item 8 and dissolve by mixing for 10 to 15 minutes at 65°C to 70°C.
6. Transfer the oil phase from step 2 into step 5 through vacuum transfer while stirring at manual 10 rpm and temperature of 60°C.
7. Homogenize at speed II at 60°C and vacuum of 0.4 bar for 10 minutes. Cool down to 45°C.
8. In a separate vessel, charge items 1 and 2 at 45°C using Ultra-Turrax homogenizer to make a slurry.
9. Add step 8 into step 7 at 10 rpm and 45°C. Rinse container with item 2 and add to mix for 10 minutes at speed II.
10. Cool down to 30°C while mixing at 10 rpm auto mode and under vacuum of 0.4 bar.
11. Fill appropriate quantity into collapsible tubes.

Hydrocortisone Cream and Ointment

For the 1% cream, the inactive ingredients are aloe vera, benzyl alcohol, ceteareth-20, cetearyl alcohol, cetyl palmitate, glycerin, isopropyl myristate, isostearyl neopentanoate, methyl paraben, and purified water. For the 1% ointment, they are butylparaben, cholesterol, methyl paraben, microcrystalline wax, mineral oil, and white petrolatum. The 0.5% cream includes aloe vera, butylparaben, cetyl palmitate, glyceryl stearate, methyl paraben, polyethylene glycol, stearamido ethyl diethylamine, and purified water. The intensive therapy cream includes cetyl alcohol, citric acid, glyceryl stearate, isopropyl myristate, methyl paraben, polyoxyl 40 stearate, polysorbate 60, propylene glycol, propyl paraben, purified water, sodium citrate, sorbic acid, sorbitan monostearate, stearyl alcohol, and white wax. Another formulation of cream with aloe contains the active ingredient hydrocortisone 1% and the inactive ingredients aloe barbadensis gel, aluminum sulfate, calcium acetate, cetearyl alcohol, glycerin, light mineral oil, maltodextrin, methyl paraben, potato dextrin, propyl paraben, purified water, sodium cetearyl sulfate, sodium lauryl sulfate, white petrolatum, and white wax. Hydrocortisone 0.5% ointment comprises active ingredient hydrocortisone, 0.5%, and inactive ingredients aloe barbadensis extract and white petrolatum. Hydrocortisone 0.5% cream includes aloe barbadensis gel, aluminum sulfate, calcium acetate, cetearyl alcohol, glycerin, light mineral oil, maltodextrin, methyl paraben, potato dextrin, propyl paraben, purified water, sodium cetearyl sulfate, sodium lauryl sulfate, white petrolatum, and white wax.

Hydrocortisone Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Hydrocortisone acetate	10.00
100.00	2	Lutrol E 400	100.00
50.00	3	Cremophor RH 40	50.00
5.00	4	Carpopol 940 (Goodrich)	5.00
495.00	5	Water	495.00
QS	6	Preservative	QS
260.00	7	Water	260.00
8.00	8	Triethanolamine	8.00
QS	9	Water	7.20

Manufacturing Directions

1. Suspend item 1 in a mixture of items 2 and 3 at 70°C that contains item 6.
2. Add item 8 and continue to stir until the gel is cool.

Hydrocortisone Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Hydrocortisone acetate	10.00
150.00	2	Cremophor A 25	150.00
20.00	3	Cremophor RH 40	20.00
QS	4	Preservative	QS
640.00	5	Water	640.00

Manufacturing Directions

1. Suspend item 1 in the mixture of items 2 and 3 at 70°C.
2. Prepare solution of item 4, heat item 5 to 70°C, and add slowly to the hot mixture item 4.
3. Continue to stir until the gel is cool (clear, colorless gel).

Hydrocortisone Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Hydrocortisone acetate	5.00
60.00	2	Cremophor RH 40	60.00
9.00	3	Triethanolamine	9.00
76.00	4	Water	76.00
600.00	5	Ethanol 96%	600.00
5.00	6	Carbopol 940 (Goodrich)	5.00
245.00	7	Water	245.00

Manufacturing Directions

1. Prepare solution of items 6 and 7 and mix slowly with solution of items 1 to 5.
2. Form a clear, colorless gel.

Hydrocortisone Ointment

Bill of Materials			
Scale (mg/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Hydrocortisone micronized 6% excess	10.60
91.50	2	White soft paraffin	915.00
7.00	3	Liquid paraffin	70.00
0.50	4	Sorbitan sesquioleate (Arlacel 83)	5.00

Manufacturing Directions

1. Charge items 2 and 4 in a melting vessel and melt at 75°C.
2. Transfer to preheated Becomix at 75°C through stainless steel mesh under 0.4 to 0.6 bar vacuum.
3. Start mixing at 10 rpm manual mode. Cool to 50°C.
4. In a separate vessel, disperse item 1 in item 3, using a spatula, in a water bath maintained at 60°C. Homogenize for 6 minutes using Ultra-Turrax homogenizer.
5. Add to step 3 while mixing.
6. Rinse with item 3 and add and mix.
7. Homogenize dispersion under vacuum at 0.4 to 0.6 bar at 10 rpm.
8. Cool down to 30°C while mixing.
9. Transfer to storage vessel.
10. Fill appropriate quantity at a suitable temperature.

Hydrogen Peroxide and Carbamide Peroxide Bleaching Oral Dentifrice

Manufacturing Directions

1. Gel composition as weight percent contains sodium fluoride, 0.32 (0.14 (w/v fluoride ion); Carbopol 974 P-NF, 1.25; sorbitol (70% soln), 10.00; glycerin, 10.00; carbamide peroxide, 14.00; sodium lauryl sulfate, 1.50; sodium saccharine, 0.20; flavor, 1.25; FD&C yellow 5, 0.15; FD&C red 40, 0.05; water purified, 29.60.
2. Paste composition in weight percent contains sodium fluoride, 0.32; hydrogen peroxide (50% solution), 10.00; Carbopol 943, 0.51; sorbitol (70% soln), 5.18; glycerin, 5.18; sodium lauryl sulfate, 1.50; sodium saccharine, 0.20; flavor, 1.25; polytetrafluoroethylene (Teflon), 52.00; water purified, 29.86.
3. Both phases (steps 1 and 2) are neutralized to a pH of approximately 5.5 and 6.5 with freshly prepared 10% sodium hydroxide and the stripe composition to the main composition is approximately 15:100.
4. The above hydrogen peroxide/carbamide peroxide blend composition is effective and stable when used topically for bleaching tooth surfaces.
5. When extruded from the tube container, the gel composition will be in the form of one or more stripes enclosed in the periphery of the toothpaste surrounded by the paste composition.
6. The gel and the paste composition must be sufficiently of heavy viscosities to prevent migration (bleeding) of the colored gel into the white paste composition.

Hydrogen Peroxide Bleaching Dentifrice Paste

Manufacturing Directions

1. Add to 50 g purified water, 1.5 g of emulsifier Carbopol 934/polyvinylpyrrolidone in 75:25 ratio and dissolve with gradual stirring.
2. To the mixture, 20 mL of hydrogen peroxide (50%) is added and mixed for additional 5 to 10 minutes.
3. The acid composition is then adjusted between pH 5.5 and 6.5 with 10% NaOH.
4. The composition thickens to a gel and set aside.
5. In a separate vessel, 210 g of methyl methacrylate crosspolymer GMX-0610 obtained from Perspere Corp is added.
6. In another separate vessel, continuous phase of the invention is prepared comprising the following ingredients: weight% sodium fluoride, 1.05; propylene glycol, 24.10; sodium lauryl sulfate, 5.04; water, 43.40; vinyl pyrrolidone/acrylic acid*, 1.02; hydroxyethyl cellulose, 2.01; glycerin, 18.85; sodium saccharine, 0.47; flavor, 2.76; sodium benzoate, 0.55; benzoic acid, 0.06; sodium EDTA, 0.14; sodium hydroxide, (10% solution) 0.55*; dry blend copolymer containing 25% vinyl pyrrolidone and 75% Carbopol.
7. The vinyl pyrrolidone in the mixture delays the solubility of the emulsion further than Carbopol alone.
8. After the bleaching composition (step 1) has been prepared to desired consistency, 50 g of this composition is added to 50 g of the water insoluble abrasive suspension (step 2) and the intimate mixture of the two immiscible phases are dispersed in each other and then, with the aid of the colloidal mill, agitated until extremely fine homogeneous dispersion is obtained.
9. 100 g of the dispersion so obtained is then added to 50 g of the continuous phase (step 3) and the two phases mixed in a colloidal mill and the resultant composition comprised the discontinuous phases (step 1) dispersed homogenously throughout the continuous phase (step 2) and (step 3) of the present invention.
10. The final formulation is as follows expressed as weight in percentage: water purified, 15.75; methyl methacrylate crosspolymer GMX-0610, 53.71; hydrogen peroxide, 10.00; Carbopol 934, 0.37; hydroxyethyl cellulose, 0.73; sodium fluoride, 0.38 (0.17% F ions); sodium lauryl sulfate, 1.83; propylene glycol, 8.75; glycerin, 6.84; sodium saccharine, 0.17; sodium benzoate, 0.20; benzoic acid, 0.02; sodium EDTA, 0.05; flavor, 1.00; sodium hydroxide (10%) QS pH 6.5, 0.20.
11. Carbopol in this composition sufficiently retards the dissolution of the emulsified hydrogen peroxide to allow the abrasive agent methyl methacrylate crosspolymer GMX-0610 to remove the dental plaque and pellicles from the enamel surface and thus allow the bleaching active hydrogen peroxide to diffuse through the plaque-free enamel with ease.

Hydrogen Peroxide Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Liquid paraffin	50.00
10.00	2	White paraffin	100.00
30.00	3	Glycerin	300.00
8.00	4	Cetostearyl alcohol	80.00
0.30	5	Methyl paraben	3.00
3.60	6	Polyoxyethylene sorbitan monostearate	36.00
2.00	7	Glyceryl monostearate	20.00
QS	8	Water purified	QS to 1 kg
8.00	9	Hydrogen peroxide[a]	80.00

[a]Hydrogen peroxide, at different strengths, is used as an anti-infective for use in the oral cavity or topically for minor wounds.

Manufacturing Directions

1. Preparation of water phase:
   a. Charge purified water, polysorbate 60, and glycerin with agitation in a melting kettle.
   b. Heat the contents to 61°C to 65°C.
   c. Add methyl paraben and mix the composition to dissolve while maintaining temperature.
2. Preparation of oil phase:
   a. In a suitable vessel, charge liquid paraffin, cetostearyl alcohol, white petrolatum, glycerol monostearate, and white beeswax and mix continuously while heating to 71°C to 75°C.
3. Mixing of phases:
   a. Transfer the mixture of step 2 to the step 1 kettle, with the water phase maintained under 300-mbar vacuum.
   b. Add hydrogen peroxide and dissolve.
   c. With mixing and keeping the temperature at 61°C to 65°C, draw the oil phase into the water phase.
   d. Mix for 15 minutes with agitation and vacuum at 300 mbar and 61°C to 65°C.
   e. While mixing and under vacuum, allow the mixture to cool gradually to room temperature.
4. Fill in appropriate container.

Hydrophilic Ointment USP

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.0250	1	Methyl paraben	0.250
0.015	2	Propyl paraben	0.15
1.00	3	Sodium lauryl sulfate	10.00
12.00	4	Propylene glycol	120.00
25.00	5	Stearyl alcohol	250.00
25.00	6	White petrolatum	250.00
37.00	7	Water purified	370.00

Manufacturing Directions

1. Melt the stearyl alcohol and the white petrolatum on a steam bath and warm to approximately 75°C.
2. Dissolve the other ingredients in the purified water and warm to approximately 75°C.
3. Mix all ingredients together and stir until the mixture congeals.

Hydroquinone Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.50	1	Ascorbyl palmitate	15.00
1.00	2	Tocopherol acetate	10.00
2.00	3	Linoleic acid	20.00
3.00	4	Safflower oil	30.00
4.00	5	Oleyl alcohol	40.00
1.00	6	Jojoba oil	10.00
8.00	7	SDA 40 anhydrous alcohol	80.00
0.50	8	Benzyl alcohol	5.00
0.50	9	Butylated hydroxyanisole	5.00
0.15	10	Sodium bisulfite	1.50
3.00	11	Petrolatum	30.00
5.00	12	PEG-4 diheptanoate	50.00
4.00	13	Glyceryl stearate SE	40.00
1.80	14	Cetyl alcohol	18.00
2.00	15	Polyacrylamide and C13-14 isoparaffin and laureth-7	20.00
0.20	16	Hydroxyethyl cellulose	2.00
QS	17	Water purified	QS
4.00	18	Hydroquinone	40.00
QS	19	Fragrance	QS

Manufacturing Directions

1. Charge linoleic acid, safflower oil, jojoba oil, petrolatum, behenyl erucate, and cetyl alcohol and heat to 70°C.
2. Add tocopherol to above just before adding the rest of the ingredients (see below).
3. Heat item 15 to 70°C and add and dissolve item 18. Add and disperse item 16.
4. In a separate vessel, add item 1 and BHA and heat to 45°C. Dissolve items 5, 7, and 8 and heat to 45°C. Add sodium bisulfite. Stir to dissolve.
5. Add step 2 to step 1 in a homogenizer and then during homogenization add step 4 and also add tocopherol. Homogenize well.
6. Add items 18 and 19 and mix well. Cool to 35°C and fill.

Hydroquinone Cream and Gel

Each gram of 4% cream contains 40 mg of hydroquinone USP in a vanishing cream base of purified water USP, stearic acid NF, propylene glycol USP, polyoxyl 40 stearate NF, polyoxyethylene (25) propylene glycol stearate, glycerol monostearate, light mineral oil NF, squalane NF, propyl paraben NF, and sodium metabisulfite NF. The sunblocking 4% cream contains 40 mg hydroquinone USP in a tinted sunblocking-cream base of purified water USP, stearic acid NF, talc USP, polyoxyl 40 stearate NF, polyoxyethylene (25) propylene glycol stearate, propylene glycol USP, glycerol monostearate, iron oxides, light mineral oil NF, squalane NF, edetate disodium USP, sodium metabisulfite NF, and potassium sorbate NF. In another formulation, each gram of 4% cream contains 40 mg hydroquinone USP, 80 mg padimate O USP, 30 mg dioxybenzone USP, and 20 mg oxybenzone USP in a vanishing cream base of purified water USP, glycerol monostearate and polyoxyethylene stearate, ootyldodecyl stearoyl stearate, glyceryl dilaurate, quaternium-26, cetearyl alcohol and ceteareth-20, stearyl alcohol NF, propylene glycol USP, diethylaminoethyl stearate, polydimethylsiloxane, polysorbate 80 NF, lactic acid USP, ascorbic acid USP, hydroxyethyl cellulose, quaternium-14 and myristalkonium chloride, edetate disodium USP, and sodium metabisulfite NF. Each gram of 4% gel contains 40 mg hydroquinone USP, 50 mg padimate O USP, and 30 mg dioxybenzone USP in a hydroalcoholic base of alcohol USP, purified water USP, propylene glycol USP, entprol, carbomer 940, edetate disodium USP, and sodium metabisulfite NF.

Hydroquinone Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.50	1	Ascorbyl palmitate	15.00
1.00	2	Tocopherol acetate	10.00
4.00	3	Linoleic acid	40.00
17.75	4	Safflower oil	177.50
12.00	5	Oleyl alcohol	120.00
12.00	6	SDA 40 anhydrous alcohol	120.00
0.50	7	Benzyl alcohol	5.00
0.50	8	Butylated hydroxyanisole	5.00
16.60	9	Cyclomethicone	166.00
0.15	10	Sodium bisulfite	1.50
2.00	11	Sorbitol laurate	20.00
5.00	12	C18-C36 acid glyco ester	50.00
5.00	13	Tribehenin	50.00
7.50	14	Petrolatum	75.00
15.00	15	Behenyl erucate	150.00
4.00	16	Hydroquinone	40.00
QS	17	Fragrance	QS

Manufacturing Directions

1. Charge ascorbyl palmitate and butylated hydroxyanisole in a suitable vessel and dissolve in oleyl alcohol, SDA anhydrous alcohol, and benzyl alcohol. Heat to 45°C.
2. Add sodium bisulfite and mix while keeping it covered. Keep it aside.
3. In a separate vessel, charge items 11 to 16 and heat to 70°C.
4. Cool to 55°C and then add tocopherol acetate, linoleic acid, and safflower oil.
5. Add step 4 into step 2 while mixing to minimize air entrapment.
6. Add item 16 and mix well. Add item 17 and mix well.
7. Cool to 30°C and fill.

Ibuprofen and Domperidone Maleate Suppository

Bill of Materials			
Scale (mg/suppository	Item	Material Name	Qty/1000 Suppositories (g)
22.50	1	Domperidone maleate	22.50
600.00	2	Ibuprofen	600.00
120.00	3	Polysorbate 60	120.00
1800.00	4	Witepsol H 185	1800.00

Manufacturing Directions

1. The polysorbate is dispersed in the molten Witepsol followed by the addition of the ibuprofen and domperidone.
2. The mixture is then injected into molds to produce a suppository shape and cooled to ambient temperature.
3. The suppository contains 600 mg ibuprofen and 22.5 mg domperidone maleate.

Ibuprofen Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Ibuprofen	50.00
24.00	2	Glyceryl stearate and PEG-75 stearate (Gelot 64)	240.00
5.00	3	Labrafil M 1944	50.00
3.00	4	Octyldodecyl myristate	30.00
0.07	5	Sodium methyl paraben	0.70
0.03	6	Sorbic acid	0.30
1.00	7	Stearic acid	10.00
15.00	8	Ethoxydiglycol (Transcutol)	150.00
0.150	9	Lavender oil	1.50
46.75	10	Water purified	467.50

Manufacturing Directions

1. Charge item 9 in Becomix and heat to 80°C. Charge items 2 to 7 one by one and mix for 20 minutes.
2. Homogenize at speed I under vacuum. Cool to 25°C.
3. In a separate container, charge items 1, 8, and 9. Dissolve and filter through polyester filter.
4. Add step 3 into step 2.
5. Mix well and fill.

Ibuprofen Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Ibuprofen	50.00
10.00	2	Alcohol	100.00
20.00	3	Propylene glycol	200.00
22.00	4	Lutrol F 127	220.00
QS	5	Preservatives	QS
43.00	6	Water purified	430.00

Manufacturing Directions

1. Heat solution of items 1 to 3 to 70°C to 80°C.
2. Dissolve item 4 and cool.
3. Add solution of item 5.
4. Fill.

Ibuprofen Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Ibuprofen	50.00
10.00	2	Alcohol	100.00
10.00	3	Propylene glycol	100.00
15.00	4	Lutrol F 127	150.00
1.00	5	Isopropyl myristate	10.00
QS	6	Preservatives	QS
59.00	7	Water purified	590.00

Manufacturing Directions

The addition of item 5 to the formulation makes the product less sticky and is preferred.

1. Heat solution of items 1 to 3 to 70°C to 80°C.
2. Dissolve items 4 and 5 and cool. Add solution of item 6.
3. Fill.

Ibuprofen Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Ibuprofen	51.00
27.35	2	Propylene glycol	273.50
10.00	3	Isopropyl alcohol	100.00
5.00	4	Isopropyl alcohol	50.00
0.10	5	Potassium sorbate	1.00
2.50	6	Carbopol 940	25.00
0.20	7	Sodium methyl paraben	2.00
0.0025	8	FD&C red No. 40	0.025
22.50	9	Ethoxydiglycol (Transcutol)	225.00
0.150	10	Lavender oil	1.50
27.09	11	Water purified	270.90

Manufacturing Directions

1. Charge and mix items 2, 3, and 11 in a stainless steel vessel.
2. Add and dissolve item 5 in step 1 by stirring.
3. Add and dissolve item 6 in step 1 after passing through a stainless steel sieve.
4. Mix and homogenize suspension.
5. Dissolve item 7 in item 11 and add to step 4.
6. Add and dissolve item 8 in item 11 separately and add to step 5.
7. Charge item 2 and in a separate vessel, dissolve, and add to step 7.
8. Charge items 9 and 10 in a separate container, mix, and transfer to step 8.
9. Mix thoroughly, transfer to storage vessel, and fill.

Ibuprofen Gel Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Ibuprofen	50.00
12.00	2	Propylene glycol	120.00
12.00	3	Isopropyl alcohol	120.00
12.00	4	Lutrol F 127	120.00
44.00	5	Water purified	440.00
15.00	6	Nonionic hydrophilic cream: DAB 1996	150.00

Ibuprofen Gel Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Polysorbate 60	50.00
10.00	2	Cetyl stearyl alcohol	100.00
10.00	3	Glycerin	100.00
25.00	4	White petrolatum	250.00
50.00	5	Water purified	500.00

Manufacturing Directions

1. Prepare solution of items 1 to 3 and cool to approximately 8°C. Dissolve item 4 in items 5 and 6.
2. Maintain cool until the air bubbles escape.

Ibuprofen Gel Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Ibuprofen	50.00
24.00	2	Glyceryl stearate and PEG-75 stearate (Gelot 64)	240.00
5.00	3	Labrafil M 1944	50.00
3.00	4	Octyldodecyl myristate	30.00
0.07	5	Sodium methyl paraben	0.70
0.03	6	Sorbic acid	0.30
1.00	7	Stearic acid	10.00
15.00	8	Ethoxydiglycol (Transcutol)	150.00
0.150	9	Lavender oil	1.50
46.75	10	Water purified	467.50

Manufacturing Directions

1. Charge item 9 in Becomix and heat to 80°C. Charge items 2 to 7 one by one and mix for 20 minutes.
2. Homogenize at speed I under vacuum. Cool to 25°C.
3. In a separate container, charge items 1, 8, and 9; dissolve and filter through polyester filter.
4. Add step 3 into step 2. Mix well and fill.

Imiquimod Cream

Each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methyl paraben, and propyl paraben.

Indomethacin Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Indomethacin	10.00
10.00	2	Cremophor RH 40	100.00
15.00	3	Lutrol F 127	150.00
74.00	4	Water purified	740.00

Manufacturing Directions

1. Dissolve indomethacin in Cremophor RH 40 at 60°C to 70°C.
2. Add the water slowly (60–70°C), stir the mixture well, and dissolve Lutrol F 127.
3. Cool to room temperature. Fill.

Indomethacin Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Indomethacin	10.00
20.00	2	Propylene glycol	200.00
20.00	3	Lutrol E 400	200.00
21.00	4	Lutrol F 127	210.00
38.00	5	Water purified	380.00

Manufacturing Directions

1. Heat solution of items 1 to 3 to approximately 70°C.
2. Dissolve item 4 with stirring for approximately 30 minutes.
3. Add and mix item 5 and cool to form a yellow gel.
4. Fill.

Indomethacin Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Indomethacin	10.00
15.00	2	Alcohol	150.00
22.00	3	Lutrol E 400	220.00
23.00	4	Lutrol F 127	230.00
39.00	5	Water purified	390.00

Manufacturing Directions

Addition of item 5 enhances the chemical stability of item 1.

1. Heat solution of items 1 to 3 to approximately 70°C.
2. Dissolve item 4 with stirring for approximately 30 minutes.
3. Add and mix item 5 and cool to form a yellow gel.
4. Fill.

Indomethacin Suppositories

The suppositories for rectal use contain 50 mg of indomethacin and the following inactive ingredients: butylated hydroxyanisole, butylated hydroxytoluene, edetic acid, glycerin, polyethylene glycol 3350, polyethylene glycol 8000, and sodium chloride.

Indomethacin Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
100.00	1	Indomethacin	100.00
0.082	2	Butylated hydroxyanisole	0.082
0.082	3	Butylated hydroxytoluene	0.082
0.163	4	Edetic acid	0.163
128.00	5	Glycerin	128.00
128.00	6	Polyethylene glycol 6000	128.00
1630.00	7	Polyethylene glycol 4000	1630.00

Manufacturing Directions

1. Charge the polyethylene glycol 6000, polyethylene glycol 4000 (16.3 kg), and glycerol to the Becomix machine.
2. Heat to 70°C to melt, stir until homogenous, and cool to 60°C to 65°C.
3. Maintain temperature at 60°C to 65°C. Apply a head of nitrogen gas to hopper, then charge to the hopper the parabens.
4. Stir until dissolved.
5. Charge indomethacin slowly to hopper while stirring. Stir until completely dissolved. A clear yellow melt is produced.
6. Charge edetic acid to the hopper and stir for 15 minutes to disperse it (material does not dissolve), then cool to 55°C to 60°C.
7. Stir the mixture for 30 minutes, maintaining the temperature at 55°C to 60°C, then commence filling into molds at filling limits 1.581 to 1.679 g.

Indomethacin Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
50.00	1	Indomethacin	50.00
8.30 μg	2	Butyl hydroxytoluene	8.30 mg
141.00	3	Lutrol E 4000	141.00
14.00	4	Lutrol E 6000	14.00
16.30 μg	5	EDTA	16.30 mg
3.00	6	Water purified	3.00

Manufacturing Directions

1. Prepare solution of items 5 and 6.
2. Mix with the melted mixture of items 1 to 4 and fill into the molds of suppositories. Fill 1.6 g/suppository.

Insect Bite Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
180.00	1	Trilaneth-4 phosphate, glyceryl stearate, and PEG-2 stearate	180.00
20.00	2	Hydrogenated palm/Kernel oil PEG-6 esters	20.00
80.00	3	Mineral oil	80.00
0.30	4	Sodium methyl paraben	0.30
0.70	5	Sorbic acid	0.70
646.70	6	Deionized water	646.70
10.00	7	Benzocaine	10.00
10.00	8	Butamben	10.00
2.00	9	Menthol	2.00
0.30	10	Resorcinol	0.30
50.00	11	Ethoxydiglycol	50.00

Manufacturing Directions

1. Dissolve items 7 to 10 in item 11.
2. Mix and heat items 1 to 6 to 75°C.
3. Allow to cool slowly with constant stirring.
4. At 35°C add this to previous mixture.
5. Homogenize if necessary.

Keratolytic Cream

Bill of Materials			
Scale (mg/10 g)	Item	Material Name	Qty/kg (g)
150.00	1	Polawax (self-emulsifying wax)	15.00
150.00	2	PPG-2 myristyl ether propionate (Crodamol PMP)	15.00
50.00	3	Sorbitol isostearate	5.00
35.00	4	Safflower oil, super-refined	3.50
20.00	5	Avocado oil, super-refined	2.00
20.00	6	Cetyl palmitate	2.00
50.00	7	Salicylic acid	5.00
1.50	8	Propyl paraben	0.15
1.00	9	Butylated hydroxyanisole	0.10
487.50	10	Deionized water	48.75
10.00	11	Sodium borate	1.00
3.00	12	Methyl paraben	0.30
2.00	13	Imidazolidinyl urea	0.20
20.00	14	Hydrolyzed collagen + hyaluronic acid (Cromoist HTA)	2.00

Manufacturing Directions

1. Dissolve item 7 in item 2 with mixing and heating to 70°C.
2. Add balance of items 1 to 9 and mix with heat to 80°C and items 10 to 13 together separately and heat to 80°C.
3. Add this mixture to the first mixture with mixing and cool to 40°C.
4. Add item 14 with mixing and cool to the desired fill temperature.
5. Adjust pH if necessary to 3 to 4 with 10% triethanolamine solution.

Ketoconazole Cream

The ketoconazole 2% cream contains the broad-spectrum synthetic antifungal agent ketoconazole, 2%, formulated in an aqueous cream vehicle consisting of propylene glycol, stearyl and cetyl alcohols, sorbitan monostearate, polysorbate 60, isopropyl myristate, sodium sulfite anhydrous, polysorbate 80, and purified water.

Ketoconazole Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.00	1	Ketoconazole micronized	20.00
20.00	2	Propylene glycol	200.00
8.00	3	Stearyl alcohol	80.00
2.00	4	Cetyl alcohol	20.00
2.00	5	Span 60	20.00
1.50	6	Tween 60	15.00
1.00	7	Isopropyl myristate	10.00
0.20	8	Sodium sulfite anhydrous	2.00
0.10	9	Tween 80	1.00
QS	10	Water purified	QS to 1 kg

Manufacturing Directions

1. Charge items 3 to 5 in a steam-jacketed kettle. Heat to 75°C and then begin stirring to ensure complete melting. Maintain temperature, keep stirring.
2. Charge items 2 and 10 in a separate heating vessel and heat to 75°C. Add item 6 and stir, preferably under vacuum of 0.5 bar to avoid frothing and add to step 1, passing through a 100-mesh screen by a pump. Rinse with item 10 and add rinsings.
3. Stir for 1 hour. Cool to 40°C while stirring.
4. In a separate vessel, add 10% of item 10 and item 1 to make a slurry, heat to 40°C, and pass through colloid mill after adding another 10% of item 10.
5. Separately dissolve in 5% of item 10, item 8, and add to step above. Mix for 30 minutes.
6. Pass again through colloid mill and add to step 3, mix, and pass again through colloid mill.
7. Fill in appropriate containers.

Kojic Dipalmitate Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.20	1	Kojic dipalmitate	2.00
6.00	2	Finetex TN	60.00
3.00	3	Bernel FAO	30.00
2.00	4	CarboSil M-5 (fumed silica)	20.00
0.30	5	Microtitanium dioxide	3.00
0.50	6	Lecithin Z-3	5.00
5.00	7	Bentone TN (hectorite compound)	50.00
2.00	8	Mineral oil	20.00
8.00	9	Isopropyl myristate	80.00
0.08	10	Fragrance	0.80

Manufacturing Directions

1. Heat the Kojic dipalmitate, Finetex, FAO, bentone, and isopropyl myristate to 70°C in a jacketed kettle.
2. Transfer to a homogenizer mill.
3. Slowly add, with high-shear agitation, the CarboSil and the microtitanium dioxide.
4. Mill and cool to 45°C to 50°C.
5. Add, with milling, the remaining ingredients except the fragrance and SD alcohol. Cool with milling (and cooling jacket if needed) to 25°C to 30°C.
6. Add, with mixing, the fragrance and alcohol. Package immediately.

Lactic Acid Cream

The cream is a formulation of 12% lactic acid neutralized with ammonium hydroxide, as ammonium lactate, with a pH of 4.4 to 5.4. The cream also contains cetyl alcohol, glycerin, glyceryl stearate, laureth-4, light mineral oil, magnesium aluminum silicate, methylcellulose, methyl and propyl parabens, PEG-100 stearate, polyoxyl 40 stearate, propylene glycol, and water. Lactic acid is a racemic mixture of 2-hydroxypropanoic acid.

Lanolin Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
60.00	1	Stearic acid	60.00
145.00	2	White petrolatum jelly	145.00
116.00	3	Mineral oil 25 cS	116.00
10.00	4	Lanolin	10.00
20.00	5	Cetearyl alcohol	20.00
QS	6	Deionized water	QS to 1 kg
14.00	7	Triethanolamine 99%	14.00
QS	8	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring. Stir to cool, adding triethanolamine at 60°C and perfuming at 40°C to 50°C.
3. This cream serves as a base for drugs as well. Triethanolamine may be omitted, because it gives a higher pH.

Lidocaine Adhesive System Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
8.00	1	Lidocaine base	80.00
5.00	2	Dipropylene glycol	50.00
8.00	3	Lecithin 60% in propylene glycol	80.00
10.00	4	Karaya gum	100.00
2.00	5	Bentonite (Polargel)[a]	20.00
0.10	6	Zinc oxide	1.00
6.00	7	Glycerin	60.00

[a]Optional ingredients.

Manufacturing Directions

1. Blend the lidocaine base, the propylene glycol, lecithin, and glycerin at approximately 70°C to 90°C until the entire drug is dissolved.
2. Cool the solution to 20°C to 35°C before adding the karaya gum and clay.
3. Once the karaya gum and clay are added, the final composition is applied to a suitable backing material such as a nonwoven polyester film (e.g., the film sold under the trademark Sontara 8100, manufactured by DuPont de Nemours, EI and Co, Wilmington, DE) and warmed to approximately 100°C to accelerate the formation of the gel into its final, finite form.

Lidocaine and Prilocaine Topical Adhesive System Cream

Lidocaine, 2.5%, and prilocaine, 2.5%, are emulsions in which the oil phase is a eutectic mixture of lidocaine and prilocaine in a ratio of 1:1 by weight. This eutectic mixture has a melting point below room temperature; therefore, both local anesthetics exist as liquid oil rather than as crystals. It is also packaged in the anesthetic disc, which is a single-dose unit contained within an occlusive dressing. The anesthetic disc is composed of a laminate backing, an absorbent cellulose disc, and an adhesive tape ring. The disc contains 1 g of emulsion, the active contact surface being approximately 10 cm^2. The surface area of the entire anesthetic disc is approximately 40 cm^2.

Lidocaine and Tribenoside Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Tribenoside	50.00
2.00	2	Lidocaine hydrochloride	20.00
5.00	3	Cetyl alcohol	50.00
9.00	4	Stearic acid	90.00
10.00	5	Liquid paraffin	100.00
2.00	6	Isopropyl palmitate	20.00
4.45	7	Cetomacrogol 1000	44.50
1.55	8	Crill 3	15.50
0.180	9	Methyl paraben	1.80
0.05	10	Propyl paraben	0.50
6.00	11	Sorbitol 70% solution	60.00
54.80	12	Water purified	548.00

Manufacturing Directions

1. Charge and dissolve items 9 and 10 in portion of item 12 at 90°C.
2. Charge item 11 into Becomix and heat to 60°C.
3. Add item 2 to step 3 and dissolve, maintaining temperature at 60°C.
4. Charge in a melting vessel items 3, 4, 7, and 8 and melt at 70°C. Cool to 55°C.
5. Add items 1, 5, and 6 to a fat-melting vessel and melt at 60°C.
6. Transfer step 5 to step 4 and mix well. Cool down to 25°C.
7. Transfer to storage vessel and fill.

Lidocaine and Tribenoside Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Tribenoside	5.00
2.00	2	Lidocaine	2.00
79.20	3	White soft paraffin	79.20
0.30	4	Hard paraffin	0.30
3.50	5	Microcrystalline wax	3.50

Manufacturing Directions

1. Charge items 3 to 5 in a melting vessel and heat to 70°C to melt, transfer to Becomix, and maintain 40°C to 45°C.
2. In a portion of the melt above, add items 1 and 2 in a separate vessel and homogenize for 5 minutes. Transfer to step 1 using the melt to rinse and adding rinsings.
3. Allow to cool to 40°C. Transfer to storage vessel and fill.

Lidocaine and Tribenoside Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
40.00	1	Lidocaine	40.00
400.00	2	Tribenoside	400.00
281.00	3	Witepsol E 85	281.00
1124.60	4	Witepsol W 35	1124.60
4.40	5	Miglyol 812 N	4.40

Manufacturing Directions

1. Load items 3 and 4 in a fat-melting vessel and heat to 50°C. Transfer molten material to Becomix through filter sieves, keeping a small portion on the side.
2. Charge items 1, 2, and 4 in step 1, rinsing the container of item 2 with the molten portions kept aside in step 1.
3. Mix for 20 minutes at 10 rpm (manual), temperature 50°C, homogenize at speed II for 4 minutes under 0.6 bar vacuum. Check for clarity; if not clear, homogenize again.
4. Set the temperature to 39°C and mix at 10 rpm.
5. Fill 1850 mg in suppository molds.

Lidocaine Anorectal Cream

Anorectal cream (lidocaine 5%) is a topical anesthetic cream. Each gram of anorectal cream contains lidocaine 50 mg, benzyl alcohol, carbomer 940, cholesterol, hydrogenated lecithin, isopropyl myristate, polysorbate 80, propylene glycol, triethanolamine, vitamin E acetate, and water.

Lidocaine, Eugenol, and Menthol Dental Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
55.2	1	Beeswax white	55.2
150.0	2	Lanolin anhydrous	150.0
723.7	3	Petrolatum	723.7
40.0	4	Lidocaine base	40.0
1.2	5	Saccharin sodium powder	1.2
QS	6	Water purified	3.0 mL
1.0	7	Eugenol	1.0
5.0	8	Menthol	5.0
0.8	9	Oil peppermint	0.8
20.16	10	Metaphen ointment base	20.16

Manufacturing Directions

1. Melt beeswax white, lanolin, and petrolatum white together at 70°C to 80°C and strain into a suitable container.
2. Do not heat above 70°C to 80°C.
3. Melt Lidocaine base and strain into the container while mixing.
4. Dissolve the sodium saccharin in purified water heated to 70°C. Add to the container while mixing. Cool down to 45°C to 50°C while mixing.
5. Liquefy eugenol, menthol, and peppermint oil together by mixing all three items.
6. Warm gently to 35°C to 40°C if necessary. Strain into the container while mixing. Gently melt metaphen ointment base and strain into the container while mixing.
7. Mix thoroughly until congealed.

Lidocaine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
20.00	1	Lidocaine hydrochloride	2
560.00	2	Water	56
200.00	3	Propylene glycol pharma	20
220.00	4	Lutrol F 127	22

Manufacturing Directions

1. Prepare solution of items 1 to 3 at room temperature, heat to 70°C or cool to 6°C, and slowly add item 4 to the well-stirred solution until it is dissolved.
2. Maintain the temperature until the air bubbles escape. A clear, colorless gel is obtained.

Lidocaine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
50.00	1	Lidocaine hydrochloride	5
500.00	2	Water	50
150.00	3	Propylene glycol pharma	15
100.00	4	Liquid paraffin	10
200.00	5	Lutrol F 127	20

Manufacturing Directions

1. Prepare solution of items 1 to 3 at room temperature and mix with item 4.
2. Heat to 70°C or cool to 6°C and slowly add item 5 to the well-stirred solution until it is dissolved. Maintain cool until the air bubbles escape. A gel cream is obtained.

Lidocaine Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Lidocaine base	50.00
28.00	2	Polyethylene glycol (PEG- 3350)	280.00
40.00	3	Polyethylene glycol (PEG-400)	400.00
25.00	4	Propylene glycol	250.00
2.00	5	Purified water	20.00

Manufacturing Directions

1. Load items 2 and 3 into a fat-melting vessel and heat to 70°C.
2. Cool to 40°C while stirring at slow speed (10–12 rpm).
3. Maintain the temperature between 40°C and 45°C under continuous stirring.
4. Heat 200 g of item 4 to 40°C to 45°C in a stainless steel container.
5. Dissolve item 1 by stirring with stirrer. Add item 5 with continuous stirring.
6. Maintain the temperature between 40°C and 45°C with continuous stirring.
7. Filter through cloth filter. Transfer the drug solution into mixer previously set with temperature at 40°C to 45°C.
8. Rinse the stainless steel container with 50 g of item 4.
9. Add the rinsing into mixer. Transfer the molten mass from the fat-melting vessel at 40°C through a stainless steel filter to the mixer containing the drug solution while mixing at 10 to 12 rpm.
10. When the transfer is over, start the homogenizer at low speed, vacuum 0.6 bar, with stirrer speed at 10 rpm (manual mode).
11. Mix and homogenize for 10 minutes with recirculation at temperature 40°C to 45°C.
12. Stop the homogenizer, set the mixer at temperature 25°C, with stirrer speed at 10 rpm (manual mode).
13. Cool the cream to 25°C. When the ointment is cooled to 25°C, unload the ointment in stainless steel container.

Lindane Lotion

Lindane lotion USP, 1%, is an ectoparasiticide and ovicide effective against *Sarcoptes scabiei* (scabies). In addition to the active ingredient, lindane, it contains glycerol monostearate, cetyl alcohol, stearic acid, trolamine, carrageenan, 2-amino-2-methyl-1-propanol, methyl paraben, butyl paraben, perfume, and water to form a nongreasy lotion, which is the highly purified gamma isomer of 1, 2, 3, 4, 5, 6-hexachlorocyclohexane.

Mafenide Acetate Cream

The cream is a soft, white, nonstaining, water-miscible antiinfective cream for topical administration to burn wounds. Cream spreads easily and can be washed off readily with water. It has a slight acetic odor. Each gram of cream contains mafenide acetate equivalent to 85 mg of the base. The cream vehicle consists of cetyl alcohol, stearyl alcohol, cetyl esters wax, polyoxyl 40 stearate, polyoxyl 8 stearate, glycerin, and water, with methyl paraben, propyl paraben, sodium metabisulfite, and edetate disodium as preservatives.

Malathion Lotion

The lotion contains 0.005 g of malathion per milliliter in a vehicle of isopropyl alcohol (78%), terpineol, dipentene, and pine needle oil.

Mandelic Acid Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.00	1	Polyoxyethylene (40) stearate	20.00
1.00	2	Polyoxyethylene (20) sorbitan monooleate	10.00
5.00	3	Glycerol monostearate	50.00
3.00	4	Beeswax	30.00
2.00	5	Mineral oil	20.00
71.00	6	Water purified	710.00
5.00	7	Propylene glycol	50.00
0.50	8	Carbopol 934	5.00
5.00	9	DL-mandelic acid	50.00
1.7 mL	10	Ammonium hydroxide concentrated	17.00 mL

Manufacturing Directions

1. Heat items 1 to 5 in a stainless steel container to 80°C.
2. In a separate container, heat items 6 to 8 to 80°C.
3. Add step 2 to step 1 with agitation.
4. After the mixture is congealed, add mandelic acid and ammonium hydroxide.
5. Continue agitation until a uniform consistency is obtained. The pH of the cream is 4.

Medicated Foot Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Lanolin	5.00
90.00	2	Stearic acid	90.00
5.00	3	Cetyl alcohol	5.00
40.00	4	Isopropyl palmitate	40.00
10.00	5	Oleyl alcohol	10.00
20.00	6	Mineral oil and lanolin alcohol (liquid base CB3929)	20.00
7.50	7	Oil of wintergreen	7.50
3.00	8	Oil of thyme	3.00
5.00	9	Oil of pine	5.00
5.00	10	Menthol	5.00
5.00	11	Camphor	5.00
QS	12	Deionized water	QS to 1 kg
80.00	13	Glycerin	80.00
18.00	14	Triethanolamine 99%	18.00
QS	15	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately at 65°C to 70°C.
2. Add water phase to oil phase while stirring.
3. Add the triethanolamine drop-wise.
4. Stir to cool.

This product can be used as a disinfecting and soothing cream for the feet.

Menthol, Methyl Salicylate, and Menthol Cream and Ointment

This cream and ointment contain menthol in an alcohol base gel, combinations of methyl salicylate, and menthol in cream and ointment bases, as well as a combination of methyl salicylate, menthol, and camphor in a nongreasy cream base; all are suitable for topical application. The varieties include the ointment (methyl salicylate, 18.3%; menthol, 16%), the cream (methyl salicylate, 15%; menthol, 10%), an arthritis formula cream (methyl salicylate, 30%; menthol, 8%), an ultrastrength pain-relieving cream (methyl salicylate, 30%; menthol, 10%; camphor, 4%), vanishing gel (2.5% menthol), and cream (10% menthol) with a fresh scent.

Mercuric Oxide Ointment

Manufacturing Directions

1. An oleaginous ointment composition containing yellow mercuric oxide as its active ingredient was prepared using the following ingredients in the relative weight percentages indicated: white petrolatum USP, 54.55; mineral oil NF, 31.50; microcrystalline wax, 5.00; stearic acid NF, 0.40; boric acid NF, 2.50; yellow mercuric oxide, 1.05; wheat germ oil, 5.00.
2. The white petrolatum, mineral oil, microcrystalline wax, and stearic acid NF were charged into a suitably sized No. 316 stainless steel tank with an agitator. The ointment base was heated while mixing to 80°C to 85°C until the base was completely melted.
3. The ointment base was then filtered through a 0.22-micrno membrane-filtering unit into the main No. 316 stainless steel mixing tank.
4. When the ointment base had cooled down to approximately 45°C, a portion of the base was withdrawn into a stainless steel container.
5. The boric acid (sterilized) was then added to the base and dispersed with the aid of a homomixer for 10 minutes.
6. The yellow mercuric oxide (sterilized) was then added to the mixture and dispersed for at least 30 minutes until a homogeneous slurry was achieved.
7. The slurry was added to the main ointment batch and mixed until the batch was homogeneous and free of lumps. The batch was then cooled to approximately 28°C and the filtered wheat germ oil added thereto. The resulting ointment was mixed for approximately 15 minutes until homogeneous.

Mesalamine Suppository

The rectal suppository contains 500 mg of mesalamine in a base of hard fat NF.

Methotrexate Cataplasms

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Diisopropanolamine	50.00
3.00	2	Methotrexate	30.00
10.00	3	Polysodium acrylate	100.00
10.00	4	Gelatin	100.00
30.00	5	Glycerin	300.00
QS	6	Water purified	QS to 1 kg

Manufacturing Directions

1. Mix diisopropanolamine and methotrexate with a portion of purified water.
2. Mix the resulting aqueous mixture with an aqueous solution of the corresponding base components (polysodium acrylate, gelatin, and glycerin) in the remaining portion of the purified water.
3. Cast the mass in step 2 on a release sheet; apply a nonwoven fabric backing to a surface of the mass.

Methotrexate Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.00	1	Stearic acid	70.00
0.50	2	Behenyl alcohol	5.00
7.00	3	Squalene	70.00
2.00	4	Polyethylene glycol monostearate	20.00
5.00	5	Glyceryl monostearate (self-emulsifying type)	50.00
0.10	6	Butyl hydroxybenzoate	1.00
0.10	7	Methyl hydroxybenzoate	2.00
5.00	8	1,3-Butylene glycol	50.00
3.00	9	Methotrexate	30.00
5.00	10	Diisopropanolamine[a]	50.00
QS	11	Water purified	QS to 1 kg

[a]May be omitted.

Manufacturing Directions

1. Mix diisopropanolamine and methotrexate with a portion of purified water.
2. Mix the resulting aqueous mixture under heat with a liquid mixture of stearic acid, behenyl alcohol, squalane, polyethylene glycol stearate, glyceryl monostearate acid, and butyl parahydroxybenzoate and also with an aqueous mixture of methyl parahydroxybenzoate, 1,3-butylene glycol, and the remaining portion of the purified water.
3. Cool the resulting mass whereby the cream is obtained.

Methotrexate Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
92.00	1	Hydrocarbon gel	920.00
5.00	2	Diisopropanolamine	50.00
3.00	3	Methotrexate	30.00

Manufacturing Directions

Mix diisopropanolamine and methotrexate and stir with gelated hydrocarbon gel, whereby the ointment is obtained. An alternate formulation mixes methotrexate directly into gel with item 2.

Methotrexate Lotion

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Stearic acid	10.00
0.50	2	Behenyl alcohol	5.00
1.00	3	Polyoxyethylene sorbitan monooleate	10.00
1.00	4	Glyceryl monostearate (self-emulsifying type)	10.00
0.10	5	Butyl hydroxybenzoate	1.00
0.10	6	Methyl hydroxybenzoate	2.00
5.00	7	1,3-Butylene glycol	50.00
1.00	8	Carboxyvinyl polymer	10.00
3.00	9	Methotrexate	30.00
5.00	10	Diisopropanolamine[a]	50.00
QS	11	Water purified	QS to 1 kg

[a]May be omitted.

Manufacturing Directions

1. Mix diisopropanolamine and methotrexate with a portion of purified water.
2. Mix the resulting aqueous mixture under heat with a liquid mixture of stearic acid, behenyl alcohol, polyoxyethylene sorbitan monostearate, glyceryl monostearate, and butyl parahydroxybenzoate and also with an aqueous mixture of methyl parahydroxybenzoate, 1,3-butylene glycol, and another portion of the purified water.
3. Cool the resulting mixture to room temperature and mix with a water-base dispersion of carboxyvinyl polymer in the remaining water, whereby the lotion is obtained.

Methoxsalen Lotion

Each milliliter of lotion contains 10 mg methoxsalen in an inert vehicle containing alcohol (71% v/v), propylene glycol, acetone, and purified water.

Methyl Salicylate and Menthol Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
130.00	1	Methyl salicylate	130.00
60.00	2	Menthol	60.00
20.00	3	Eucalyptus oil	20.00
5.00	4	Lanolin	5.00
1.00	5	Chloroxylenol	1.00
150.00	6	Glyceryl stearate and PEG-100 stearate	150.00
73.00	7	Cetearyl alcohol	73.00
70.00	8	Glyceryl stearate	70.00
QS	9	Deionized water	QS to 1 kg
QS	10	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 30°C.

Methyl Salicylate and Menthol Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
110.00	1	Methyl salicylate	110.00
50.00	2	Menthol	50.00
200.00	3	Lutrol E 400	200.00
60.00	4	Cremophor RH 40	60.00
70.00	5	Propylene glycol pharma	70.00
320.00	6	Lutrol F 127	320.00
190.00	7	Water	190.00

Manufacturing Directions

1. Dissolve item 6 in solution of items 1 to 5 and mix with item 7.
2. The clear gel can be diluted with water. Because of the high concentration of the active ingredients and of Lutrol F 127, the consistency of the colorless clear gel is extremely hard. By reducing the concentration of the active ingredients, the amount of Lutrol F 127 could be reduced too and the consistency of the gel will be normal.

Methyl Salicylate and Menthol Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Methyl salicylate	150.00
70.00	2	Menthol	70.00
10.00	3	Lanolin oil	10.00
30.00	4	PEG-40 stearate	30.00
20.00	5	Glyceryl stearate	20.00
QS	6	Deionized water	QS
1.50	7	Carbopol 980	1.50
10.00	8	Potassium hydroxide (10% aqueous solution)	10.00
QS	9	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases (except potassium hydroxide) separately to 65°C to 70°C.
2. Add water phase to oil phase while stirring. Add potassium hydroxide solution to neutralize.
3. Stir to cool. Fill at 30°C.

Methyl Salicylate and Menthol Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Polawax	150.00
100.00	2	Methyl salicylate	100.00
50.00	3	Menthol	50.00
100.00	4	Mineral oil 70 cS	100.00
QS	5	Deionized water	QS to 1 kg
QS	6	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water to oil phase while stirring. Stir to cool. Fill at 30°C.

Methyl Salicylate Clear Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
25.00	1	Hydroxypropyl cellulose	25.00
QS	2	Deionized water	QS to 1 kg
400.00	3	Ethanol DEB 100	400.00
100.00	4	Menthol	100.00
150.00	5	Methyl salicylate	150.00
25.00	6	DEA-oleth-3-phosphate	25.00

Manufacturing Directions

1. Hydrate hydroxypropyl cellulose in water at 60°C to 65°C.
2. Stir to cool. Add ethanol.
3. Add remaining ingredients and stir until homogenous.

Methyl Salicylate Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
30.00	1	Tromethamine magnesium aluminum silicate (Veegum PRO)	30.00
30.00	2	Hydroxypropyl cellulose	30.00
350.00	3	Deionized water	350.00
350.00	4	Ethanol	350.00
40.00	5	Cocoyl sarcosine (Vanseal CS)	40.00
25.00	6	Oleath-10	25.00
25.00	7	PEG-25 hydrogenated castor oil	25.00
50.00	8	Isopropyl myristate	50.00
20.00	9	Triethanolamine	20.00
5.00	10	Camphor	5.00
5.00	11	Menthol	5.00
2.00	12	Eucalyptus oil	2.00
65.00	13	Methyl salicylate	65.00
QS	14	Preservatives	QS

Manufacturing Directions

1. Dry blend items 1 and 2 and slowly add them to items 2 and 4, agitating to ensure homogenous dispersion.
2. Combine items 5 to 9 separately and items 10 to 14 separately and mix them together. Add this mixture to the first mix and then mix until uniform.

Methyl Salicylate Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
15.00	1	Magnesium aluminum silicate (Veegum)	1.50
547.00	2	Deionized water	54.70
2.00	3	Simethicone emulsion	0.20
30.00	4	Propylene glycol	3.00
150.00	5	Methyl salicylate	15.00
50.00	6	Menthol	5.00
6.00	7	Polysorbate	0.60
50.00	8	C18-C36 acid	5.00
150.00	9	Glyceryl stearate and PEG-100 stearate	15.00
QS	10	Preservatives	QS

Manufacturing Directions

1. Add item 1 slowly to water and mix vigorously to smooth dispersion.
2. Add items 3 and 4, mixing one at a time. Heat to 75°C to 80°C.
3. Separately mix and heat items 5 to 9 to 75°C to 80°C and add the two parts while mixing. Cool while mixing and add item 10 at 40°C.

Methyl Salicylate Heat Rub Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
25.00	1	PPG-5-Cetech-10-phosphate (Crodafos SG)	25.00
40.00	2	Emulsifying wax, NF (Polawax)	40.00
45.00	3	PPG-1 cetyl ether (Procetyl 10)	45.00
10.00	4	Menthol	10.00
10.00	5	Camphor	10.00
75.00	6	Methyl salicylate	75.00
30.00	7	Glycerin	30.00
10.00	8	Gelatin, NF (Crodyne BY-19)	10.00
3.00	9	Diethanolamine	3.00
742.00	10	Deionized water	742.00
10.00	11	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	10.00

Manufacturing Directions

1. Premix items 4, 5, and 6 with item 3.
2. When completely dissolved, add items 1 and 2 and heat to 75°C to 80°C.
3. Dissolve item 8 in water and add items 7 and 9.
4. Heat to 80°C. Slowly add this part to previous part using good mechanical mixing.
5. Allow to cool while mixing to 40°C and then add item 11.
6. Cool to 30°C and fill.

Methyl Salicylate Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
25.00	1	PPG-5-cetech-10-phosphate (Crodafos SG)	25.00
40.00	2	Emulsifying wax NF (Polawax)	40.00
45.00	3	PPG-1 cetyl ether (Procetyl 10)	45.00
10.00	4	Menthol	10.00
10.00	5	Camphor	10.00
75.00	6	Methyl salicylate	75.00
30.00	7	Glycerin	30.00
10.00	8	Gelatin (Crodyne BY-19)	10.00
3.00	9	Diethanolamine	3.00
742.00	10	Deionized water	742.00
10.00	11	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	10.00

Manufacturing Directions

1. Premix items 4, 5, and 6 with item 3.
2. When completely dissolved, add items 1 and 2 and heat to 75°C to 80°C.
3. Dissolve item 8 in water and add items 7 and 9.
4. Heat to 80°C. Add this part to previous part slowly, using good mechanical mixing.
5. Allow to cool while mixing to 40°C and then add item 11. Cool to 30°C and fill.

Methyl Salicylate, Thyme, Pine, and Menthol Foot Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Lanolin	5.00
90.00	2	Stearic acid	90.00
5.00	3	Cetyl alcohol	5.00
40.00	4	Isopropyl palmitate	40.00
10.00	5	Oleyl alcohol	10.00
20.00	6	Mineral oil and lanolin alcohol (liquid base CB3929)	20.00
7.50	7	Oil of wintergreen	7.50
3.00	8	Oil of thyme	3.00
5.00	9	Oil of pine	5.00
5.00	10	Menthol	5.00
5.00	11	Camphor	5.00
QS	12	Deionized water	QS to 1 kg
80.00	13	Glycerin	8.00
18.00	14	Triethanolamine 99%	1.80
QS	15	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately at 65°C to 70°C.
2. Add water phase to oil phase while stirring. Add the triethanolamine dropwise.
3. Stir to cool. This product can be used as a disinfectant and soothing cream for the feet.

Metoclopramide Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
005.00	1	Metoclopramide (5.0% excess)	5.25
894.75	2	Hard fat (Suppocire AM)	894.75
QS	3	Ethanol 95%[a]	35.00

[a]To be evaporated during manufacturing process.

Manufacturing Directions

1. Load item 2 in the fat-melting vessel and heat to 65°C ± 2°C.
2. Transfer the molten mass in a stainless steel container through clean polyester cloths.
3. Wash the mixer with purified water (65°C ± 2°C). Set the temperature to 65°C ± 2°C. Transfer the molten mass to the mixer.
4. Heat 32.5 g of item 3 in a stainless steel container using a water bath at 65°C ± 2°C.
5. Dissolve item 1 in hot item 3 (step 4) by a stirrer. Maintain temperature at 65°C.
6. Add the ethanol–drug solution to the molten suppository base in mixer at 65°C ± 2°C while mixing.
7. Wash the drug container with 2.5 g of hot item 3 (65°C ± 2°C) and add the rinsing to the mixer while mixing.
8. Set the mixer under vacuum with air circulation. Maintain temperature at 50°C ± 2°C, mixing 10 rpm manual mode. Homogenize under vacuum with air circulation at temperature 50°C ± 2°C for 1 hour 45 minutes.
9. After completion of evaporation, continue the mixing of the mass under vacuum 0.4 to 0.6 bar while cooling it to 40°C ± 2°C.
10. Heat the storage vessel, set temperature at 40°C ± 2°C.
11. Transfer the molten mass from the mixer to the storage vessel.
12. Hold the molten mass 40°C ± 2°C while mixing continuously at low speed.
13. Fill 900 mg/suppository.

Metoclopramide Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
10.00	1	Metoclopramide (5% excess)	10.50
1339.50	2	Hard fat (Suppocire AM)	1339.50
QS	3	Ethanol 95%[a]	62.00

[a]To be evaporated during manufacturing process.

Manufacturing Directions

1. Load item 2 in the fat-melting vessel and heat to 65°C ± 2°C.
2. Transfer the molten mass in a stainless steel container through clean polyester cloths.
3. Wash the mixer with purified water (65°C ± 2°C). Set the temperature to 65°C ± 2°C. Transfer the molten mass to the mixer.
4. Heat 57 g of item 3 in a stainless steel container using a water bath at 65°C ± 2°C.
5. Dissolve item 1 in hot item 3 (step 4) by a stirrer. Maintain temperature at 65°C.
6. Add the ethanol–drug solution to the molten suppository base in the mixer at 65°C ± 2°C while mixing.
7. Wash the drug container with 5 g of hot item 3 (65°C ± 2°C) and add the rinsing to the mixer while mixing.
8. Set the mixer under vacuum with air circulation. Maintain temperature at 50°C ± 2°C, mix, homogenize under vacuum with air circulation at temperature 50°C ± 2°C for 1 hour 45 minutes.
9. After completion of evaporation, continue the mixing of the mass under vacuum 0.4 to 0.6 bar while cooling to 40°C ± 2°C.
10. Heat the storage vessel, set temperature at 40° ± 2°C.
11. Transfer the molten mass from mixer to the storage vessel.
12. Hold the molten mass at 40°C ± 2°C while mixing continuously at low speed.
13. Fill 1350 mg/suppository.

Metoclopramide Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
20.00	1	Metoclopramide (5% excess)	21.00
1779.00	2	Hard fat (Suppocire AM)	1779.00
QS	3	Ethanol 95%[a]	90.00

[a]To be evaporated during manufacturing process.

Manufacturing Directions

Fill weight: 1800 mg/suppository.

Precaution: The molten suppository mass must be kept under stirring throughout the storage period, during manufacturing, and during filling to avoid the sedimentation of the active drug.

1. Load item 2 in the fat-melting vessel and heat to 65°C ± 2°C.
2. Transfer the molten mass in a stainless steel container through clean polyester cloths.
3. Wash the mixer with purified water (65±2°C). Set the temperature to 65°C ± 2°C. Transfer the molten mass to the mixer.
4. Heat 82.5 g of item 3 in a stainless steel container using a water bath at 65°C ± 2°C.
5. Dissolve item 1 in hot item 3 (step 4) by a stirrer. Maintain temperature at 65°C.
6. Add the ethanol–drug solution to the molten suppository base in the mixer at 65°C ± 2°C while mixing.
7. Wash the drug container with 7.5 g of hot item 3 (65°C ± 2°C) and add the rinsing to the mixer while mixing.
8. Set the mixer under vacuum with air circulation. Maintain temperature at 50°C ± 2°C, homogenize under vacuum with air circulation at temperature 50° ± 2°C for 1 hour 45 minutes.
9. After completion of evaporation, continue the mixing of the mass under vacuum 0.4 to 0.6 bar while cooling to 40°C ± 2°C.
10. Heat the storage vessel, set temperature at 40°C ± 2°C.
11. Transfer the molten mass from mixer to the storage vessel.
12. Hold the molten mass at 40°C ± 2°C while mixing continuously at low speed.
13. Fill 1800 mg/suppository.

Metoclopramide Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
10.00	1	Metoclopramide base 5% excess	10.50
1339.00	2	Suppocire AM	1339.00
QS	3	Alcohol	QS

Manufacturing Directions

1. Add and melt item 2 in a melting vessel at 65°C. Transfer to mixing vessel through filter sieve at 65°C.
2. Heat item 3 to 65°C in a separate vessel and add item 1 to dissolve. Add to step 1.
3. Set mixing vessel under vacuum with air circulation and at 50°C. Homogenize at speed II.
4. Completely evaporate alcohol and continue to mix at 0.4 to 0.6 bar and cool down to 40°C.
5. Fill suppository mold.

Metronidazole Cream

The topical cream contains metronidazole USP at a concentration of 7.5 mg/g (0.75%) in an emollient cream consisting of emulsifying wax, sorbitol solution, glycerin, isopropyl palmitate, benzyl alcohol, lactic acid or sodium hydroxide to adjust pH, and purified water. Metronidazole is a member of the imidazole class of antibacterial agents and is classified therapeutically as an antiprotozoal and antibacterial agent. For metronidazole cream, 1%, each gram contains 10 mg micronized metronidazole USP in a base of purified water USP, stearic acid NF, glyceryl monostearate NF, glycerin USP, methyl paraben NF, trolamine NF, and propyl paraben NF.

Metronidazole Gel Solution

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Metronidazole	10.00
5.00	2	Hydroxy-beta-cyclodextrin	50.00
0.15	3	Methyl paraben	1.50
0.03	4	Propyl paraben	0.30
5.00	5	Glycerin	50.00
1.50	6	Hydroxyethyl cellulose	15.00
0.05	7	Disodium edetate	0.50
QS	8	Water purified	QS to 1 kg

Metronidazole Lotion

Metronidazole lotion contains metronidazole USP at a concentration of 7.5 mg/g (0.75% w/w) in a lotion consisting of benzyl alcohol, carbomer 941, cyclomethicone, glycerin, glyceryl stearate, light mineral oil, PEG-100 stearate, polyethylene glycol 400, potassium sorbate, purified water, steareth-21, stearyl alcohol, and sodium hydroxide or lactic acid to adjust pH. Metronidazole is an imidazole and is classified therapeutically as an antiprotozoal and antibacterial agent.

Metronidazole Vaginal Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.20	1	Metronidazole	1.20
21.00	2	Lutrol F 127	21.00
40.00	3	Lutrol E 400	40.00
37.80	4	Water purified	37.80

Manufacturing Directions

1. Heat mixture of items 1 to 3 to 70°C to 80°C and slowly add the water heated to approximately 70°C.
2. Maintain the temperature until the air bubbles disappear.

Miconazole Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.00	1	Cetostearyl alcohol	70.00
1.50	2	Cremophor A6	15.00
1.50	3	Cremophor A 25	15.00
12.00	4	Liquid paraffin	120.00
0.10	5	Parabens mixture	1.00
67.80	6	Water purified	678.00
8.00	7	Propylene glycol	80.00
2.00	8	Miconazole nitrate	20.00

Manufacturing Directions

1. Heat the mixture of items 1 to 5 and the water separately to approximately 80°C.
2. Add the water to the obtained solution with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with step 2, and continue to stir during cooling to room temperature.

Miconazole Mouth Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.00	1	Miconazole nitrate	20.00
0.10	2	Orange flavor	1.00
20.00	3	Lutrol F 127	200.00
10.00	4	Cremophor RH 40	100.00
10.00	5	Propylene glycol	100.00
5.00	6	Kollidon 90F	50.00
0.30	7	Saccharin sodium	3.00
52.60	8	Water purified	526.00

Manufacturing Directions

1. Dissolve items 1 and 2 in the molten mixture of items 3 and 4.
2. Heat solution of items 6 to 8 to 90°C and mix slowly with step 1.
3. Let cool to room temperature when the air bubbles have escaped.

Miconazole Nitrate Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
21.00	1	Miconazole nitrate (5% excess)	21.00
200.0	2	Tefose 63	200.0
30.00	3	Labrafil M[a]	30.00
30.00	4	Mineral oil (liquid paraffin)	30.00
0.05	5	Butylated hydroxyanisole	0.05
2.00	6	Benzoic acid	2.00
720.00	7	Purified water	720.00

[a]Synonyms: Labrafil M 1944 CS, oleoyl macrogolglycerides, apricot kernel oil PEG-6 complex.

Manufacturing Directions

1. Melt items 2, 3, and 4 (fatty phase) in fat-melting vessel.
2. Heat to 65°C to 70°C.
3. Disperse items 5 and 1 in the fatty phase while mixing at high speed for 20 minutes.
4. Add item 7 to the mixer and heat to 80°C to 90°C.
5. Dissolve item 6 and cool down to 65°C to 70°C.
6. Transfer the fatty phase to the mixer with vacuum at 0.2 to 0.3 bar.
7. Start cooling down while mixing at 10 rpm and homogenize at high speed for 20 minutes, then cool down to 25°C to 28°C while mixing at a vacuum of 0.2 to 0.3 bar (65–45°C) or 0.5 to 0.7 bar (45–25°C).

Miconazole Nitrate Vaginal Suppositories

Bill of Materials			
Scale (mg/ovule)	Item	Material Name	Qty/1000 Ovules (g)
200.00	1	Miconazole nitrate micronized	200.00
1250.00	2	Hard fat (Witepsol H 37)	1250.00
1250.00	3	Hard fat (Witepsol H 35®)	1250.00

Manufacturing Directions

Fill weight: 2700 mg/ovule. The following are additional requirements: All particle sizes must be below 30 μm and 60% to 80% must be less than 20 μm.

Precaution: The molten suppository mass must be kept under stirring throughout the storage period, during the manufacturing, and during filling to avoid the sedimentation of the active drug. Check the molten witepsols for phase separation by draining approximately 18 to 37 mL of molten witepsols in a glass beaker.

1. Load items 2 and 3 in the fat-melting vessel and heat to 50°C ± 3°C.
2. Check the molten mass for phase separation.
3. Transfer the molten mass to the mixer through filter sieves. Set the temperature at 40°C ± 2°C.
4. Load item 1 to the mixer containing molten Witepsol (items 2 and 3).
5. Carefully mix the powder with the Witepsol melt.
6. Set the mixer at temperature 40°C ± 2°C, speed 10 rpm (manual mode), and mix for 10 minutes.
7. Set the mixer at temperature 40°C ± 2°C, speed 10 rpm (manual mode), vacuum 0.6 bar.
8. Homogenize at low speed while mixing for 5 minutes.
9. Homogenize at high speed while mixing for 3 minutes.
10. Continue mixing of the mass under vacuum in mixer.
11. Heat the storage vessel, set the temperature at 40°C ± 2°C.
12. Transfer the molten mass from the mixer to the storage vessel.
13. Hold the mass at 40°C ± 2°C, while mixing continuously at low speed. Fill.

Miconazole Nitrate Vaginal Suppositories (400 mg)

Bill of Materials			
Scale (mg/ovule)	Item	Material Name	Qty/1000 Ovules (g)
400.00	1	Miconazole nitrate micronized	200.00
1150.00	2	Hard fat (Witepsol H 37)	1250.00
1150.00	3	Hard fat (Witepsol H 35)	1250.00

Manufacturing Directions

1. Load items 2 and 3 in the fat-melting vessel and heat to 50°C ± 3°C.
2. Check the molten mass for phase separation.
3. Transfer the molten mass to the mixer through filter sieves. Set the temperature at 40°C ± 2°C.
4. Load item 1 to the mixer containing molten Witepsol (items 2 and 3).
5. Carefully mix the powder with the Witepsol melt.
6. Set the mixer at temperature 40°C ± 2°C, speed 10 rpm (manual mode), and mix for 10 minutes.
7. Set the mixer at temperature 40°C ± 2°C, mix under vacuum 0.6 bar.
8. Homogenize at low speed while mixing for 5 minutes.
9. Homogenize at high speed while mixing for 3 minutes.
10. Continue mixing of the mass under vacuum in mixer.
11. Heat the storage vessel, set the temperature at 40°C ± 2°C.
12. Transfer the molten mass from the mixer to the storage vessel.
13. Hold the mass at 40°C ± 2°C while mixing continuously at low speed. Fill.
14. Fill 2700 mg.

Minoxidil Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20	1	Minoxidil	20
5	2	Carbopol 934	5
5	3	Propylene glycol	5
3	4	Ethanol	3
QS	5	Triethanolamine	QS
2	6	Water	2

Manufacturing Directions

Dissolve minoxidil in the mixture of ethanol:propylene glycol:water in 50:30:20 proportion, adjust pH to 7.4 with triethanolamine and gel the solution by adding 0.5% Carbopol 934 with constant stirring at 900 to 1000 rpm.

Minoxidil Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20	1	Minoxidil	20
40	2	HPMC	40
5	3	Propylene glycol	5
3	4	Ethanol	3
QS	5	Triethanolamine	QS
2	6	Water	2
40	7	HPC	40

Manufacturing Directions

Dissolve minoxidil in the mixture of ethanol:propylene glycol:water in 50:30:20 proportion, adjust pH to 7.4 with triethanolamine and gel the solution by adding 4% HPMC and 4% HPC with constant stirring at 900 to 1000 rpm.

Minoxidil Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20	1	Minoxidil	20
60	2	HPMC	60
5	3	Propylene glycol	5
3	4	Ethanol	3
QS	5	Triethanolamine	QS
2	6	Water	2

Manufacturing Directions

Dissolve minoxidil in the mixture of ethanol:propylene glycol:water in 50:30:20 proportion, adjust pH to 7.4 with triethanolamine and gel the solution by adding 6% HPMC with constant stirring at 900 to 1000 rpm.

Minoxidil Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20	1	Minoxidil	20
80	2	HPC	80
5	3	Propylene glycol	5
3	4	Ethanol	3
QS	5	Triethanolamine	QS
2	6	Water	2

Manufacturing Directions

Dissolve minoxidil in the mixture of ethanol:propylene glycol:water in 50:30:20 proportion, adjust pH to 7.4 with triethanolamine and gel the solution by adding 8% HPC with constant stirring at 900 to 1000 rpm.

Mometasone Furoate Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.20	1	Mometasone furoate micronized	2.00
40.00	2	Isopropyl alcohol	400.00
0.15	3	Hydroxypropyl cellulose	1.50
0.226	4	Sodium acid phosphate	0.226
30.00	5	Propylene glycol	300.00
QS	6	Water purified	QS to 1 kg
QS	7	Phosphoric acid to adjust pH (10% w/v solution)	QS

Manufacturing Directions

1. Charge item 2 to a suitable vessel, add item 1, and mix for 25 minutes to dissolve completely.
2. Add item 3 slowly to step 1 and mix for 15 minutes to disperse evenly.
3. In a separate vessel, dissolve item 4 in a suitable quantity of item 6 and add to step above and mix for 10 minutes. Circulate cold water in the jacket to aid in gel formation.
4. Add item 5 to step above and mix until uniform.
5. Check and adjust the pH to 4.5 ± 0.2 with 10% w/v phosphoric acid solution. Mix the batch for at least 2 hours for pH adjustment and check the final pH.
6. Adjust the volume, pass through 100-mesh screen.
7. Fill in a suitable container.

Mometasone Furoate Lotion

Each gram of cream, 0.1%, contains 1 mg mometasone furoate in a cream base of hexylene glycol, phosphoric acid, propylene glycol stearate, stearyl alcohol and ceteareth-20, titanium dioxide, aluminum starch ocetenylsuccinate, white wax, white petrolatum, and purified water. Each gram of ointment, 0.1%, contains 1 mg mometasone furoate in an ointment base of hexylene glycol, phosphoric acid, propylene glycol stearate, white wax, white petrolatum, and purified water. Each gram of lotion, 0.1%, contains 1 mg of mometasone furoate in a lotion base of isopropyl alcohol (40%), propylene glycol, hydroxypropyl cellulose, sodium phosphate, and water. It may also contain phosphoric acid and sodium hydroxide used to adjust the pH to approximately 4.5.

Monobenzone Cream

Each gram of benoquin cream contains 200 mg monobenzone USP in a water-washable base consisting of purified water USP, cetyl alcohol NF, propylene glycol USP, sodium lauryl sulfate NF, and white wax NF.

Multivitamin Oral Gel Veterinary

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
18,700 IU	1	Vitamin A palmitate1.7 million IU/g (BASF)	1.10
1.06	2	Vitamin E acetate (BASF)	10.60
0.50	3	Butyl hydroxytoluene	500.00
20.00	4	Cremophor RH 40	20.00
725.00	5	Water	725.00
0.35	6	Thiamine hydrochloride (BASF)	3.55
0.03	7	Riboflavin (BASF)	0.35
0.17	8	Pyridoxine hydrochloride (BASF)	1.77
0.03	9	Cyanocobalamin gelatin coated 1%	0.35
0.35	10	Nicotinamide	3.53
0.03	11	Folic acid	0.35
0.35	12	Dexpanthenol (BASF)	3.53
0.30	13	EDTA sodium	3.00
0.43	14	Ferrous sulfate (7 H2 O)	4.38
0.63	15	Manganese chloride (4 H2 O)	6.38
0.11	16	Potassium iodide	1.15
50.00	17	Kollidon 90 F	50.00
100.00	18	Lutrol F 127	100.00
100.00	19	Lutrol F 127	100.00

Manufacturing Directions

1. Heat mixture of items 1to 4 to approximately 60°C to obtain a clear solution and slowly add the water (item 5) to the well-stirred solution.
2. Dissolve items 6 to 16 and item 17 separately in this mixed solution at room temperature, cool to approximately 6°C, add item 19, and stir until all Lutrol F 127 is dissolved.
3. Maintain the cool temperature until the air bubbles have escaped.

Multivitamin Oral Gel with Linoleic and Linolenic Acid

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/100 mL (g)
0.050	1	Evening primrose oil (EPO Pure, Prima Rosa/SA)	5.0 mL
0.30	2	Vitamin A palmitate 1.7 million IU/g (BASF)	0.30
0.190	3	Vitamin E acetate (BASF)	0.19
0.00150	4	Vitamin D_3 40 million IU/g	150 μg
200.00	5	Cremophor RH 40	20.0
550.00	6	Water	55.0
0.030	7	Thiamine hydrochloride (BASF)	0.03
0.030	8	Riboflavin (BASF)	0.03
0.150	9	Pyridoxine hydrochloride (BASF)	0.15
0.001	10	Cyanocobalamin, crystalline	10 μg
0.001	11	Calcium D-pantothenate (BASF)	0.10
0.005	12	Nicotinamide	0.50
10.00	13	Ascorbic acid, crystalline (BASF)	1.0
140.00	14	Lutrol F 127	14.0
50.00	15	Lutrol F 127	5.0

Manufacturing Directions

1. Prepare mixture of items 1to 5 and heat to approximately 65°C.
2. Add the warm water (item 6 at 65°C) slowly to the well-stirred mixture as before.
3. Dissolve items 7 to 14 at 20°C to 25°C in this clear solution.
4. Cool the obtained solution to approximately 5°C and dissolve the rest of Lutrol F 127 item 15.
5. Maintain the cool temperature until the air bubbles have escaped.
6. A clear yellow gel was obtained. 5 mL of evening primrose oil epopure contains 3.5 g linoleic acid and 0.45 g gamma-linolenic acid.

Mupirocin Calcium Cream

Mupirocin calcium cream 2% contains the dihydrate crystalline calcium hemisalt of the antibiotic mupirocin. Cream is a white cream that contains 2.15% w/w mupirocin calcium (equivalent to 2.0% mupirocin free acid) in an oil- and water-based emulsion. The inactive ingredients are benzyl alcohol, cetomacrogol 1000, cetyl alcohol, mineral oil, phenoxyethanol, purified water, stearyl alcohol, and xanthan gum.

Mupirocin Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.00	1	Mupirocin crystalline USE mupirocin calcium dihydrate equivalent	20.00
1.00	2	Hydrocortisone	10.00
87.30	3	White soft paraffin	873.00
4.85	4	Softisan 649	48.50

Manufacturing Directions

1. Heat appropriate proportions of white soft paraffin and Softisan 649 together to meet at 60°C to 70°C.
2. Mix thoroughly.
3. Allow to cool with stirring to room temperature.
4. Add items 2 and 3 with stirring.
5. Pass ointment through a mill (such as triple roller mill).

Mupirocin Ointment

Each gram of mupirocin ointment, 2%, contains 20 mg mupirocin in a bland water-miscible ointment base (polyethylene glycol ointment NF) consisting of polyethylene glycol 400 and polyethylene glycol 3350. Mupirocin is a naturally occurring antibiotic. The nasal ointment, 2%, contains the dihydrate crystalline calcium hemisalt of the antibiotic mupirocin. It is a white to off-white ointment that contains 2.15% w/w mupirocin calcium (equivalent to 2% pure mupirocin free acid) in a soft, white ointment base. The inactive ingredients are paraffin and a mixture of glycerin esters (Softisan®).

Naftifine Hydrochloride Cream

The cream, 1%, contains the synthetic, broad-spectrum antifungal agent naftifine hydrochloride. It is for topical use only. The active ingredient is naftifine hydrochloride, 1%; the inactive ingredients are benzyl alcohol, cetyl alcohol, cetyl esters wax, isopropyl myristate, polysorbate 60, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol. Hydrochloric acid may be added to adjust pH.

Naftifine Hydrochloride Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
39.00	1	Urea	390.00
0.15	2	Carbopol 940	1.50
5.94	3	Petrolatum	59.40
12.06	4	Mineral oil	120.60
1.875	5	Glyceryl stearate	187.50
0.626	6	Cetyl alcohol	6.26
3.00	7	Propylene glycol	30.00
0.05	8	Xanthan gum	0.50
0.15	9	Trolamine	1.50
1.00	10	Naftifine hydrochloride[a]	10.00

[a]This formulation can serve as a generic formula for topical antifungals.

Nanoxynol Suppository with Bacterial Culture

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
125.00	1	Benzalkonium chloride or methyl benzethonium chloride	125.00
110.00	2	Imidiazolidinyl urea	110.00
11.00	3	Diazolidinyl urea	11.00
400.00	4	Hydroxypropylmethylcellulose	400.00
200.00	5	Microcrystalline cellulose	200.00
100.00	6	Ascorbic acid	100.00
110.00	7	Nanoxynol 9	110.00
QS	8	Lactic acid for pH adjustment	QS
1 million	9	Encapsulated lactobacilli (bacteria)[a]	1 billion
30.00	10	Magnesium stearate	30.00
30.00	11	Silicon dioxide	30.00
30.00	12	Lactose	30.00
QS	13	Sterile normal saline	QS

[a]Encapsulation methods: Viable lyophilized lactobacilli bacteria that have been lyophilized after the removal of the media are used for encapsulation. The organisms are grown to log phase in nutrient media. The removal of the nutrient media is done by centrifugation at 14,000 *g* at 0°C to 4°C and then washing with sterile, balanced salts and 5% glucose solution at least 3 times after the initial centrifugation. The bacteria are then "snap frozen" with liquid nitrogen and lyophilized under high vacuum. The freshly obtained, washed, and lyophilized bacteria are suspended in 10 mL of 5% glucose saline solution in such volume so as to obtain a heavy suspension of bacteria that contains between 1 and 10 billion organisms per milliliter at 0°C to 4°C. The suspension of bacteria is rapidly, but gently, stirred while 0.2 to 0.4 mL of sodium alginate solution (1.5% weight by volume) is added. The above mixture is then transferred into a 4-L round-bottom flask by using a nitrogen stream through a sheathed 14-gauge needle. The 4-L round-bottom flask was previously washed with a 5% albumin solution and, thereafter, heated for at least 10 hours at 65°C, and the needle and the tubing used in the process have also been treated this way. Thereafter, the above mixture is forced through a 30-gauge multibeveled needle under pressure, using a large syringe and nitrogen stream. Very small droplets are generated at the end of the needle, which are dried by the nitrogen and airstream around the 30-gauge needle, and the droplets are collected in an aqueous solution of 1.3 to 2% calcium chloride, where they gel. Thereafter, they are washed at least three times with 0.08 to 0.13% 2-(N-cyclohexyl-amino) ethanesulfonic acid (CHES) solution and 1.0 to 1.5% calcium chloride solution. The gelled droplets or little spheres are further washed with at least a fivefold excess of the 0.1% CHES 1.1% calcium chloride and normal saline solution. The resultant spheres are then "snap frozen" in liquid nitrogen and then lyophilized. After these steps, the encapsulated organisms can be used in the formulation below.

Manufacturing Directions

1. The benzalkonium chloride or methylbenzethonium chloride, imidiazolidinyl urea, and diazolidinyl urea are added slowly, while thoroughly stirring, to a suspension of hydroxypropylmethylcellulose and microcrystalline cellulose in a sterile normal saline solution (quantity sufficient to make a thick paste) at 35°C to 37°C.
2. The pH is slowly lowered to approximately 6.0 to 6.3 with reagent grade lactic acid. (This step binds the antimicrobials to the "cellulose" excipients.)
3. The suspension is stirred for 2 hours and then ascorbic acid that was dissolved in approximately 10 to 15 mL sterile saline is slowly added with gentle stirring.
4. The material is, at this point, a very thick paste. Spermicide (Nonoxynol 9) is now added and thoroughly mixed. After this step, the process is performed at 0°C to 4°C.
5. The pH of the mixture is then lowered to 4.3 to 4.5 with reagent-grade lactic acid.
6. Then freshly obtained encapsulated lactobacilli bacteria are added to achieve a final concentration of at least 1 million viable bacteria per suppository. (In as much as the goal is to achieve a final concentration of at least 1 million viable bacteria per suppository, a four- to sixfold excess of bacteria are usually added because some loss of the viability occurs during the various mixing processes. This means that approximately 500 mg of the encapsulated bacteria are usually added.) It is important to mix these organisms not only thoroughly to ensure uniformity but also quickly because moisture adversely affects the viability of the organisms.
7. Rapid and thorough mixing can be done, for example, by spreading the paste in a thin layer on a sterile glass plate and then using a replicator to spread the bacteria evenly over the paste.
8. Magnesium stearate and silicon dioxide are added, with or without lactose.
9. After the materials are thoroughly mixed at 0°C to 4°C, they are pressed into a mold and dried in a desiccating jar under vacuum at 0°C to 4°C. [Drying at room temperature (25°C) or at higher temperatures decreases the number of viable bacteria.]
10. The suppositories are then sealed in air- and moisture-proof containers until used. During storage they should be protected from moisture and extreme temperatures to ensure the viability of the lactobacilli.

Neomycin and Bacitracin Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
50,000 IU	1	Bacitracin zinc, 8% excess (69 IU/mg)	7.80
0.50	2	Neomycin sulfate, 8% excess	5.40
85.00	3	White soft paraffin	850.00
5.00	4	Hard paraffin	50.00
10.00	5	Liquid paraffin	100.00
0.10	6	Edetate disodium	1.00

Manufacturing Directions

1. Charge items 3 and 4 and half of item 5 in a melting vessel and heat to 100°C; bubble nitrogen gas to remove moisture and reduce oxygen load.
2. In a separate vessel, charge balance of item 5 and mix items 1 and 2 to make a paste.
3. Add step 2 to step 1 and mix at 30°C for 2 hours.

Neomycin Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.50	1	Neomycin sulfate	0.50
50.00	2	Propylene glycol	50.00
5.00	3	Parabens	5.00
200.00	4	Lutrol F 127	200.00
745.00	5	Water	745.00

Manufacturing Directions

1. Dissolve the parabens and Lutrol F 127 in water heated to approximately 80°C.
2. Add the propylene glycol and dissolve neomycin sulfate.
3. Either cool to room temperature when the air bubbles escape or dissolve parabens in hot water, cool to 5°C to 10°C, dissolve Lutrol F 127, add propylene glycol, and dissolve neomycin sulfate.
4. Maintain the cool temperature until the air bubbles have escaped.

Neomycin, Polymyxin B Sulfate, and Bacitracin Zinc Opthalmic Ointment

The neomycin and polymyxin B sulfates and bacitracin zinc ophthalmic ointment is a sterile antimicrobial ointment for ophthalmic use. Each gram contains neomycin sulfate equivalent to 3.5 mg neomycin base, polymyxin B sulfate equivalent to 10,000 polymyxin B units, bacitracin zinc equivalent to 400 bacitracin units, and white petrolatum, QS.

Nicotine Polymer Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
66.70	1	N-30 PVP	667.00
28.60	2	Lauryl methylacrylate	286.00
5.00	3	Sodium stearate	50.00
1.25	4	Hydrogen peroxide (30%)	12.50
QS	5	Water purified	QS to 1 kg

Manufacturing Directions

1. The emulsion copolymerization of 66.7 parts N-30 vinyl pyrrolidone and 28.6 parts lauryl methacrylate is carried out in 200 parts water containing 5 parts sodium stearate and 1.25 parts 30% hydrogen peroxide as catalyst.
2. The mixture is heated with stirring and the polymerization is carried out at 75°C for approximately 10 hours. The conversion is approximately 92%.
3. The emulsion is spray dried at approximately 210°C to yield a fine off-white powder.
4. The nitrogen content of the copolymer is 8.6%, indicating an item 1 content of 68%.
5. A gel base is prepared by vigorously mixing the following ingredients (in parts by weight): copolymer prepared above, 6.75; propylene glycol, hydroxypropyl cellulose, isopropyl myristate, stearic acid, cetyl alcohol, fumed silica, 12.45; and ethanol, 80.80. The resultant gel has a viscosity of 12,000 cps and a specific gravity of 0.8.
6. To 40 g of the above gel is added 140 mg nicotine. Mix thoroughly to obtain a composition containing 3.5 mg/g (2.8 mg/mL).

Nitrofurazone Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.20	1	Nitrofurazone, 4% excess	2.08
7.20	2	Cetostearyl alcohol	72.00
1.80	3	Cetomacrogol 1000	18.00
6.00	4	Liquid paraffin	60.00
15.00	5	White soft paraffin	150.00
1.00	6	Propylene glycol	10.00
0.020	7	Chlorocresol	0.20
69.00	8	Water purified	690.00

Manufacturing Directions

1. Charge items 3, 4, 5 (90%), and 6 in a melting vessel after passing it through a stainless steel sieve and heat to melt. In a separate vessel, heat two-thirds of item 9 to 50°C and dissolve item 8 in it. Add to step 1.
2. Add and mix item 1 with item 5 (balance) and add to step 2.
3. Fill.

Nondetergent Neutral Dry Skin Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
60.00	1	Stearic acid	60.00
145.00	2	White petrolatum jelly	145.00
116.00	3	Mineral oil (25 cS)	116.00
10.00	4	Lanolin	10.00
20.00	5	Cetearyl alcohol	20.00
QS	6	Deionized water	QS to 1 kg
14.00	7	Triethanolamine (99%)	14.00
QS	8	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool, adding triethanolamine at 60°C and perfuming at 40°C to 50°C.
4. This cream serves as a base for drugs as well.
5. Triethanolamine may be omitted, because it gives a higher pH.

Nystatin Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
80.00	1	Cetostearyl alcohol	80.00
20.00	2	Polyoxyl 20 cetostearyl ether (Cetomacrogol 1000)	20.00
80.00	3	Mineral oil (liquid paraffin)	80.00
2.00	4	Methyl paraben	2.00
100,000 IU	5	Nystatin microfine[a] (30% excess) 5420 IU/mg	24.00
1.00	6	Propyl paraben	1.00
100.00	7	Propylene glycol	100.00
4.86	8	Dibasic sodium phosphate	4.86
2.36	9	Monobasic sodium phosphate	2.36
180.00	10	Petrolatum (soft white paraffin)	180.00
506.00	11	Purified water	506.00

[a]Particle size NLT 90% less than 45 μm and 100% less than 80 μm.

Manufacturing Directions

1. Charge item 3 to the fat-melting vessel.
2. Heat to 70°C while stirring.
3. Charge items 1, 2, and 10 to the fat-melting vessel while stirring.
4. Mix well and maintain the temperature at 65°C to 70°C.
5. Load 466 g of item 11 and item 7 into mixer and heat to 90°C.
6. Add items 4 and 6 to dissolve while stirring on manual mode.
7. Mix for 15 minutes at 10 rpm.
8. Cool to 65°C to 70°C.
9. Add items 8 and 7 to the parabens solution to dissolve.
10. Mix for 5 to 10 minutes at 10 rpm.
11. Maintain temperature at 65°C to 70°C.
12. Take a sample of approximately 0.40 mL from mixer and cool to 25°C.
13. Check the pH (6.3–7.0).
14. Withdraw 80 g of preservative/buffer solution from mixer at 65°C to 70°C in a stainless steel container.
15. Cool the solution in stainless steel container to 30°C to 35°C.
16. Disperse item 5 carefully using a spatula.
17. Homogenize using homogenizer to make a smooth dispersion.
18. Transfer the molten fat to the mixer containing the preservative/buffer solution through a stainless steel sieve by vacuum at 0.6 bar while mixing at 10 rpm in manual mode at a temperature of 65°C.
19. Homogenize and mix the cream for 10 minutes at low speed (10 rpm, manual mode) and vacuum of 0.6 bar.
20. Cool to 40°C ± 5°C.
21. Transfer the 104 g of drug phase (35 ±5°C) to the mixer while mixing.

22. Rinse the stainless steel container of the drug phase with 40 g of item 11 (25–35°C) and transfer to the mixer while mixing.
23. Rinse the homogenizer and the container with item 11 and transfer the rinsing to the mixer.
24. Mix for 5 minutes.
25. Set the mixer at a mixing speed of 10 rpm (manual mode) and the homogenizer at low speed with a vacuum of 0.6 bar.
26. Mix and homogenize for 15 minutes.
27. Cool to 30°C with mixer speed of 10 rpm and vacuum of 0.6 bar.
28. Transfer the cream to a stainless steel drum.

Nystatin Ointment

Bill of Materials			
Scale mg/g	Item	Material Name	Qty/kg (g)
21.05	1	Nystatin microfine[a]	21.05
22.00	2	Cetostearyl alcohol	22.00
8.00	3	Paraffin (hard paraffin)	8.00
100.00	4	Mineral oil (liquid paraffin)	100.00
848.95	5	Petrolatum (white soft paraffin)	848.95

[a]Actual quantity to be calculated as per the actual potency; adjust with soft paraffin. Meets the current USP requirements with following additional requirement: particle size not less than 90% less than 45 μm, 100% less than 80 μm.

Manufacturing Directions

1. Melt items 2, 3, and 5 at 70°C in a fat-melting vessel.
2. Disperse item 1 in 80 g of item 4 in a separate stainless steel container by using a spatula.
3. Pass the dispersion through homogenizer twice, then transfer the dispersion to mixer.
4. Rinse the homogenizer and container with 20 g of item 4 and transfer the rinsings to the mixer.
5. Homogenize the dispersion at high speed for 15 minutes. Set the mixer at 40°C to 45°C.
6. Transfer the molten mass from the fat-melting vessel to the mixer at 45°C to 50°C.
7. Mix for 10 minutes at manual mode and 10 minutes at auto mode at 12 rpm and vacuum 0.4 to 0.6 bar.
8. Homogenize at high speed for 10 minutes with recirculation. Mix until the temperature of the ointment reaches 28°C to 30°C.
9. Transfer the ointment to a stainless steel drum. Keep tightly closed.

Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
22.96	1	Nystatin microfine[a]	22.96
4.43	2	Neomycin sulfate[b]	4.43
0.28	3	Gramicidin[c]	0.28
1.00	4	Triamcinolone acetonide micronized	1.00
80.00	5	Cetostearyl alcohol	80.00
20.00	6	Polyoxyl 20 cetostearyl ether (cetomacrogol 1000)	20.00
80.00	7	Mineral oil (liquid paraffin)	80.00
2.00	8	Methyl paraben	2.00
1.00	9	Propyl paraben	1.00
60.00	10	Propylene glycol	60.00
4.86	11	Dibasic sodium phosphate	4.86
2.36	12	Monobasic sodium phosphate	2.36
180.00	13	Petrolatum (white soft paraffin)	180.00
531.86	14	Purified water	531.86

[a]Actual quantity to be calculated as per the actual potency. Difference in quantity to be adjusted by purified water. Meets current USP requirements with the following additional requirement: particle size NLT 90% less than 45 μm, 100% less than 80 μm.
[b]Meets the current USP requirements with the following additional requirement: particle size 99% less than 20 μm, 75% less than 10 μm.
[c]Meets the current USP requirements with the following additional requirement: particle size 98% less than 50 μm.

Manufacturing Directions

1. Load items 5, 6, 7, and 13 in a fat-melting vessel and heat to 70°C. Stir to melt. Maintain temperature 70°C to 75°C. Heat 420 g of item 14 to 90°C in mixer.
2. Dissolve items 8 and 9 by stirring. Mix for 15 minutes at 10 to 12 rpm.
3. Cool to 65°C to 70°C. Dissolve items 11 and 12 in 71.86 g of item 14 at 40°C to 45°C in a stainless steel drum.
4. Check the pH limit 6.3 to 7.0 (at 25°C).
5. Dissolve item 2 into 79.08 g phosphate solution. The solution should be clear.
6. Disperse item 1 in the neomycin–phosphate solution above.
7. Homogenize twice to make a smooth dispersion. The dispersion should be smooth with no lumps.
8. Add 50 g of item 10 in a separate stainless steel container and heat to 40°C to 45°C, then dissolve item 3 by using homogenizer. The solution should be clear. Disperse item 4 in the clear solution of gramicidin–propylene glycol by using the homogenizer. Homogenize until there are no lumps.
9. Maintain temperature at 40°C to 45°C.
10. Transfer the melt from the step above to the mixer through a stainless steel sieve while mixing at temperature 65°C.
11. Homogenize at high speed for 10 to 12 minutes at 60°C to 65°C, vacuum 0.6 bar. Scrap the sides and blade. Cool down to 50°C. Transfer the homogenized dispersion from the mixer.
12. Rinse the container with 10 g item 10. Add to the mixer and mix for 10 minutes. Transfer the dispersion to the mixer.
13. Rinse the container with 40 g item 14. Add to the mixer and mix for 10 minutes.
14. Homogenize at high speed for 20 minutes at temperature 45°C, mixer speed 10 to 12 rpm, and vacuum 0.6 bar.
15. Cool down to 25°C to 30°C while mixing. Transfer the cream to stainless steel drum.

Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
22.96	1	Nystatin microfine[a]	22.96
4.43	2	Neomycin sulfate[a]	4.43
0.28	3	Gramicidin[a]	0.28
1.00	4	Triamcinolone acetonide micronized	1.00
100.00	5	Mineral oil (liquid paraffin)	100.00
10.00	6	Syncrowax	10.00
861.33	7	Petrolatum (white soft paraffin)	861.33

[a]Actual quantity to be calculated as per the actual potency. Difference in quantity to be adjusted by white soft paraffin.

Manufacturing Directions

1. Melt item 7 at 70°C in a fat-melting vessel.
2. Add item 6 to the melt while mixing. Transfer the melt to the mixer through filters and cool to 40°C while mixing.
3. Add 60 g of item 5 in stainless steel container and disperse item 1 manually by using a spatula. Homogenize 2 times with homogenizer (gap setting 1) to make smooth dispersion and then transfer to the mixer.
4. Add 20 g of item 5 in a stainless steel container and disperse items 2, 3, and 4 by using homogenizer to make a smooth dispersion. Homogenize until no lumps.
5. Transfer the dispersion to the mixer. Rinse the homogenizer and stainless steel container with 20 g of item 5 and transfer the rinsing to the mixer.
6. Mix for 10 minutes, mixer speed 10 rpm, vacuum 0.4 to 0.6 bar, and set thermostat at 28°C to 30°C. Homogenize at high speed for 20 minutes with recirculation.
7. Mix until the temperature of the ointment reaches 28°C to 30°C.
8. Transfer the ointment to a stainless steel drum. Keep tightly closed.

Octyl Methoxycinnamate, Octyl Salicylate, and Oxybenzone Gel

The active ingredients in octyl methoxycinnamate, octyl salicylate, and oxybenzone gel are octyl methoxycinnamate, 7.5%, octyl salicylate, 4%, and oxybenzone, 3%. The inactive ingredients are purified water, C12-15 alkyl benzoate, cetearyl alcohol and ceteareth-20, cetyl alcohol, glyceryl monostearate, propylene glycol, petrolatum, diazolidinyl urea, triethanolamine, disodium ethylene diamine tetraacetate, xanthan gum, acrylates/C10-30 alkyl acrylate crosspolymer, tocopheryl acetate, iodopropynyl butylcarbamate, fragrance, carbomer.

Olibanum Gum Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Gum olibanum powder	50.00
26.00	2	Emulsifying ointment	260.00
0.15	3	Methyl paraben	1.50
0.15	4	Propyl paraben	1.50
QS	5	Water purified	QS to 1 kg

Manufacturing Directions

1. The naturally occurring gum olibanum exudate in dry state is taken as it is.
2. The lumps (1 kg) are powdered in an edge runner mill for 30 minutes.
3. The powdered raw gum olibanum is passed through a 100-mesh sieve.
4. Weighed quantity of the powder is dispersed in appropriate quantity of water along with methyl paraben (0.15%).
5. Weighed quantity of emulsifying ointment is melted in another vessel and propyl paraben (0.15%) is dispersed in it (oily phase).
6. The dispersion containing gum olibanum powder and methyl paraben is also heated to the same temperature as that of emulsifying ointment.
7. The aqueous dispersion containing gum olibanum powder is added to the molten emulsifying ointment and the mixture is stirred continuously at 10,000 rpm for 1 hour using a homogenizer to obtain cream consistency.

Oxiconazole Cream and Lotion

The cream and lotion formulations contain the antifungal active compound oxiconazole nitrate. Both formulations are for topical dermatologic use only. The cream contains 10 mg oxiconazole per gram of cream in a white to off-white, opaque cream base of purified water USP, white petrolatum USP, stearyl alcohol NF, propylene glycol USP, polysorbate 60 NF, and cetyl alcohol NF, with benzoic acid USP 0.2% as a preservative. The lotion contains 10 mg oxiconazole per gram of lotion in a white to off-white, opaque lotion base of purified water USP, white petrolatum USP, stearyl alcohol NF, propylene glycol USP, polysorbate 60 NF, and cetyl alcohol NF, with benzoic acid USP, 0.2%, as a preservative.

Oxymorphone Hydrochloride Suppositories

The rectal suppository is available in a concentration of 5 mg of oxymorphone hydrochloride in a base consisting of polyethylene glycol 1000 and polyethylene glycol 3350.

Oxytetracycline Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.00	1	Oxytetracycline hydrochloride micronized	3.00
93.00	2	White soft paraffin	93.00
3.70	3	Liquid paraffin	3.70
0.02	4	Vitamin E oily	0.02

Manufacturing Directions

1. Charge item 2 in a fat-melting vessel and heat to 75°C.
2. In a separate vessel, add and mix items 1, 3, and 4 and mix manually using a spatula.
3. Transfer step 1 to Becomix through a stainless steel mesh. Cool down to 50°C.
4. Add step 2 to step 3 and mix for 20 minutes. Check for smoothness of dispersion.
5. Homogenize under 0.4 to 0.6 bar vacuum and cool down to 30°C.
6. Fill.

Panthenol and Chlorhexidine Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/1000 Tablets (g)
25.00	1	D-Panthenol (adjusted for potency)	26.25
2.50	2	DL-Lactone pure	2.50
1.00	3	Sequestrene disodium	1.00
3.00	4	Chlorhexidine hydrochloride micropowder	3.00
5.00	5	POEG 300-stearate[a]	5.00
50.00	6	Paraffin oil low viscosity	50.00
5.00	7	Polydimethylsiloxane M 350	5.00
3.00	8	Perfume PCV 1155/8	3.00
–	9	Purified water	QS to 1 L

[a]POEG 300 is a mixture of monoesters and diesters of polyoxyethylene glycol 300, with palmitic and stearic acids and free polyoxyethylene glycol 300.

Manufacturing Directions

1. Aqueous phase: Prepare a solution of DL-lactone (previously liquefied at approximately 100°C) in water.
2. Add the DL-lactone solution to the main part of water at 70°C.
3. Incorporate the D-panthenol (previously liquefied at approximately 45°C).
4. Admix and dissolve sequestrene disodium.
5. Fatty phase: Melt at approximately 65°C under stirring POEG 300-stearate, paraffin oil, and polydimethylsiloxane M 350.
6. Emulsion: Add the fatty phase at 65°C to the aqueous phase at approximately 45°C. Cool to approximately 36°C while stirring and homogenizing.
7. Chlorhexidine suspension: Suspend chlorhexidine in water. Lotion: Add the chlorhexidine suspension to the emulsion at approximately 36°C. Stir, homogenize, and deaerate.
8. Finally, add the perfume, homogenize again, and filter.

Panthenol Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Protegin X	50.00
18.00	2	Cetyl alcohol	18.00
12.00	3	Stearyl alcohol	12.00
40.00	4	Wax white	40.00
250.00	5	Wool fat deodorized	250.00
130.00	6	Vaseline® (white)	130.00
50.00	7	Almond oil	50.00
150.00	8	Paraffin oil	150.00
50.00	9	D-Panthenol	50.00
250.00	10	Deionized water	250.00

Manufacturing Directions

1. Place wool fat, Vaseline, almond oil, and paraffin in a heating vessel. Heat and melt the fats together at 80°C with stirring to keep the fatty phase at this temperature until further processing.
2. In a separate container, add protegin X, cetyl alcohol, stearyl alcohol, and wax white; melt these fats with stirring at 80°C. Add to above. The final temperature in the melt should be approximately 70°C. Keep this temperature until further processing.
3. Transfer D-panthenol into a suitable container by pouring and then rinsing it with hot deionized water 1.67 kg, continue to mix another 5 minutes, check the final weight, and make up for evaporated water.
4. Place into kettle and heat to 70°C while stirring. Transfer the melted fatty mass under vacuum (–0.3 mm) through the inline sieve (mesh size 0.150 mm). After the addition, evacuate again to –0.3 atm, then stir for another 15 minutes and homogenize for 5 minutes under the same condition.
5. Cool to 30°C. (The cooling should be within 4 hours.) When this temperature is reached, continue stirring until the ointment has reached 24°C to 26°C. Stop cooling. Then evacuate to –0.3 atm and stir for 5 minutes.
6. Transfer the ointment in a mixer and mix for 5 minutes with electric mixture. Fill the ointment.

Panthenol Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L Tablets (g)
26.25	1	D-Panthenol (2.5%)[a]	26.25
2.50	2	DL-Lactone (pure)	2.50
1.00	3	Sequestrene disodium	1.00
3.00	4	Chlorhexidine hydrochloride (micropowder)	3.00
5.00	5	POEG 300-stearate[b]	5.00
50.00	6	Paraffin oil (low viscosity)	50.00
5.00	7	Polydimethylsiloxane M 350	5.00
3.00	8	Perfume PCV 1155/8	3.00
—	9	Purified water	QS to 1 L

[a] Based on 100% content; adjust for assay.
[b] POEG 300 is a mixture of monoesters and diesters of polyoxyethylene glycol 300, with palmitic and stearic acids and free polyoxyethylene glycol 300.

Manufacturing Directions

1. Aqueous phase: Prepare a solution of DL-lactone (previously liquefied at approximately 100°C) in water.
2. Add the DL-lactone solution to the main part of water at 70°C.
3. Incorporate the D-panthenol (previously liquefied at approximately 45°C).
4. Admix and dissolve sequestrene disodium.
5. Fatty phase: Melt at approximately 65°C under stirring POEG 300 stearate, paraffin oil, and polydimethylsiloxane M 350.
6. Emulsion: Add the fatty phase at 65°C to the aqueous phase at approximately 45°C.
7. Cool to approximately 36°C while stirring and homogenizing.
8. Chlorhexidine suspension: Suspend chlorhexidine in water.
9. Lotion: Add the chlorhexidine suspension to the emulsion at approximately 36°C.
10. Stir, homogenize, and deaerate.
11. Finally, add the perfume, homogenize again, and filter.

Pantoprazole–Cholesterol Complex Suppository

1. 7 g of cholesterol and 5 g of ethocel are dissolved in 100 mL of dichloromethane.
2. 5 g of pantoprazole sodium sesquihydrate is suspended in the solution.
3. The suspension is spray-dried in a laboratory spray dryer.
4. Spray conditions: drying gas nitrogen, inlet temperature 51°C; pump output 10%. 100 g of cetyl alcohol is heated to 65°C. Spray congealing: 50 g of pantoprazole sodium sesquihydrate is slowly added.
5. The mixture is stirred until a homogeneous suspension is obtained and subsequently sprayed through a nozzle in a spray dryer.
6. A white free-flowing powder is obtained with particle size in the range 10 to 40 microns.
7. By variation of the spraying conditions, larger or smaller particles can be obtained.
8. 194.7 g of suppository base (Adeps solidus/Neutralis) are fused to give a clear mass at 40°C to 45°C.
9. After cooling the mass to 39°C to 40°C, the preparation obtained above (15.3 g) is introduced homogeneously using a stirrer.
10. The suspension obtained is cooled to 37°C to 38°C and cast into suppositories of 2.1 g each containing 45.6 mg of pantoprazole sodium sesquihydrate.

Papain Chewing Gum

Formulation

Gum base, 31.20%; sorbitol, 28.08%; mannitol, 5.23%; papain, 1.00%; acesulfame K, 0.16%; aspartame, 0.16%; menthol powder, 1.00%; liquid flavor, 0.47%; isomalt PF, 11.70%; isomalt DC, 16.00%; anticaking agents (magnesium stearate, talc, or silica gel), 4.00%; flavor, 2.00%.

Papain Ointment

The ointment is an enzymatic debriding-healing ointment that contains standardized papain USP (not less than 521,700 USP units per gram of ointment), urea USP, 10%, and chlorophyllin copper complex sodium, 0.5%, in a hydrophilic base composed of purified water USP, propylene glycol USP, white petrolatum USP, stearyl alcohol NF, polyoxyl 40 stearate NF, sorbitan monostearate NF, boric acid NF, chlorobutanol (anhydrous) NF (as a preservative), and sodium borate NF. In another formulation, each gram of enzymatic debriding ointment contains papain (8.3×10^5 USP units of activity) and 100 mg urea in a hydrophilic ointment base composed of purified water, emulsifying wax, glycerin, isopropyl palmitate, potassium phosphate monobasic, fragrance, methyl paraben, and propyl paraben.

Penciclovir Cream

The cream contains penciclovir, an antiviral agent active against herpes viruses for topical administration as a 1% white cream. Each gram of cream contains 10 mg penciclovir and the following inactive ingredients: cetomacrogol 1000 BP cetostearyl alcohol, mineral oil, propylene glycol, purified water, and white petrolatum.

Peppermint Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
25.00	1	Sorbitol stearate	25.00
15.00	2	Polysorbate 60	15.00
300.00	3	Peppermint oil	300.00
20.00	4	Cetyl alcohol	20.00
40.00	5	Stearic acid	40.00
10.00	6	Triethanolamine 99%	10.00
2.00	7	Carbopol 980	2.00
QS	8	Deionized water	QS
QS	9	Preservative, color	QS

Manufacturing Directions

1. Hydrate Carbopol in water 60°C to 65°C.
2. Add remaining water-phase ingredients.
3. Heat oil and water phases separately to 70°C to 75°C.
4. Add water phase to oil phase while stirring. Stir to cool, neutralizing at 65°C with triethanolamine.

Permethrin Cream and Lotion

Permethrin cream, 5%, is a topical scabicidal agent for the treatment of infestation with *S. scabiei* (scabies). It is available in an off-white vanishing cream base. Each gram of cream, 5%, contains permethrin 50 mg (5%) and the inactive ingredients butylated hydroxytoluene, carbomer 934P, coconut oil, glycerin, glyceryl stearate, isopropyl myristate, lanolin alcohols, light mineral oil, polyoxyethylene cetyl ethers, purified water, and sodium hydroxide. Formaldehyde 1 mg (0.1%) is added as a preservative. Each fluid ounce of lotion contains permethrin 280 mg (1%) as its active ingredient and balsam fir Canada, cetyl alcohol, citric acid, FD&C yellow No. 6, fragrance, hydrolyzed animal protein, hydroxyethyl cellulose, polyoxyethylene 10 cetyl ether, propylene glycol, stearalkonium chloride, water, isopropyl alcohol 5.6 g (20%), methyl paraben 56 mg (0.2%), and propyl paraben 22 mg (0.08%) as its inactive ingredients.

Petrolatum and Lanolin Ointment

Active ingredients in petrolatum and lanolin ointment are petrolatum, 53.4%, and lanolin, 15.5%. Inactive ingredients are cod liver oil (contains vitamins A and D), fragrance, light mineral oil, microcrystalline wax, and paraffin.

Phenylephrine Ointment, Cream, Suppositories, and Gel

The ointment contains petrolatum, 71.9%, mineral oil, 14%, shark liver oil, 3%, and phenylephrine HCl, 0.25%. The cream contains petrolatum, 18%, glycerin, 12%, shark liver oil, 3%, and phenylephrine HCl, 0.25%. The suppositories contain cocoa butter, 85.5%, shark liver oil, 3%, and phenylephrine HCl, 0.25%. The cooling gel contains phenylephrine HCl, 0.25%, and witch hazel, 50%.

Piroxicam Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Piroxican	10.00
1.00	2	Carbopol 940	10.00
30.00	3	Alcohol	300.00
30.00	4	Propylene glycol	300.00
1.50	5	Diethanolamine	15.00
0.50	6	Hydroxyethyl cellulose	5.00
0.50	7	PVP K-30	5.00
QS	8	Water purified	QS to 1 kg

Manufacturing Directions

All items are blended uniformly together to produce an ointment formulation having a pH of 7.9. The Carbopol is neutralized using item 5.

Piroxicam and Dexpanthenol Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.50	1	Piroxicam	5.00
25.00	2	1, 2-Propylene glycol	250.00
5.00	3	Alcohol	50.00
0.40	4	Triethanolamine	~4.00
23.00	5	Lutrol F 127	230.00
46.00	6	Water purified	460.00

Manufacturing Directions

1. Prepare the solution of piroxicam in propylene glycol and dexpanthenol at 70°C to 80°C.
   a. Add ethanol and Lutrol F 127.
   b. Stir the highly viscous mixture. Add 50% of the hot water (70°C).
   c. Adjust the pH with triethanolamine to approximately 7.
   d. Add the rest of the water, cool to room temperature when the air bubbles escape, and adjust the pH to approximately 8.

or

1. Dissolve piroxicam in propylene glycol, dexpanthenol, and triethanolamine.
   a. Cool the mixture of Lutrol F 127 and water to approximately 5°C and mix with the piroxicam solution.
   b. Add the ethanol.
   c. Maintain the cool temperature until the air bubbles escape.

Polymyxin, Bacitracin, Hydrocortisone, and Zinc Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
18.00	1	Wax	180.00
69.80	2	Petrolatum	698.00
7.50	3	Polymyxin B sulfate	75.00
0.60	4	Bacitracin	6.00
4.00	5	Zinc oxide	40.00
0.50	6	Hydrocortisone acetate	5.00

Manufacturing Directions

1. Add items 1 and 2 to a melting vessel. Heat to 75°C.
2. Add items 3 to 5 one by one and mix to dissolve.
3. Cool to 40°C and fill.

Povidone–Iodine and Lidocaine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
10.00	2	Lidocaine hydrochloride	10.00
10.00	3	Sodium chloride	10.00
200.00	4	Lutrol F 127	200.00
79.00	5	Sodium hydroxide solution, 1 M	79.00
61.10	6	Water	61.10

Manufacturing Directions

1. Dissolve items 1 to 3 in item 6, cool to approximately 6°C, dissolve item 4, and adjust the pH value (4.5–5.0) with item 5.
2. Maintain the cool temperature until the air bubbles escape. Viscosity (Brookfield, 23°C) 54,000 mPa.

Povidone–Iodine Bar Soap

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PVP–iodine 30/06	50.00
10.00	2	Fragrance	10.00
75.00	3	Water	75.00
940.00	4	Syndet base	940.00

Manufacturing Directions

1. Dissolve PVP–iodine in water, and mix the solution with the fragrance and the syndet base.
2. Pass the blend 4 times through a three-roller mill.
3. Blend 3 times through a plodder with a narrow sieve hole disk.
4. Pass the blended material through a wide sieve hole disk combined with a mouth hole disk.
5. Heat the area of the two disks to 50°C using a heating collar.
6. Cut the bar in pieces on a lab stamper.
7. Composition of the syndet base (in sequence of concentration): disodium lauryl sulfosuccinate, sodium lauryl sulfate, cetyl stearyl alcohol, paraffin, glycerol stearate, water, titanium dioxide.

Povidone–Iodine Bar Soap

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PVP–iodine 30/06	50.00
75.00	2	Water	75.00
241.5	3	Texapon® K 12	241.5
241.5	4	Setacin® F special paste	241.5
241.5	5	Emcol® 4400.1	241.5
145.00	6	Cetyl stearyl alcohol	145.00
96.50	7	Paraffin	96.50
226.00	8	Glycerol monostearate	226.00

Manufacturing Directions

1. Heat mixture of items 3 to 8 to 75°C to 80°C and cool to approximately 50°C stirring well.
2. Add solution of items 1 and 2 and let cool to room temperature, stirring continuously.
3. Pass the blend 4 times through a three-roller mill and let dry overnight at room temperature.
4. Cut the bar into pieces on a lab stamper.

Povidone–Iodine Bar Soap

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PVP–iodine 30/06	50.00
75.00	2	Water	75.00
241.50	3	Texapon K 12	241.50
145.00	4	Cetyl stearyl alcohol	145.00
96.50	5	Paraffin	96.50
226.00	6	Glycerol monostearate	226.00

Manufacturing Directions

1. Heat mixture of items 3 to 8 to 75°C to 80°C and cool to approximately 50°C stirring well.
2. Add solution of item 1 and let cool to room temperature, stirring continuously.
3. Pass the blend 4 times through a three-roller mill and let dry overnight at room temperature.
4. Cut the bar into pieces on a lab stamper.

Povidone–Iodine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP-iodine 30/06	100.00
241.00	2	Citric acid solution, 0.1 M	241.00
369.00	3	Na_2HPO_4 solution, 0.2 M	369.00
20.00	4	Cremophor A 6	20.00
20.00	5	Cremophor A 25	20.00
100.00	6	Cetyl stearyl alcohol	100.00
100.00	7	Liquid paraffin	100.00
50.00	8	Glycerol	50.00

Manufacturing Directions

1. Prepare a basic cream from the emulsifying agents and the fatty substances, items 4 to 8.
2. Stir in the PVP–iodine dissolved in the buffer solutions made from items 2 and 3.
3. Brown cream having a pH of 4.5 is obtained.

Povidone–Iodine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
100.00	2	Liquid paraffin	100.00
100.00	3	Vaseline	100.00
50–80	4	Cetyl stearyl alcohol	50–80
20.00	5	Cremophor A 6	20.00
20.00	6	Cremophor A 25	20.00
50.00	7	Propylene glycol pharma	50.00
530–560	8	Water	530–560

Manufacturing Directions

This cream is suitable for veterinary mastitis treatment.

1. Dissolve PVP–iodine in the solvents, items 7 and 8.
2. Mix items 2 to 6 by heating, stir the solution in the previous mixture, and cool by stirring.

Povidone–Iodine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
241.00	2	Citric acid (0.1-M solution)	241.00
369.00	3	Na_2HPO_4 (0.2-M solution)	369.00
20.00	4	Cremophor A 6	20.00
20.00	5	Cremophor A 25	20.00
100.00	6	Cetyl stearyl alcohol	100.00
100.00	7	Liquid paraffin	100.00
50.00	8	Glycerol	50.00

Manufacturing Directions

1. Prepare a basic cream from the emulsifying agents and the fatty substances (items 4–8).
2. Stir in the PVP–iodine dissolved in the buffer solutions made from items 2 and 3.
3. A brown cream having a pH of 4.5 is obtained.

Povidone–Iodine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP-iodine 30/06	100.00
359.00	2	Citric acid solution, 0.1 M	359.00
181.00	3	$NA_2HPO_4 \bullet 12H_2O$ solution, 0.2 M	181.00
50.00	4	Lutrol E 400	50.00
100.00	5	Liquid paraffin	100.00
150.00	6	Lutrol F 127	150.00
70.00	7	Lutrol F 127	70.00

Manufacturing Directions

1. Dissolve item 1 in a solution of items 2 to 4, mix with item 5, and dissolve item 6 at approximately 20°C.
2. Cool to 5°C to 8°C and dissolve item 7. Maintain cool until all air bubbles have disappeared (brown turbid gel).

Povidone–Iodine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
10.00	2	Sodium chloride	10.00
200.00	3	Lutrol F 127	200.00
79.00	4	Sodium hydroxide solution, 1 M	79.00
610.00	5	Water	610.00

Manufacturing Directions

1. Dissolve items 1 and 2 in item 5 and cool to approximately 6°C.
2. Dissolve Lutrol F 127 and item 2 and adjust the pH value with item 4.
3. Maintain cool until all air bubbles have escaped. Viscosity 61,000 mPa to 54,000 mPa (Brookfield, 23°C); pH value (20% in water) 2.2 to 4.6.

Povidone–Iodine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP-iodine 30/06	100.00
600.00	2	Lutrol E 400	600.00
46.00	3	Sodium hydroxide, 1 M solution	46.00
4.00	4	Water	4.00
250.00	5	Lutrol E 4000	250.00

Manufacturing Directions

1. Prepare solution of items 1 to 4, heat to approximately 60°C, incorporate item 6, stir very well, and cool to room temperature.
2. A transparent ointment like a gel having a pH of 4 is achieved, miscible and washable with water.

Povidone–Iodine Gel Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
359.00	2	Citric acid (0.1-M solution)	359.00
181.00	3	$NA_2HPO_4 \cdot 12H_2O$ (0.2-M solution)	181.00
50.00	4	Lutrol E 400	50.00
100.00	5	Liquid paraffin	100.00
150.00	6	Lutrol F 127	150.00
70.00	7	Lutrol F 127	70.00

Manufacturing Directions

1. Dissolve item 1 in solution of items 2 to 4, mix with item 5, and dissolve item 6 at approximately 20°C.
2. Cool to 5°C to 8°C and dissolve item 7.
3. Maintain cool temperature until all air bubbles have disappeared.
4. A brown, turbid gel is obtained.

Povidone–Iodine Gels

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
10.00	2	Sodium chloride	10.00
200.00	3	Lutrol F 127	200.00
79.00	4	Sodium hydroxide (1-M solution)	79.00
610.00	5	Water	610.00

Manufacturing Directions

1. Dissolve items 1 and 2 in item 5 and cool to approximately 6°C.
2. Dissolve Lutrol F 127 and item 2 and adjust the pH value with item 4.
3. Maintain cool until all air bubbles escape.
4. Viscosity (Brookfield, 23°C) is 61,000 to 54,000 mPa; pH value (20% in water) is 2.2 to 4.6.

Povidone–Iodine Glucose Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	PVP–iodine 30/06, with excess	26.00
45.00	2	Ethanol (96%)	45.00
849.00	3	Glucose	849.00
34.00	4	Lutrol E 4000	34.00
6.00	5	Glycerol	6.00
6.00	6	Water	6.00

Manufacturing Directions

1. Dissolve Lutrol E 4000 in the hot mixture of glycerol and water and add the glucose warmed to 60°C to 80°C.
2. Incorporate item 4 to obtain a brown, viscous, and turbid paste.

Povidone–Iodine Glucose Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	PVP–iodine 30/06, with excess	26.00
45.00	2	Ethanol 96%	45.00
849.00	3	Glucose	849.00
34.00	4	Lutrol E 4000	34.00
6.00	5	Glycerol	6.00
6.00	6	Water	6.00

Manufacturing Directions

1. Dissolve Lutrol E 4000 in the hot mixture of glycerol and water and add the glucose warmed to 60°C to 80°C.
2. Incorporate solution in the obtained paste (brown viscous and turbid paste).

Povidone–Iodine Mastitis Cream for Cattle

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
100.00	2	Liquid paraffin	100.00
100.00	3	Vaseline	100.00
50–80	4	Cetyl stearyl alcohol	50–80
20.00	5	Cremophor A 6	20.00
20.00	6	Cremophor A 25	20.00
50.00	7	Propylene glycol	50.00
QS	8	Water	530–560

Manufacturing Directions

1. Dissolve PVP–iodine in the solvents (items 7 and 8).
2. Mix items 2 to 6 by heating, stir the solution in the previous mixture, and cool by stirring.

Povidone–Iodine Soft Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	PVP–iodine 30/06	10.00
25.00	2	Natrosol® HR 250	25.00
QS	3	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve PVP–iodine and Natrosol HR 250 in the water and stir well to produce a clear, brown gel.
2. Viscosity (Brookfield, 23°C) is 31,500 mPa.

Povidone–Iodine Transparent Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
600.00	2	Lutrol E 400	600.00
46.00	3	Sodium hydroxide (1-M solution)	46.00
4.00	4	Water	4.00
250.00	5	Lutrol E 4000	250.00

Manufacturing Directions

1. Prepare solution of items 1 to 4, heat to approximately 60°C, incorporate item 6 (stirring very well), and cool to room temperature.
2. The transparent ointment, similar to a gel, has a pH of 4 and is miscible and washable with water.

Povidone–Iodine Vaginal Ovule

Bill of Materials			
Scale (mg/Ovule)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	PVP—iodine 30/06	5.00
200.00	2	Lutrol E 400	10.00
170.00	3	Lutrol E 4000	85.00

Manufacturing Directions

1. Melt the Lutrol E grades by gentle heating.
2. Stir in the micronized PVP–iodine product in small portions into the melt.
3. After a uniform suspension has been obtained, pour it into polyethylene molds.
4. The homogeneous brown-colored ovule has a weight of 2 g.

Povidone–Iodine Vaginal Ovule

Bill of Materials			
Scale (mg/ovule)	Item	Material Name	Qty/kg (g)
200.00	1	PVP–iodine 30/06	200.00
100.00	2	Lutrol E 400	100.00
100.00	3	Lutrol E 1500	100.00
700.00	4	Lutrol E 4000	700.00

Manufacturing Directions

1. Melt the Lutrol E grades by gentle heating.
2. Stir in the micronized PVP–iodine product in small portions into the melt.
3. After a uniform suspension has been obtained, pour it into polyethylene molds.
4. The homogeneous brown-colored ovule has a weight of 2 g.

Povidone–Iodine Vaginal Ovules

Bill of Materials			
Scale (mg/ovule)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	PVP–iodine 30/06 M 10	5
200.00	2	Lutrol E 400	10
170.00	3	Lutrol E 4000	85

Manufacturing Directions

1. Melt the Lutrol E grades by gentle heating. Stir the micronized PVP–iodine product in small portions into the melt.
2. After a uniform suspension has been obtained, pour it into polyethylene molds. The result is a homogeneous brown-colored ovule having a weight of 2 g.

Povidone–Iodine Vaginal Ovules

Bill of Materials			
Scale (mg/ovule)	Item	Material Name	Qty/kg (g)
200.00	1	PVP-iodine 30/06 M 10	200.00
100.00	2	Lutrol E 400	100.00
100.00	3	Lutrol E 1500	100.00
700.00	4	Lutrol E 4000	700.00

Manufacturing Directions

1. Melt the Lutrol E grades by gentle heating. Stir the micronized PVP-iodine product in small portions into the melt.
2. After a uniform suspension has been obtained, pour it into polyethylene mold. The result is a homogeneous brown-colored ovula having a weight of 2 g.

Pramoxine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Cetyl alcohol[a]	150.00
50.00	2	Cetyl esters wax[a]	50.00
0.72 mL	3	Water purified	720 mL
1.80	4	Methyl paraben	1.80
0.20	5	Propyl paraben	0.20
20.00	6	Sodium lauryl sulfate	20.00
50.00	7	Glycerin	50.00
10.00	8	Pramoxine hydrochloride	10.00

[a]Beeswax 75.00 mg/g can be added and adjusted with items 1 and 2.

Manufacturing Directions

1. Phase A: Add the cetyl alcohol (item 1) and the cetyl esters wax (item 2) to a suitable jacketed stainless steel tank fitted with efficient agitation. Heat to 60°C to 65°C and mix until materials are melted and phase is uniform.
2. Preheat a suitable jacketed stainless steel batch tank to 60°C to 65°C. Strain phase A (step 1) into the batch tank, maintaining temperature at 60°C to 65°C and gentle agitation.
3. Phase B: Charge 530 mL of purified water (item 3) into a suitable jacketed stainless steel tank fitted with a high-speed mixer. Adjust the water temperature to 80°C to90°C and add methyl paraben (item 4) and propyl paraben (item 5). Stir until dissolved, ensuring that no solids are entrained in the bottom valve. Commence cooling to 60°C to 65°C.
4. Add the sodium lauryl sulfate (item 6) with care and stir to dissolve.
5. Add the glycerin (item 7) and mix until uniform. *Caution:* Do not create excessive foam.
6. Cool to 60°C to 65°C.
7. Strain phase A and sweep mix. Rinse through with 12 mL of purified water.
8. Phase C: To a suitable jacketed stainless steel tank fitted with high-speed agitation, charge 166 mL of purified water and raise the temperature to 60°C to 65°C. Add the pramoxine hydrochloride (item 8) and mix until dissolved. Strain the solution via a 100- to 150-μm aperture mesh into the mass from step above. Rinse through with 12 mL of purified water. Reduce agitation rate to prevent air entrainment and commence cooling to 32°C to 36°C. Please note that you should maintain cooling water at 10°C below batch temperature until 45°C, switching then to full cooling.
9. Fill.

Pramoxine Hydrochloride and Zinc Acetate Lotion and Ointment

The lotion contains pramoxine hydrochloride, 1%, and zinc acetate, 0.1%, and inactive ingredients alcohol USP, camphor, citric acid, diazolidinyl urea, fragrance, glycerin, hydroxypropylmethylcellulose, methyl paraben, oil of lavender, oil of rosemary, polysorbate 40, propylene glycol, propyl paraben, purified water, and sodium citrate. The ointment contains active ingredients pramoxine HCl, 1%, zinc oxide, 12.5%, and mineral oil as well as benzyl benzoate, calcium phosphate dibasic, cocoa butter, glyceryl monooleate, glyceryl monostearate, kaolin, peruvian balsam, and polyethylene wax.

Pramoxine Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
1782.00	1	Witepsol H 15®	1782.00
18.00	2	Pramoxine hydrochloride	18.00

Manufacturing Directions

1. Conventional method:
   a. In a suitable jacketed stainless steel tank, premelt the Witepsol H 15 at 35°C to 45°C.
   b. Transfer 200 g of premelted Witepsol H 15 from step 1 into a suitable premix tank fitted with an efficient agitator. Slowly add the pramoxine and mix for 15 minutes.
   c. Run the premix through a suitable colloid mill into a jacketed stainless steel batching tank fitted with a suitable homogenizer. Maintain the temperature at 40°C.
   d. Flush the premix tank, lines, and colloid mill with 50 g of premelted Witepsol H 15 from step 1 into the batching tank. Homogenize the contents of the batch tank at high speed for 15 minutes.
   e. Add the balance of the premelted Witepsol H 15 from step 1 to the contents of the batching tank. Homogenize for 15 minutes, then cool with mixing to 27°C to 38°C.
   f. Commence batch recirculation through a 150-µm aperture screen. Maintain until the batch is filled. Fill 1.8 g/suppository.
2. Turbomixer/Emulsifier method:
   a. In a suitable jacketed stainless steel tank fitted with a turbomixer/emulsifier, premelt the Witepsol H 15 at 35°C to 45°C.
   b. After melting, adjust the mixer/emulsifier in a batching tank containing the premelted mass to maximum speed and slowly add the pramoxine and mix.
   c. Homogenize the contents of the batching tank at 38°C with mixer at high speed. Then cool to 35°C to 36°C, always maintaining the whole mass under agitation.
   d. Filter the mass through a 150-µm screen and maintain the blending until the batch is filled.
3. Fill 1.8 g/suppository.

Pramoxine Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
1781.00	1	Witepsol W 32	1781.00
17.10	2	Pramoxine base	17.10
1.01	3	Pramoxine hydrochloride	1.01

Manufacturing Directions

This formula is less irritating and preferred.

1. In a suitable stainless steel tank fitted with an efficient agitator, melt Witepsol W 32 (No. 3) at approximately 45°C.
2. Activate mixer and maintain temperature of 40°C to 50°C.
3. Weigh pramoxine base into a separate suitable stainless steel container.
4. Slowly add pramoxine hydrochloride to step 3 and premix using homomixer or similar. Take precaution to minimize spread of powder to adjacent areas.
5. Continue to mix for 15 minutes. Make certain that pramoxine hydrochloride is completely dispersed and the mixture is free of lumps.
6. Verify that Witepsol W 32 from step 2 is completely melted and is less than 50°C, then add the premix to it from step 5.
7. Continue mixing at least 15 minutes while maintaining temperature less than 50°C.
8. Commence batch recirculation through a 150-µm aperture stainless steel screen. Maintain until batch is filled.
9. Cool batch slowly, approximately 3°C per hour, until it reaches 31°C.
10. Maintain product temperature at 31°C to 33.5°C with constant recirculation or mixing throughout filling operation. Adjust mixing as necessary to prevent aeration of the product.

Pranoprofen Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Pranoprofen	10.00
2.00	2	Triisopropanolamine	20.00
5.00	3	Carboxyvinyl polymer solution (Hiviswako 104)	50.00
52.00	4	Alcohol	520.00
QS	5	Water purified	QS to 1 kg

Manufacturing Directions

1. To 52 g of ethanol are added 1 g of pranoprofen and 2 g of triisopropanolamine. To the mixture are added 30 g of a 5% carboxyvinyl polymer solution and 15 g of purified water.
2. The pH of ointment thus obtained is 6.6 and the viscosity, which is measured at 20°C and 20 rpm, is 460 poises.

Prednicarbate Emollient Cream

Prednicarbate emollient cream, 0.1%, contains prednicarbate. Each gram of emollient cream, 0.1%, contains 1 mg of prednicarbate in a base consisting of white petrolatum USP, purified water USP, isopropyl myristate NF, lanolin alcohols NF, mineral oil USP, cetostearyl alcohol NF, aluminum stearate, edetate disodium USP, lactic acid USP, and magnesium stearate DAB 9.

Prochlorperazine Suppositories

Prochlorperazine suppositories contain prochlorperazine base. Each suppository contains 2.5, 5, or 25 mg of prochlorperazine with glycerin, glyceryl monopalmitate, glyceryl monostearate, hydrogenated coconut oil fatty acids, and hydrogenated palm kernel oil fatty acids.

Progesterone Gel

Progesterone gel is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single-use, one-piece polyethylene vaginal applicators. The carrier vehicle is an oil-in-water emulsion containing the water-swellable, but insoluble polymer, polycarbophil. The progesterone is partially soluble in both the oil and the water phases of the vehicle, with the majority of the progesterone existing as a suspension. The active ingredient, progesterone, is present in either a 4% or an 8% concentration (w/w). Each applicator delivers 1.125 g of gel containing either 45 mg (4% gel) or 90 mg (8% gel) of progesterone in a base containing glycerin, mineral oil, polycarbophil, carbomer 934P, hydrogenated palm oil glyceride, sorbic acid, sodium hydroxide, and purified water.

Promethazine Hydrochloride Suppositories

Each rectal suppository contains 12.5, 25, or 50 mg promethazine hydrochloride with ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter.

Promethazine Suppository

Each rectal suppository contains 12.5, 25, or 50 mg promethazine hydrochloride with ascorbyl palmitate, silicon dioxide, white wax, and cocoa butter. Promethazine hydrochloride is a racemic compound; the empirical formula is $C_{17}H_{20}N_2S.HCl$ and its molecular weight is 320.88. Phenergan suppositories are for rectal administration only.

Psoriasis Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Lanolin alcohol	40.00
50.00	2	White petroleum jelly	50.00
120.00	3	Paraffin wax 140F	120.00
300.00	4	Mineral oil (70 cS)	300.00
20.00	5	Coal tar	20.00
2.50	6	Allantoin	2.50
QS	7	Deionized water	QS to 1 kg
QS	8	Preservative	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Slowly add water phase in increments to the oil phase.
3. Allow each addition time to be fully incorporated.
4. Stir to cool.
5. Fill just above melting point.
6. Further homogenization may improve stability prior to filling.

Psoriasis Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
160.00	1	Stearic acid	16.00
60.00	2	Oleyl alcohol	6.00
20.00	3	Lanolin	2.00
20.00	4	Coal tar	2.00
6.00	5	Triethanolamine (99%)	0.60
2.50	6	Allantoin	0.25
QS	7	Deionized water	QS to 1 kg
—	8	Preservative	QS

Manufacturing Directions

1. Heat water and oil phases separately to 80°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Pass through homogenizer.
5. Fill at 40°C.

Resorcinol Acne Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Polychol 10 (Laneth-10)	20.00
5.00	2	Lanolin alcohols (Super Hartolan)	5.00
55.00	3	Cetyl alcohol C90	55.00
60.00	4	Polawax	60.00
14.00	5	Sulfur	14.00
QS	6	Deionized water	QS
40.00	7	Veegum regular	40.00
20.00	8	Propylene glycol	20.00
20.00	9	Resorcinol	20.00
QS	10	Perfume, preservative	QS

Manufacturing Directions

1. Hydrate Veegum in water. Add rest of water-phase ingredients and heat to 70°C.
2. Heat oil phase to 70°C. Disperse sulfur in oil phase.
3. Add oil phase to water phase while stirring. Stir to cool. Fill.

Rubefacient Analgesic Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Polawax, NF	150.00
100.00	2	Methyl salicylate	100.00
50.00	3	Menthol	50.00
100.00	4	Mineral oil (70 cS)	100.00
QS	5	Deionized water	QS to 1 kg
QS	6	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 30°C.

Salicylic Acid Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Glyceryl stearate and PEG-75 stearate	150.00
5.00	2	Stearic acid	5.00
80.00	3	Mineral oil	80.00
665.00	4	Deionized water	665.00
100.00	5	Salicylic acid	100.00

Manufacturing Directions

1. Mix and heat items 1 to 4 to 75°C.
2. Allow to cool with gentle stirring.
3. At 30°C, add item 5. Homogenize if necessary.

Salicylic Acid Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/100 g (g)
150.00	1	Polawax (self-emulsifying wax)	15.00
150.00	2	PPG-2 myristyl ether propionate (Crodamol PMP)	15.00
50.00	3	Sorbitol isostearate	5.00
35.00	4	Safflower oil, super refined	3.50
20.00	5	Avocado oil, super refined	2.00
20.00	6	Cetyl palmitate	2.00
50.00	7	Salicylic acid	5.00
1.50	8	Propyl paraben	0.15
1.00	9	Butylated hydroxyanisole	0.10
487.50	10	Deionized water	48.75
10.00	11	Sodium borate	1.00
3.00	12	Methyl paraben	0.30
2.00	13	Imidazolidinyl urea	0.20
20.00	14	Hydrolyzed collagen + hyaluronic acid (Cromoist HTA)	2.00

Manufacturing Directions

1. Dissolve item 7 in item 2 with mixing and heating to 70°C.
2. Add balance of items 1 to 9 and mix with heat to 80°C.
3. Mix together items 10 to 13 separately and heat to 80°C.
4. Add this mixture to earlier mixture with mixing and cool to 40°C.
5. Add item 14 with mixing and cool to desired fill temperature.
6. Adjust pH if necessary to 3 to 4 with 10% triethanolamine solution.

Salicylic Acid Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
422.00	1	Witch hazel distilled, 14% alcohol	422.00
5.00	2	Salicylic acid	5.00
5.00	3	Aloe vera gel	5.00
10.00	4	Sorbitol	10.00
500.00	5	Polyglycerylmethylacrylate	500.00
10.00	6	Propylene glycol	10.00
0.80	7	Methyl paraben	0.80
0.20	8	Propyl paraben	0.20

Manufacturing Directions

1. Premix items 1to 4. Add item 5 with low-shear mixing until homogenous.
2. Mix items 6 to 8 together and then add them to the formulation.

Scopolamine Transdermal Therapeutic System

The transdermal scopolamine system is a circular flat patch designed for continuous release of scopolamine following application to an area of intact skin on the head, behind the ear. Each system contains 1.5 mg of scopolamine base. The transdermal system is a film 0.2 mm thick and 2.5 cm^2, with four layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are a backing layer of tan-colored, aluminized polyester film; a drug reservoir of scopolamine, light mineral oil, and polyisobutylene; a microporous polypropylene membrane that controls the rate of delivery of scopolamine from the system to the skin surface; and an adhesive formulation of mineral oil, polyisobutylene, and scopolamine. A protective peel strip of siliconized polyester, which covers the adhesive layer, is removed before the system is used. The inactive components, light mineral oil (12.4 mg) and polyisobutylene (11.4 mg), are not released from the system.

Selenium Sulfide Detergent Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.0	1	Selenium sulfide	10.0
2.0	2	Methyl paraben	2.0
10.0	3	Magnesium aluminum silicate type IIA	10.0
20.0	4	Titanium	20.0
0.170	5	Dye	0.170
230.0	6	Sodium alkyl ether sulfate/Sulfonate	230.0
30.0	7	Surfactant cocamide DEA	30.0
40.0	8	Cocoamphocarboxyglycinate	40.0
10.0	9	Protein hydrolyzed	10.0
4.0	10	Perfume	4.0
QS	11	Acid citric	QS
QS	12	Sodium chloride	QS
QS	13	Water purified	QS to 1 L

Note: Item 11 used for pH adjustment, if necessary. Item 12 used for viscosity adjustment, if necessary.

Manufacturing Directions

1. Selenium sulfide is toxic. Handle carefully and use approved respiratory protection.
2. Add selenium sulfide. Seal the mill and agitate for approximately 10 minutes to wet down the powdered material.
3. Recycle for approximately 5 minutes. Stop agitation. If necessary, add purified water (25–30°C) to nearly cover the grinding media.
4. Seal the mill and recirculate the slurry for 1 to 2 hours to the required particle size specifications for the selenium sulfide.
5. Load 250 mL of purified water into a suitable jacketed mixing tank and heat to 60°C to 70°C. With good stirring, add and dissolve methyl paraben. Slowly add and disperse magnesium aluminum silicate. Continue mixing until fairly smooth. Stop mixing and allow hydrating for 1 hour.
6. Add and disperse titanium dioxide. Mix for 30 minutes.
7. With good stirring, add selenium sulfide slurry and rinse the mill with purified water. Mix for 30 minutes.
8. Stop mixing and add sodium lauryl ether sulfate/sulfonate. Mix slowly for 5 minutes. Add cocamide DEA. Mix slowly for approximately 3 minutes.
9. Add cocoamphocarboxyglycinate. Mix slowly for 30 minutes.
10. Separately dissolve hydrolyzed protein (Hydro gel) in 4 mL of purified water and mix until uniform. Add solution from above to the tank and mix until uniform.
11. Add perfume and mix for 1 minute. Dissolve dye in 2 mL warm purified water (50–60°C) and add to mixing tank. Mix until uniform. Check and record pH and adjust it to 4.5 to 5.0, if necessary, using citric acid.
12. Add purified water QS to 980 mL. Mix for 30 minutes. Check and record viscosity. If necessary, adjust by adding sodium chloride.
13. Deaerate by slow stirring under vacuum or use of a suitable deaerator. Mix for 1 hour.

Selenium Sulfide Lotion

The active ingredient for selenium sulfide lotion is selenium sulfide, 2.5% w/v, in aqueous suspension; it also contains bentonite, lauric diethanolamide, ethylene glycol monostearate, titanium dioxide, amphoteric-2, sodium lauryl sulfate, sodium phosphate (monobasic), glyceryl monoricinoleate, citric acid, captan, and perfume.

Silicone Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Polawax NF	150.00
40.00	2	Oleyl alcohol	40.00
50.00	3	PEG-75 lanolin	50.00
150.00	4	Mineral oil 70 cS	150.00
50.00–100.00	5	Dimethicone	50.00–100.00
QS	6	Deionized water	QS to 1 kg

Manufacturing Directions

1. Heat water and oil phase separately to 60°C to 65°C.
2. Add water phase to oil phase while stirring. Stir to cool to 30°C. Add perfume or color as desired.

Silver Sulfadiazine Cream

Silver sulfadiazine cream, 1%, is a soft, white water-miscible cream containing the antimicrobial agent silver sulfadiazine in micronized form. Each gram of cream, 1%, contains 10- mg micronized silver sulfadiazine. The cream vehicle consists of white petrolatum, stearyl alcohol, isopropyl myristate, sorbitan monooleate, polyoxyl 40 stearate, propylene glycol, and water, with methyl paraben, 0.3%, as a preservative.

Silver Sulfadiazine Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Silver sulfadiazine	10.00
5.00	2	Cetyl alcohol	50.00
8.00	3	Glyceryl monostearate A/S	80.00
8.00	4	Liquid paraffin	80.00
3.00	5	Tween 80	30.00
2.00	6	Tween 60	20.00
15.00	7	Propylene glycol	150.00
58.00	8	Water purified	580.00

Manufacturing Directions

1. Charge items 2 to 6 in a fat-melting vessel, heat to 75°C, and then cool down to 60°C.
2. Charge item 8 to Becomix and heat to 90°C. Cool down to 65°C.
3. Transfer step 1 into step 2, mix under vacuum, cool to 40°C.
4. In a separate vessel, add items 7 and 1 and homogenize.
5. Add to step 3 and mix. Cool to 25°C.
6. Transfer to storage vessel and fill.

Sodium Chloride Ointment

Sodium chloride ointment is a sterile ophthalmic ointment used to draw water out of the cornea of the eye. Each gram contains active ingredient sodium chloride, 5%, and inactives lanolin, mineral oil, white petrolatum, and purified water. Sodium chloride (approximately 0.9%) is used for treating cold sores and fever blisters and lesions associated with herpes virus.

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Liquid paraffin	50.00
10.00	2	White paraffin	100.00
30.00	3	Glycerin	300.00
8.00	4	Cetostearyl alcohol	80.00
0.30	5	Methyl paraben	3.00
3.60	6	Polyoxyethylene sorbitan monostearate	36.00
2.00	7	Glyceryl monostearate	20.00
QS	8	Water purified	QS to 1 kg
0.90	9	Sodium chloride	9.00

Manufacturing Directions

1. Preparation of water phase:
   a. Charge purified water, polysorbate 60, and glycerin with agitation to a melting kettle.
   b. Heat the contents to 61°C to 65°C.
   c. Add methyl paraben and mix the composition to dissolve while maintaining temperature.
2. Preparation of oil phase:
   a. In a suitable vessel, charge liquid paraffin, cetostearyl alcohol, white petrolatum, glycerol monostearate, and white beeswax and mix continuously while heating to 71°C to 75°C.
3. Mixing of phases:
   a. The mixture of step 2 is transferred to step 1's kettle, with the water phase maintained at less than 300 mbar vacuum.
   b. Add sodium chloride and dissolve.
   c. With mixing and keeping the temperature at 61°C to 65°C, draw the oil phase into the water phase.
   d. Mix for 15 minutes with agitation and vacuum at 300 mbar and 61°C to 65°C.
   e. While mixing and under vacuum, allow the mixture to cool gradually to room temperature.
4. Fill in appropriate container.

Sodium Sulfacetamide Lotion

Each milliliter of sodium sulfacetamide lotion 10% contains 100 mg of sodium sulfacetamide in a vehicle consisting of purified water, propylene glycol, lauramide DEA and diethanolamine, polyethylene glycol 400 monolaurate, hydroxyethyl cellulose, sodium chloride, sodium metabisulfite, methyl paraben, xanthan gum, EDTA, and simethicone. Sodium sulfacetamide is a sulfonamide with antibacterial activity. Chemically, sodium sulfacetamide is N'-[(4-aminophenyl)sulfonyl]-acetamide, monosodium salt, monohydrate.

Spermatocidal Effervescent Suppository

Manufacturing Directions

1. 80 g of polyethylene glycol (average molecular weight 950–1050), 23.5 g of polyethylene glycol (average molecular weight 1300–1600), 6 g of Menfegol, and 0.5 g of dioctyl sodium sulfosuccinate were melted together by heating to obtain a uniform mixture.
2. To this mixture was added 5 g of anhydrous sodium sulfate and the mixture was stirred thoroughly to disperse. Then, 10 g of sodium bicarbonate, 25 g of potassium hydrogentartrate, and 0.15 g of saponin were added successively, stirred, and kneaded to uniformly disperse.
3. The mixture was injected, while hot, into a mold having a predetermined shape and cooled to below room temperature. Thereby, an effervescent vaginal suppository having a spermatocidal effect and weighing 1.5 g per unit was obtained.

Squalene Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Polyoxyethylene sorbitan monooleate	50.00
23.00	2	Cetyl alcohol	230.00
0.40	3	Cholesterol	4.00
0.20	4	Squalene	2.00
56.00	5	Water purified	560.00
10.00	6	Propylene glycol	100.00
5.00	7	L-cysteic acid	50.00
1.00 mL	8	Ethanolamine	10.00 mL

Manufacturing Directions

1. Heat items 1to 4 in a jacketed kettle to 70°C.
2. In a separate kettle, heat items 5 to 8 to 70°C.
3. Add step 1 to step 2 at 72°C slowly with agitation.
4. Continue agitation until the mixture is congealed. The water-washable cream thus prepared consists of 5% active ingredient.

Starch Ointment

The active ingredient in starch ointment is topical starch, 51%. It also contains benzyl alcohol, hydrogenated vegetable oil, and tocopheryl acetate.

Sucralafate and Hyaluronic Acid Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
30.00	1	Sucralafate (2–10 μm)	300.00
0.60	2	Hyaluronic acid	6.00
10.00	3	Pectin	100.00
10.00	4	Gelatin	100.00
4.00	5	Carboxymethylcellulose	40.00
60.00	6	Fractionated coconut oil	600.00

Manufacturing directions

1. Mix finely divided sucralfate with the other ingredients also in finely divided form.
2. Add fractionated coconut oil to the resulting powder and homogenize.

Sucralafate Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
30.00	1	Sucralafate (2–10 μm)	300.00
10.00	2	Pectin	100.00
10.00	3	Gelatin	100.00
10.00	4	Carboxymethylcellulose	100.00
60.00	5	Fractionated coconut oil	600.00

Manufacturing Directions

1. Mix finely divided sucralfate thoroughly with the other ingredients also in finely divided form.
2. Add fractionated coconut oil to the resulting powder to a suitable consistency and homogenize.

Sucralafate Opthalmic Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.00	1	Sucralafate (micronized less than 10 μm)	20.00
0.50	2	Carbopol 934	5.00
5.00	3	Mannitol	50.00
0.01	4	Benzalkonium chloride	0.10
0.05	5	Sodium EDTA	0.50
QS	6	Sodium hydroxide	QS
QS	7	Water purified	QS to 1 kg

Sulfacetamide Ointment

Sulfacetamide sodium ophthalmic solution and ointment USP, 10%, are sterile topical antibacterial agents for ophthalmic use. They contain sulfacetamide sodium, 10% (100 mg/g). The preservative is phenylmercuric acetate (0.0008%). Inactive ingredients are white petrolatum, mineral oil, and petrolatum and lanolin alcohol.

Sulfacetamide Sodium and Prednisolone Acetate Opthalmic Ointment

The sulfacetamide sodium and prednisolone acetate ophthalmic ointment USP is a sterile topical ophthalmic ointment combining an antibacterial and a corticosteroid. Active ingredients are sulfacetamide sodium, 10%, and prednisolone acetate, 0.2%. Inactives are phenylmercuric acetate (0.0008%), mineral oil, white petrolatum, and petrolatum and lanolin alcohol.

Sulfanilamide Suppositories

The suppositories contain sulfanilamide, 15%, in a watermiscible, nonstaining base made from lactose, propylene glycol, stearic acid, diglycol stearate, methyl paraben, propyl paraben, trolamine, and water, buffered with lactic acid to an acid pH of approximately 4.3. Each suppository contains sulfanilamide 1.05 g with lactose in a base made from polyethylene glycol 400, polysorbate 80, polyethylene glycol 3350, and glycerin, buffered with lactic acid to an acid pH of approximately 4.5. The suppositories have an inert, white nonstaining covering that dissolves promptly in the vagina. The covering is composed of gelatin, glycerin, water, methyl paraben, propyl paraben, and coloring.

Sulfathiazole Cream

The cream contains sulfathiazole (benzenesulfonamide, 4-amino-N-2-thiazolyl-N1-2-thiazolylsulfanilamide), 3.42%, sulfacetamide (acetamide,N-[(4-aminophenyl)sulfonyl]-N-sulfanilylacetamide), 2.86%, and sulfabenzamide (benzamide,N-[(4-aminophenyl)sulfonyl]-N-sulfanilylbenzamide), 3.7%, compounded with cetyl alcohol, 2%, cholesterol, diethylaminoethyl stearamide, glyceryl monostearate, lanolin, lecithin, methyl paraben, peanut oil, phosphoric acid, propylene glycol, propyl paraben, purified water, stearic acid, and urea.

Sulfur Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
15.00	1	Sulfur precipitated	15.00
85.00	2	Kaolin	85.00
QS	3	White petroleum jelly	QS to 1 kg
60.00	4	Isopropyl palmitate	60.00
13.00	5	Camphor	13.00
13.00	6	Methyl salicylate	13.00
20.00	7	Lanolin	20.00
50.00	8	Tribehenin	50.00
50.00	9	Ozokerite wad	50.00
35.00	10	Sorbitan oleate	35.00
15.00	11	Deionized water	15.00
4.00	12	Salicylic acid	4.00
24.00	13	Glycerin	24.00
QS	14	Preservative	QS

Manufacturing Directions

1. Heat oils except sulfur and lanolin to 70°C. Disperse sulfur and kaolin in oil phase.
2. Heat water, glycerin, and salicylic acid gently. Add to oil phase while stirring. Stir to 55°C.
3. Mill to disperse sulfur.

Tacrolimus Ointment

Tacrolimus ointment contains tacrolimus, a macrolide immunosuppressant produced by *Streptomyces tsukubaensis.* Each gram of ointment contains (w/w) either 0.03% or 0.1% of tacrolimus in a base of mineral oil, paraffin, propylene carbonate, white petrolatum, and white wax.

Terconazole Vaginal Cream

Terconazole vaginal cream, 0.4%, is a white to off-white water-washable cream for intravaginal administration containing 0.4% of the antifungal agent terconazole, compounded in a cream base consisting of butylated hydroxyanisole, cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, propylene glycol, stearyl alcohol, and purified water. Terconazole vaginal cream, 0.8%, is a white to off-white water-washable cream for intravaginal administration containing 0.8% of the antifungal agent terconazole, cis-1-[p-([2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy)phenyl]-4-isopropylpiperazine, compounded in a cream base consisting of butylated hydroxyanisole, cetyl alcohol, isopropyl myristate, polysorbate 60, polysorbate 80, propylene glycol, stearyl alcohol, and purified water.

Terconazole Vaginal Suppositories

Terconazole vaginal suppositories are white to off-white suppositories for intravaginal administration containing 80 mg of the antifungal agent terconazole, cis-1-[p-([2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy)phenyl]-4-isopropylpiperazine in triglycerides derived from coconut or palm kernel oil (a base of hydrogenated vegetable oils) and butylated hydroxyanisole.

Testosterone Gel

Testosterone gel is a clear, colorless hydroalcoholic gel containing 1% testosterone. It provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen, for 24 hours following a single application to intact, clean dry skin of the shoulders, upper arms, or abdomen. A daily application of 5, 7.5, or 10 g contains 50, 75, or 100 mg of testosterone respectively, to be applied daily to the skin surface. Approximately 10% of the applied testosterone dose is absorbed across skin of average permeability during a 24-hour period. The active pharmacologic ingredient is testosterone. Testosterone USP is a white to practically white crystalline powder chemically described as 17-beta hydroxyandrost-4-en-3-one. Inactive ingredients are ethanol 68.9%, purified water, sodium hydroxide, carbomer 940, and isopropyl myristate; these ingredients are not pharmacologically active.

Testosterone Transdermal System

The testosterone transdermal system provides continuous delivery of testosterone (the primary endogenous androgen) for 24 hours following application to intact, nonscrotal skin (e.g., back, abdomen, thighs, and upper arms). Two strengths are available that deliver in vivo either 2.5 or 5 mg of testosterone per day across skin of average permeability. It has a central drug delivery reservoir surrounded by a peripheral adhesive area. The 2.5-mg system has a total contact surface area of 37 cm^2 with a 7.5-cm^2 central drug delivery reservoir containing 12.2 mg testosterone USP dissolved in an alcohol-based gel. The 5-mg system has a total contact surface area of 44 cm^2 with a 15-cm^2 central drug delivery reservoir containing 24.3 mg testosterone USP dissolved in an alcohol-based gel. The delivery systems have six components. Proceeding from the top toward the surface attached to the skin, the system is composed of (1) metallized polyester/Surlyn (E.I. DuPont de Nemours Co; ethylene-methacrylic acid copolymer)/ethylene vinyl acetate backing film with alcohol-resistant ink; (2) a drug reservoir of testosterone USP, alcohol USP, glycerin USP, glycerol monooleate, methyl laurate, and purified water USP, gelled with an acrylic acid copolymer; (3) a permeable polyethylene microporous membrane; and (4) a peripheral layer of acrylic adhesive surrounding the central, active drug delivery area of the system. Before opening of the system and application to the skin, the central delivery surface of the system is sealed with a peelable laminate disc (5) composed of a five-layer laminate containing polyester/polyester urethane adhesive/aluminum foil/polyester urethane adhesive/polyethylene. The disc is attached to and removed with the release liner (6), a silicone-coated polyester film, which is removed before the system can be used.

Tetracaine Gel and Cream

Tetracaine gel's active ingredient is tetracaine HCl, 2%, and it also contains ethoxydiglycol, eucalyptus oil, hydroxyethyl cellulose, maleated soybean oil, methyl paraben, propyl paraben, sodium lauryl sulfate, and water. The cream contains active ingredient tetracaine 2% as well as chloroxylenol, eucalyptus oil, hydrochloric acid, lauramide DEA, methyl paraben, sodium borate, sodium lauryl sulfate, steareth-2, steareth-21, stearic acid, water, and white wax.

Tetracycline Hydrochloride Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
3.00	1	Tetracycline hydrochloride micronized (10% excess)	33.00
93.00	2	Petrolatum (white soft paraffin)	930.00
3.70	3	Mineral oil (liquid paraffin)	37.00
0.02	4	Vitamin E (oily)	0.20

Manufacturing Directions

1. Melt item 2 at 75°C in a fat-melting vessel.
2. In a suitable stainless steel container, disperse item 1 in items 3 and 4 manually by using a spatula.
3. Transfer 89 to 111 g of molten item 2 from step 1 to the mixer through stainless steel mesh. Cool down to 50°C.
4. Load tetracycline dispersion from step 2 to the mixer. Start mixer at speed 10 rpm, homogenizer high speed for 20 minutes. Check evenness and smoothness of the dispersion.
5. Transfer the remaining quantity of molten item 2 from step 1 at 50°C to 55°C to the mixer through stainless steel mesh while mixing and cooling at mixer speed 10 rpm, homogenizer high speed, under vacuum 0.4 to 0.6 bar for 30 minutes.
6. Stop homogenizer, continue mixing at 10 rpm, under vacuum 0.4 to 0.6 bar. Cool down to 28°C. Fill.

TGF Alpha-Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
35.00	1	Polyethylene glycol 8000	350.00
36.70	2	Mineral oil	367.00
0.70	3	Tween 80	7.00
QS	4	Water purified	QS to 1 kg
29.30	5	Hydroxypropylmethylcellulose	293.00
2.50 mg	6	TGF-alpha	25.00 mg

Manufacturing Directions

1. Dissolve item 1 and add item 4 and heat to 80°C.
2. Add item 2 to step 1 and pass the mixture through a homogenizer until a fine emulsion is obtained.
3. Add item 5 to the emulsion in step 2 with vigorous mixing.
4. Homogenize again.
5. Sterilize the ointment at 121°C for 15 minutes in an autoclave.
6. Under sterile condition and at 4°C, transfer item 6 and mix thoroughly.
7. Sterile fill 5 g in capped ointment tube.

Therapeutic Skin Lotion

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
73.44	1	Water purified	734.40
2.50	2	Aloe vera gel	25.00
2.00	3	Walnut oil	20.00
2.00	4	Tocopherol acetate (vitamin E)	20.00
2.00	5	Glycerin	20.00
2.00	6	Stearic acid	20.00
2.00	7	1-Hexadecanol	20.00
2.00	8	Polysorbate 60	20.00
2.00	9	Apricot kernel oil	20.00
2.00	10	Jojoba oil	20.00
2.00	11	Glyceryl stearate	20.00
1.00	12	PEG-100 stearate	10.00
1.00	13	Dimethicone	10.00
1.00	14	PVP	10.00
0.50	15	Hyaluronic acid	5.00
0.50	16	Fibronectin	5.00
0.50	17	Allantoin	5.00
0.50	18	Triethanolamine	5.00
0.20	19	Carbopol 934	2.00
0.20	20	Potassium chloride	2.00
0.06	21	Urea	0.60
0.03	22	Calcium phosphate	0.30

Tolnaftate and Undecylenate Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Glyceryl stearate and PEG-75 stearate	150.00
20.00	3	Hydrogenated palm/palm kernel oil PEG-6 esters	20.00
60.00	4	Mineral oil	60.00
0.50	5	Sorbic acid	0.50
0.50	6	Sodium methyl paraben	0.50
509.00	7	Deionized water	509.00
50.00	8	Undecylenic acid	50.00
200.00	9	Zinc undecylenate	200.00
10.00	10	Tolnafate	10.00

Manufacturing Directions

1. Mix and heat items 1 to 8 to 75°C.
2. Allow to cool and with gentle stirring. At 30°C add items 9 and 10.
3. Homogenize if necessary.

Tretinoin and Alpha-Bisabolol Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.05	1	Tretinoin	0.50
5.00	2	Lutrol E400	50.00
6.00	3	Cremophor RH400	60.00
0.04	4	Butylated hydroxytoluene	0.40
0.10	5	(-)Alpha-bisabolol natural (BASF)	1.00
70.30	6	Water purified	703.00
QS	7	Preservatives	QS
18.50	8	Lutrol F127	185.00

Manufacturing Directions

1. Add solution of items 7 and 6 slowly to the clear solution of items 1 to 5 at approximately 40°C.
2. Heat to approximately 50°C and dissolve approximately 14 g of item 8 in the combined solution of step 1.
3. Cool to approximately 6°C and dissolve the rest of the items. Maintain cool until the air bubbles have escaped.

Tretinoin and Dexpanthenol Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
50.00 mg	1	Tretinoin (BASF)	0.50
5.00	2	Lutrol E400	50.00
6.00	3	Cremophor RH40	60.00
40.00 mg	4	Butyl hydroxytoluene	0.40
68.40	5	Water purified	684.00
2.50	6	Dexpanthenol (BASF)	25.00
18.00	7	Lutrol F127	180.00

Manufacturing Directions

1. Add items 5 and 6 slowly to the clear solution of items 1 to 4 at approximately 40°C.
2. Heat to approximately 50°C and dissolve approximately 40 g of item 7 in step 1.
3. Cool to approximately 6°C and dissolve the rest of item 7.
4. Maintain cool until the air bubbles have escaped.

Tretinoin Cream

Tretonin cream, a topical retinoid, contains tretinoin 0.025% by weight in a hydrophilic cream vehicle of stearic acid, polyolprepolymer-2, isopropyl myristate, polyoxyl 40 stearate, propylene glycol, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene, and purified water. The tretinoin cream, 0.02%, contains the active ingredient tretinoin in a cream base. It is available at a concentration of 0.02% w/w in an oil-in-water emulsion formulation consisting of benzyl alcohol, butylated hydroxytoluene, caprylic/capric triglyceride, cetyl alcohol, edetate disodium, fragrance, methyl paraben, propyl paraben, purified water, stearic acid, stearyl alcohol, steareth 2, steareth 20, and xanthan gum.

Tretinoin Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.05	1	Tretinoin (BASF)	0.50
8.00	2	Luvitol EHO	80.00
3.00	3	Cremophor A6	30.00
1.50	4	Cremophor A25	15.00
3.00	5	Glyceryl monostearate	30.00
3.00	6	Cetyl alcohol	30.00
0.50	7	Tegiloxan 100 (Goldschmidt)	5.00
0.04	8	Butyl hydroxytoluene	0.40
4.00	9	Propylene glycol	40.00
0.50	10	Preservatives	5.00
0.20	11	Perfumes	2.00
76.20	12	Water purified	762.00

Manufacturing Directions

1. Separately prepare solution of items 1 and 2 and a mixture of items 3 to 7 by heating to approximately 75°C.
2. Heat mixture of items 8 to 12 until a clear solution is formed.
3. To the warm mixture of step 2, mix step 1 and cool by stirring.

Tretinoin Gel

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.05	1	Tretinoin (BASF)	0.50
15.00	2	Alcohol	150.00
1.00	3	Cremophor RH40	10.00
QS	4	Perfume	QS
0.04	5	Butyl hydroxytoluene	0.40
0.50	6	Carbopol 940	5.00
76.00	7	Water purified	760.00
0.70	8	Triethanolamine	7.00
6.60	9	Water purified	66.00

Manufacturing Directions

1. Prepare suspension of items 6 and 7 and add solution of items 8 and 9 to the well-stirred suspension.
2. When a clear mixture is formed, add solution of items 1 to 5.

Tretinoin Gel Microsphere

Tretinoin gel microsphere, 0.1%, is a formulation containing 0.1% by weight tretinoin for the topical treatment of acne vulgaris. This formulation uses patented methyl methacrylate/glycol dimethacrylate crosspolymer porous microspheres (Microsponge System®) to enable inclusion of the active ingredient tretinoin in an aqueous gel. Other components of this formulation are purified water, carbomer 934P, glycerin, disodium EDTA, propylene glycol, sorbic acid, PPG-20 methyl glucose ether distearate, cyclomethicone and dimethicone copolyol, benzyl alcohol, trolamine, and butylated hydroxytoluene.

Triacontanol Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.0250	1	Methyl paraben	0.250
0.015	2	Propyl paraben	0.15
1.00	3	Sodium lauryl sulfate	10.00
12.00	4	Propylene glycol	120.00
25.00	5	Stearyl alcohol	250.00
25.00	6	White petrolatum	250.00
37.00	7	Water purified	370.00
0.01	8	Triacontanol	0.10

Manufacturing Directions

1. The stearyl alcohol and the white petrolatum are melted on a steam bath and warmed to approximately 75°C.
2. The other ingredients are dissolved in the purified water and are also warmed to approximately 75°°C.
3. All ingredients are then mixed together and stirred until the mixture congeals.

Triclosan Foot Care Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Glyceryl stearate (Gelol)	50.00
50.00	2	Propylene glycol stearate	50.00
100.00	3	Octyldodecyl myristate	100.00
50.00	4	Isostearyl isostearate	50.00
20.00	5	Dimethicone (100 cS)	20.00
651.00	6	Deionized water	651.00
50.00	7	Sucrose distearate	50.00
4.00	8	Phenoxyethanol, methyl paraben, ethyl paraben, and propyl paraben	4.00
20.00	9	Propylene glycol	20.00
3.00	10	Triclosan	3.00
2.00	11	Fragrance	2.00

Manufacturing Directions

1. Heat items 1 to 5 and items 6 to 7 separately to 75°C. Mix the two parts with turbine mixing for 1 minute.
2. Cool with gentle stirring.
3. Add items 9 and 10 and then item 11 with mixing at 30°C to 35°C.

Triclosan Foot Cream

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
30.00	1	Alcohol and ceteareth-20 (Cosmowax EM5483)	30.00
30.00	2	Isopropyl myristate (Crodamol IPM)	30.00
5.00	3	Cetyl esters (Crodamol SS)	5.00
20.00	4	Oleyl alcohol	20.00
5.00	5	Propylene glycol	5.00
5.00	6	Carbopol 980	5.00
QS	7	Deionized water	QS to 1 L
300.00	8	Ethanol DEB100	300.00
2.00	9	Triclosan (Irgasan DP300)	2.00
0.50	10	Menthol	0.50
4.00	11	Triethanolamine 99% approximately to give pH 6–7	4.00

Manufacturing Directions

1. Preblend ethanol, Irgasan, and menthol and warm to 50°C.
2. Heat water and oil phases separately to 70°C.
3. Add water phase to oil phase while stirring. Stir to cool, adding the preblend at 60°C. Adjust pH.

Tridax procumbens Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	*Tridax procumbens* leaf extract	50.00
3.00	2	Carbopol 934	30.00
0.15	3	Methyl paraben	1.50
0.15	4	Propyl paraben	1.50
QS	5	Monoethanol amine	QS
QS	6	Propylene glycol: water purified (50:50)	QS to 1 kg

Manufacturing Directions

1. The leaves of *T. procumbens* are shade dried for 48 hours at room temperature.
2. The crushed leaves (500 g) are then soaked with water (1 L) for 72 hours at room temperature.
3. Water is decanted and then concentrated to 100 mL by evaporating under vacuum at room temperature.
4. This concentrated solution is then lyophilized to obtain powder (item 1).
5. The *T. procumbens* leaf extract is dispersed in pure propylene glycol along with propyl paraben (0.15%).
6. The mixture is thoroughly agitated to get a clear solution. Carbopol 934 is dispersed in a propylene glycol and water (50:50) mixture along with methyl paraben in another vessel.
7. The mixture is stirred continuously at 300 rpm for 2 to 3 hours.
8. The *T. procumbens* solution is then added and stirring is continued for approximately 1 hour until a gel preparation is obtained.
9. The pH of this gel is adjusted to 6 using monoethanolamine.

Trolamine Salicylate Cream

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/kg (g)
50.00	1	Glyceryl stearate	5.00
25.00	2	Cetyl alcohol	2.50
30.00	3	Cetyl phosphate and DEA cetyl phosphate	3.00
40.00	4	Stearyl stearoyl stearate	4.00
40.00	5	Cococaprylate/Caprate	4.00
40.00	6	Cetyl palmitate	4.00
5.00	7	Dimethicone	0.50
502.00	8	Deionized water	50.20
10.00	9	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	1.00
5.50	10	Magnesium aluminum silicate	0.55
2.50	11	Xanthan gum	0.25
100.00	12	Deionized water	10.00
100.00	13	Trolamine salicylate (TEA salicylate)	10.00
50.00	14	Propylene glycol	5.00

Manufacturing Directions

1. Heat items 8 and 9 to 85°C, add items 10 and 11, and mix until well dispersed.
2. Add items 1to 7 and mix well at 80°C to 85°C. Continue mixing.
3. While cooling to 65°C, add items 12 to 14 and continue mixing and cooling to 35°C. pH should be 5.5 to 5.6.

Ulinastatin Suppository

Manufacturing Directions

1. Hard fat (Witepsol W 35, 167.4 g), pluronic F-127 (0.6 g), propyl paraoxybenzoate (0.2 g), and methyl paraoxybenzoate (0.2 g) were weighed, melted at 50°C, and processed to prepare a uniform oil-phase component which was held at 35°C to 45°C.
2. An aqueous solution of ulinastatin (ulinastatin: 4900 U/mL) was prepared to have a sodium chloride concentration of 9 mg/mL; to 24 mL of the solution, there were added gelatin (2.4 g), concentrated glycerin (4.8 g), and arginine hydrochloride (0.4 g) and the mixture was heated to prepare a uniform aqueous-phase component which was held at 35°C to 45°C.
3. Steps 1 and 2 were mixed and emulsified with a homomixer, filled into suppository containers such that each contained a 1.7 g portion. The contents were left to cool and solidify, yielding suppositories containing ulinastatin in a uniform amount.

Ultrasonic Adhesive Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Preservative (e.g., parabens)	5.00
754.00	2	Water	754.00
6.00	3	Carbopol 940 (Goodrich)	6.00
20.00	4	Sodium hydroxide solution 10%	20.00
15.00	5	Kollidon 30	15.00
200.00	6	Water	200.00

Manufacturing Directions

1. Prepare solution of item 1 in item 2 by heating to 70°-°C and add item 3 slowly to obtain a homogeneous suspension.
2. Add items 4 to 6. A clear, colorless adhesive gel is obtained. Addition of sodium chloride changes consistency.

Vitamin A Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
2.20	1	Vitamin A propionate	22.00
70.00	2	Alcohol SD40-A	700.00
5.00	3	Glycolic acid	50.00
20.00	4	Propylene glycol	200.00
4.00	5	Hydroxypropyl cellulose	40.00
5.00	6	Aloe vera extract	50.00
0.10	7	Lactil	1.00

Manufacturing Directions

1. Add 2.2 g vitamin A propionate to 70 g alcohol (SD40-A) and mix.
2. Add 5 g of glycolic acid to 20 g of propylene glycol and mix.
3. Add step 1 to step 2 at room temperature until the solution is homogeneous.
4. Sift in 4 g hydroxypropyl cellulose slowly, more than approximately 15 minutes while blending to avoid clumping.
5. While stirring, add 5 g extract of the aloe vera plant and 0.1 g Lactil.
6. Stir gently until cellulose is dissolved.

Vitamin A Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
150,000 IU	1	Vitamin A palmitate 1.7 M IU/g	88.23 g
1.00	2	Butyl hydroxytoluene	10
400.00	3	Cremophor RH 40	400
800.00	4	Lutrol E 1500	800
500.00	5	Lutrol E 4000	505

Manufacturing Directions

1. Dissolve butyl hydroxytoluene in the warm vitamin A, add Cremophor, and mix with the molten Lutrol E grades.
2. Fill into molds of suppositories to obtain the weight of 2 g.

Vitamin C Vaginal Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
12.50	1	Vitamin C	125.00
21.80	2	White Vaseline	218.00
23.00	3	Cetyl stearyl alcohol	230.00
39.50	4	Liquid paraffin	395.00

Manufacturing Directions

1. Charge items 2 to 4 in a melting tank and melt at 80°C.
2. Stir and homogenize for 20 minutes and cool.
3. At 30°C, add item 1 under vacuum and homogenize.

Vitamin E Gel Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Vitamin E acetate	100.00
150.00	2	Propylene glycol pharma	150.00
200.00	3	Lutrol F 127	200.00
550.00	4	Water	550.00

Manufacturing Directions

1. Mix vitamin E acetate with propylene glycol and add the water. After cooling to approximately 6°C, dissolve Lutrol F 127 slowly in the well-stirred mixture.
2. Maintain cool until the air bubbles escape. A turbid white gel forms at temperatures between 20°C and 50°C. Viscosity at 25°C is approximately 120,000 mPa.

Wound Debriding Ointment

Directions

1. (% w/w) Castor oil, 90.0; hydrogenated castor oil, 10.0. The hydrogenated castor oil was added to the castor oil while mixing with a high shear mixer and mixed until a semisolid was formed.
2. Wound debriding ointment
   (% w/w) Castor oil, 68.8; hydrogenated castor oil, 10.0; balsam Peru oil, 8.70; aluminum/magnesium hydroxide stearate, 2.00; trypsin, 0.018; safflower oil, QS add 100%.
3. In step 3, the wound debrider, the aluminum/magnesium hydroxide stearate was dispersed in the castor oil.
4. Thereafter the hydrogenated castor oil was added while mixing with a high shear mixer, in particular, a turbo shear mixer.
5. Mixing was continued until a semisolid formed. The remaining ingredients were then blended to the semisolid until homogeneous mixing appeared.

Zinc Oxide and Vitamin E Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
7.50	1	Zinc oxide	75.00
5.00	2	White soft paraffin	50.00
6.50	3	Cetostearyl alcohol	65.00
11.00	4	Lanolin anhydrous	110.00
2.00	5	Castor oil	20.00
12.00	6	Liquid paraffin	120.00
0.50	7	Vitamin E oily	5.00
1.04	8	Sodium lauryl sulfate	10.40
10.00	9	Propylene glycol	100.00
1.00	10	Simethicone M30	10.00
0.04	11	Lavender oil	0.40
43.20	12	Water purified	432.00

Manufacturing Directions

1. Charge item 12 (two-thirds) to Becomix, heat to 80°C to 85°C, and transfer to a stainless steel covered container.
2. Charge in a melting vessel items 2 to 7, one at a time, and heat to 70°C. Stir to meet and maintain temperature at 70°C to 75°C.
3. Transfer step 2 to Becomix after passing through a stainless steel sieve while mixing.
4. Load item 12, set aside in a separate vessel, and stir to dissolve item 8 at 70°C to 75°C. Transfer this solution to Becomix through a stainless steel sieve.
5. Homogenize for 10 minutes under vacuum 0.4 to 0.6 bar at 70°C to 75°C.
6. Cool down to 40°C to 45°C while mixing.
7. Charge balance of item 12 at 70°C to 75°C and items 9 and 1 in a separate vessel. Mix using a stirrer, then cool down to 40°C to 45°C. Disperse zinc oxide in the solution while stirring and then pass dispersion twice through a homogenizer.
8. Transfer dispersion to Becomix and mix at slow speed.
9. Use item 12 to rinse vessel and add rinsings.
10. Homogenize at 35°C to 45°C under vacuum.
11. Add items 11 and 12 and mix again, homogenize again, and cool down to 25°C to 30°C.
12. Transfer to storage container and fill.

Zinc Oxide Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
7.00	1	Magnesium aluminum silicate	7.00
641.00	2	Water	641.00
7.00	3	Unimulse C	7.00
30.00	4	Propylene glycol	30.00
30.00	5	Eucalyptus oil	30.00
30.00	6	Lanolin oil	30.00
50.00	7	Dimethicone 350 cs	50.00
50.00	8	C12-C15 alcohols benzoate	50.00
100.00	9	Polysorbate 80	100.00
50.00	10	Zinc oxide	50.00
10.00	11	Cornstarch	10.00
QS	12	Preservatives	QS

Manufacturing Directions

1. Add item 1 to the water slowly, agitating with maximum shear until smooth.
2. Add item 3 and 4, mixing each time, until uniform.
3. Mix items 5 to 10 until uniform and mix with other portions until uniform.
4. Add item 11 and 12 and mix until smooth.

Zinc Oxide Ointment

(% w/w) Methyl benzethonium chloride, 0.1; sebacic acid, 10.0; acetylated lanolin, 2.0 ; zinc oxide, 20.0; perfume, 0.075; mineral oil gelled with 5% polyethylene (Plastibase 50W), 67.825.

Zinc Oxide Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
120.00	1	Cetearyl alcohol, PEG-40 castor oil, and sodium cetearyl sulfate	120.00
180.00	2	Petrolatum	180.00
60.00	3	Oleayl oleate	60.00
60.00	4	Mineral oil, light	60.00
100.00	5	Zinc oxide	100.00
QS	6	Water	QS to 1 kg
10.00	7	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	10.00

Manufacturing Directions

1. Mix and heat item 1 to 5 to 70°C to 75°C.
2. Mix and heat items 6 and 7 to 70°C to 75°C. While stirring, add this to the mixture made earlier.
3. Begin cooling, continue stirring until batch reaches 30°C, and then homogenize.

Zinc Oxide Ointment with Vitamin E and Aloe

Zinc oxide ointment with vitamin E and aloe's active ingredient is zinc oxide (11.3%). Its inactive ingredients are aloe vera gel, balsam (specially purified balsam Peru), beeswax, benzoic acid, dimethicone, methyl paraben, mineral oil, propyl paraben, purified water, sodium borate, and tocopheryl (vitamin E acetate).

Zinc Pyrithione Detergent Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
547.50	1	Deionized water	547.50
7.50	2	Hydroxyethyl cellulose	7.50
347.00	3	TEA-lauryl sulfate	347.00
43.00	4	PEG-20 lanolin alcohol ether	43.00
20.00	5	Glycol stearate	20.00
15.00	6	Cocamide MEA	15.00
10.00	7	Zinc pyrithione 48%	20.00
QS	8	Fragrance, preservative	QS

Manufacturing Directions

1. Add item 2 to the water and mix. In a separate vessel, combine items 3 to 5, heat to 80°C, and mix.
2. Cool to 50°C. Add items 6 and 7 and mix. Add this mixture to mixture of item 2.
3. Cool to 40°C and add item 8.

Zinc Undecylenate Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
7.50	1	Magnesium aluminum silicate	7.50
487.50	2	Deionized water	487.50
100.00	3	Sorbitol 70%	100.00
10.00	4	Polysorbate 80	10.00
200.00	5	Zinc undecylenate	200.00
50.00	6	Caprylic acid	50.00
30.00	7	C12-C15 alcohols benzoate	30.00
15.00	8	Polysorbate 80	15.00
20.00	9	C18-C36 acid	20.00
80.00	10	Glyceryl stearate and PEG-100 stearate	80.00
QS	11	Preservatives	QS

Manufacturing Directions

1. Slowly add item 1 in the water, mixing with maximum available shear until smooth.
2. Add items 2 to 5 in order, mixing each until uniform. Avoid incorporating air. Heat while stirring to 70°C to 75°C.
3. Heat items 6 to 10 separately to 70°C to 75°C and add to the above mixture, mixing while cooling. Fill at 45°C to 50°C.

Zirconium Oxide Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
15.00	1	Magnesium aluminum silicate	15.00
3.00	2	Carboxymethylcellulose sodium medium viscosity	3.00
796.50	3	Water	796.50
40.00	4	Zirconium oxide	40.00
50.00	5	Propylene glycol	50.00
80.00	6	Isopropyl alcohol	80.00
15.00	7	Benzocaine	15.00
0.50	8	Menthol	0.50
QS	9	Preservative	QS

Manufacturing Directions

1. Dry blend items 1 and 2 and add them to water slowly while agitating with maximum shear until smooth.
2. Add items 4 and 5 and then items 6 to 9. Mix.

COMMERCIAL PHARMACEUTICAL FORMULATIONS

Accuzyme contains papain, USP (6.5 × 10.5 USP units of activity based on Lot I0C389 per gram of ointment) and urea, USP 10%, in a hydrophilic ointment base composed of emulsifying wax, fragrance, glycerin, isopropyl palmitate, lactose, methyl paraben, potassium phosphate monobasic, propyl paraben, and purified water.

- Acticin (permethrin) cream 5% is available in an off-white vanishing cream base. It is a yellow to light orange-brown, low-melting solid or viscous liquid. Each gram of Acticin cream, 5%, contains permethrin 50 mg (5%) and the inactive ingredients butylated hydroxytoluene, carbomer 934P, coconut oil, glycerin, glyceryl stearate, isopropyl myristate, lanolin alcohols, light mineral oil, polyoxyethylene cetyl ethers, purified water, and sodium hydroxide. Formaldehyde 1 mg (0.1%) is added as a preservative.
- Aldara, each gram of the 5% cream contains 50 mg of imiquimod in an off-white oil-in-water vanishing cream base consisting of isostearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methyl paraben, and propyl paraben.
- Anbesol, active ingredients: Anbesol is an oral anesthetic which is available in a maximum strength gel and liquid. Anbesol Junior, available in a gel, is an oral anesthetic. Baby Anbesol, available in a grape-flavored gel, is an oral anesthetic and is alcohol free. Maximum strength Anbesol gel and liquid contain benzocaine, 20%. Anbesol junior gel contains benzocaine, 10%. Baby Anbesol gel contains benzocaine, 7.5%. Inactive ingredients: maximum strength gel: benzyl alcohol, carbomer 934P, D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 40, flavor, glycerin, methyl paraben, polyethylene glycol, propylene glycol, saccharin. Maximum strength liquid: benzyl alcohol, D&C yellow No. 10, FD&C blue No. 1, FD&C red No. 40, flavor, methyl paraben, polyethylene glycol, propylene glycol, saccharin. Junior gel: artificial flavor, benzyl alcohol, carbomer 934P, D&C red No. 33, glycerin, methyl paraben, polyethylene glycol, potassium acesulfame. Grape baby gel: benzoic acid, carbomer 934P, D&C red No. 33, edetate disodium, FD&C blue No. 1, flavor, glycerin, methyl paraben, polyethylene glycol, propyl paraben, saccharin, water.
- AndroGel® (testosterone gel), 1%, is a clear, colorless hydroalcoholic gel containing 1% testosterone. AndroGel provides continuous transdermal delivery of testosterone, the primary circulating endogenous androgen, for 24 hours following a single application to intact, clean dry skin of the shoulders, upper arms, and/or abdomen. A daily application of AndroGel 5, 7.5, or 10 g contains 50, 75, or 100 mg of testosterone respectively, to be applied daily to the skin's surface. Approximately 10% of the applied testosterone dose is absorbed across skin of average permeability during a 24-hour period. The active pharmacologic ingredient in AndroGel is testosterone. Testosterone USP is a white to practically white crystalline powder. Inactive ingredients in AndroGel are ethanol, 67.0%, purified water, sodium hydroxide, carbomer 980 and isopropyl myristate; these ingredients are not pharmacologically active.
- Avar™- E emollient cream (sodium sulfacetamide, 10%, and sulfur, 5%) in each gram contains 100 mg of sodium sulfacetamide and 50 mg of colloidal sulfur in an emollient cream vehicle containing purified water, isostearyl palmitate, glyceryl stearate and PEG-100 stearate, sodium lactate USP, glycerin USP, self-emulsifying wax NF, zinc oxide USP, benzyl alcohol NF, nicotinamide, cetyl alcohol NF, dimethicone, sodium thiosulfate, phenoxyethanol, disodium EDTA, fragrance. Each gram of Avar- E green cream (sodium sulfacetamide 10% and sulfur 5%) color corrective emollient cream contains 100 mg of sodium sulfacetamide and 50 mg of colloidal sulfur in an emollient cream vehicle containing purified water, isostearyl palmitate, glyceryl stearate and PEG-100 stearate, sodium lactate USP, glycerin USP, self-emulsifying wax NF, zinc oxide USP, benzyl alcohol NF, chromium oxide green, nicotinamide, cetyl alcohol NF, dimethicone, sodium thiosulfate, phenoxyethanol, disodium EDTA, fragrance.
- Avar gel (sodium sulfacetamide 10% and sulfur 5%) in each gram contains 100 mg of sodium sulfacetamide and 50 mg of colloidal sulfur in an aqueous-based emollient

gel vehicle containing purified water USP, sodium magnesium silicate, emulsifying lipids, nicotinamide, disodium EDTA, sodium thiosulfate, zinc oxide, benzyl alcohol, phenoxyethanol, glycerin, xanthan gum, sodium lactate, polyacrylamide, C13-C14 isoparaffin, laureth-7, fragrance. Each gram of Avar green (sodium sulfacetamide, 10%, and sulfur, 5%) color corrective gel contains 100 mg of sodium sulfacetamide and 50 mg of colloidal sulfur in an aqueous-based emollient gel vehicle containing purified water USP, sodium magnesium silicate, emulsifying lipids, nicotinamide, disodium EDTA, sodium thiosulfate, zinc oxide, benzyl alcohol, phenoxyethanol, glycerin, xanthan gum, sodium lactate, polyacrylamide, C13-C14 isoparaffin, laureth-7, fragrance, chromium oxide green.

- Avita® cream, a topical retinoid, contains tretinoin 0.025% by weight in a hydrophilic cream vehicle of stearic acid, polyolprepolymer-2, isopropyl myristate, polyoxyl 40 stearate, propylene glycol, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene, and purified water.
- Avita gel, a topical retinoid, contains tretinoin 0.025% by weight in a gel vehicle of butylated hydroxytoluene, hydroxypropyl cellulose, polyolprepolymer-2, and ethanol (denatured with tertiary butyl alcohol and brucine sulfate) 83% w/w.
- BenzaClin® topical gel contains clindamycin phosphate. BenzaClin topical gel also contains benzoyl peroxide for topical use. Each gram of BenzaClin topical gel contains, as dispensed, 10 mg (1%) clindamycin as phosphate and 50 mg (5%) benzoyl peroxide in a base of carbomer, sodium hydroxide, dioctyl sodium sulfosuccinate, and purified water.
- Brevoxyl-4 creamy wash and Brevoxyl-8 creamy wash are topical preparations containing benzoyl peroxide as the active ingredient. Brevoxyl-4 creamy wash and Brevoxyl-8 creamy wash contain 4% and 8% benzoyl peroxide respectively, in a lathering cream vehicle containing cetostearyl alcohol, cocamidopropyl betaine, cornstarch, dimethyl isosorbide, glycerin, glycolic acid, hydrogenated castor oil, imidurea, methyl paraben, mineral oil, peg-14M, purified water, sodium hydroxide, sodium PCA, sodium potassium lauryl sulfate, titanium dioxide.
- Brevoxyl-4 gel and Brevoxyl-8 gel are topical preparations containing benzoyl peroxide 4% and 8% respectively, as the active ingredient in a gel vehicle containing purified water, cetyl alcohol, dimethyl isosorbide, fragrance, simethicone, stearyl alcohol, and ceteareth-20.
- Camptosar injection (irinotecan hydrochloride injection) is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes: 2 mL fill vials contain 40 mg irinotecan hydrochloride and 5 mL fill vials contain 100 mg irinotecan hydrochloride. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 45 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range: 3.0–3.8) with sodium hydroxide or hydrochloric acid. Camptosar is intended for dilution with 5% dextrose injection, USP (D5W), or 0.9% sodium chloride injection, USP, prior to intravenous infusion. The preferred diluent is 5% dextrose injection, USP.
- Carac® (fluorouracil cream) cream, 0.5%, contains fluorouracil for topical dermatologic use. Carac cream contains 0.5% fluorouracil, with 0.35% being incorporated into a patented porous microsphere (Microsponge) composed of methyl methacrylate/glycol dimethacrylate crosspolymer and dimethicone. The cream formulation contains the following other inactive ingredients: carbomer 940, dimethicone, glycerin, methyl gluceth-20, methyl methacrylate/glycol dimethacrylate crosspolymer, methyl paraben, octyl hydroxy stearate, polyethylene glycol 400, polysorbate 80, propylene glycol, propyl paraben, purified water, sorbitan monooleate, stearic acid, and trolamine.
- Caverject contains alprostadil as the naturally occurring form of prostaglandin E 1. Caverject Impulse is available as a disposable, single-dose dual-chamber syringe system. The system includes a glass cartridge, which contains sterile, freeze-dried alprostadil in the front chamber and sterile bacteriostatic water for injection in the rear chamber. The alprostadil is reconstituted with the sterile bacteriostatic water just before injection. Caverject Impulse is available in two strengths for intracavernosal administration: 10 μg—The reconstituted solution has a volume of 0.64 mL. The delivered volume, 0.5 mL, contains 10 μg of alprostadil, 324.7 μg of alpha-cyclodextrin, 45.4 mg of lactose, 23.5 μg of sodium citrate, and 4.45 mg of benzyl alcohol. 20 μg—The reconstituted solution has a volume of 0.64 mL. The delivered volume, 0.5 mL, contains 20 μg of alprostadil, 649.3 μg of alpha-cyclodextrin, 45.4 mg of lactose, 23.5 μg of sodium citrate, and 4.45 mg of benzyl alcohol. When necessary, the pH of the alprostadil for injection was adjusted with hydrochloric acid and/or sodium hydroxide before lyophilization.
- Claripel cream, active ingredient: Hydroquinone USP 4%. Other ingredients: avobenzone, ceteareth-20, cetostearyl alcohol, citric acid, diethylaminoethyl stearate, dimethicone, edetate disodium, glyceryl dilaurate, glyceryl monostearate, glyceryl stearate, PEG-100 stearate, hydroxyethyl cellulose, methyl paraben, octyldodecyl stearoyl stearate, octinoxate, oxybenzone, polysorbate 80, propylene glycol, propyl gallate, propyl paraben, purified water, quaternium-26, sodium metabisulfite, sodium PCA, squalane, ubiquinone, stearyl alcohol, water, glycerin, *Rumex occidentalis* extract.
- Cleocin vaginal ovules are semisolid, white to off-white suppositories for intravaginal administration. Each 2.5-g suppository contains clindamycin phosphate equivalent to 100 mg clindamycin in a base consisting of a mixture of glycerides of saturated fatty acids.
- Climara Pro™ (estradiol/levonorgestrel transdermal system) is an adhesive-based matrix transdermal patch designed to release both estradiol and levonorgestrel, a progestational agent, continuously upon application to intact skin. The 22 cm^2 Climara Pro system contains 4.40 mg estradiol and 1.39 mg levonorgestrel and provides a nominal delivery rate (mg/d) of 0.045 estradiol and 0.015 levonorgestrel. The ClimaraPro system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene backing film, (2) an acrylate adhesive matrix containing estradiol and levonorgestrel, and (3) a protective liner of either siliconized or fluoropolymer-coated polyester film. The protective liner is attached to the adhesive surface and must be removed before the system can be used. The active components of the system are estradiol and levonorgestrel. The remaining components of the system (acrylate copolymer adhesive and polyvinylpyrrolidone/vinyl acetate copolymer) are pharmacologically inactive.
- Climara®, estradiol transdermal system, is designed to release 17(beta)-estradiol continuously upon application to intact skin. Six (6.5, 9.375, 12.5, 15.0, 18.75, and 25.0 cm^2) systems are available to provide nominal in vivo delivery of 0.025, 0.0375, 0.05, 0.060, 0.075, or 0.1 mg respectively of

estradiol per day. The period of use is 7 days. Each system has a contact surface area of either 6.5, 9.375, 12.5, 15.0, 18.75, or 25.0 cm^2 and contains 2.0, 2.85, 3.8, 4.55, 5.7, or 7.6 mg of estradiol USP respectively. The composition of the systems per unit area is identical. The Climara system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film and (2) an acrylate adhesive matrix containing estradiol USP. A protective liner (3) of siliconized or fluoropolymer-coated polyester film is attached to the adhesive surface and must be removed before the system can be used. The active component of the system is 17(beta)-estradiol. The remaining components of the system (acrylate copolymer adhesive, fatty acid esters, and polyethylene backing) are pharmacologically inactive.

- Clindagel® (clindamycin phosphate gel) topical gel, 1%, a topical antibiotic, contains clindamycin phosphate, USP, at a concentration equivalent to 10 mg clindamycin per gram in a gel vehicle consisting of carbomer 941, methyl paraben, polyethylene glycol 400, propylene glycol, sodium hydroxide, and purified water.
- Clindesse™ is a semisolid white cream, which contains clindamycin phosphate, USP, at a concentration equivalent to 20 mg clindamycin base per gram. The cream also contains edetate disodium, glycerol monoisostearate, lecithin, methyl paraben, microcrystalline wax, mineral oil, polyglyceryl-3-oleate, propyl paraben, purified water, silicon dioxide, and sorbitol solution.
- Clobevate® (clobetasol propionate gel) for topical administration contains clobetasol propionate 0.5 mg in a base of propylene glycol, carbomer 934P, sodium hydroxide, and purified water.
- Colace® (glycerin) suppositories, active ingredient (per suppository): Colace suppositories contain glycerin, USP 2.1 g. Inactive ingredients: purified water, sodium hydroxide, stearic acid. Colace suppositories contains glycerin, USP 1.2 g.
- CombiPatch® (estradiol/norethindrone acetate transdermal system) is an adhesive-based matrix transdermal patch. The remaining components of the system are pharmacologically inactive. Two systems are available, providing the following delivery rates of estradiol and norethindrone acetate: 9 scm^2 round 0.62 mg estradiol and 2.7 mg NETA; release rates: 0.05/0.14 mg/d; 16 cm^2 round 0.51 estradiol and 4.8 mg NETA; release rates 0.05/0.25 mg/d respectively. Estradiol USP (estradiol) is a white to creamy-white, odorless crystalline powder. Norethindrone acetate USP is a white to creamy-white, odorless crystalline powder. CombiPatch transdermal systems are comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin film backing; (2) an adhesive layer containing estradiol, norethindrone acetate, acrylic adhesive, silicone adhesive, oleyl alcohol, oleic acid NF, povidone USP and dipropylene glycol; and (3) a polyester-release protective liner, which is attached to the adhesive surface and must be removed before the system can be used.
- Cutivate (fluticasone propionate ointment) ointment, 0.005%, contains fluticasone propionate, a synthetic fluorinated corticosteroid for topical dermatologic use. Each gram of Cutivate ointment contains fluticasone propionate 0.05 mg in a base of liquid paraffin, microcrystalline wax, propylene glycol, and sorbitan sesquioleate. Each gram of Cutivate lotion contains 0.5 mg fluticasone propionate in a base of cetostearyl alcohol, isopropyl myristate, propylene glycol, cetomacrogol 1000, dimethicone 360, citric acid, sodium citrate, and purified water, with imidurea, methyl paraben, and propyl paraben as preservatives. Each gram of Cutivate cream contains fluticasone propionate 0.5 mg in a base of propylene glycol, mineral oil, cetostearyl alcohol, ceteth-20, isopropyl myristate, dibasic sodium phosphate, citric acid, purified water, and imidurea as preservative.
- Denavir containing penciclovir is available for topical administration as a 1% white cream. Each gram of Denavir contains 10 mg of penciclovir and the following inactive ingredients: cetomacrogol 1000 BP, cetostearyl alcohol, mineral oil, propylene glycol, purified water, and white petrolatum.
- Diastat rectal delivery system is a nonsterile diazepam gel provided in a prefilled, unit-dose, rectal delivery system. Diastat contains 5 mg/mL diazepam, propylene glycol, ethyl alcohol (10%), hydroxypropylmethylcellulose, sodium benzoate, benzyl alcohol (1.5%), benzoic acid, and water. Diastat is clear to slightly yellow and has a pH between 6.5 and 7.2. Diazepam, the active ingredient of Diastat, is a benzodiazepine anticonvulsant with the chemical name 7-chloro-1, 3-dihydro-1-methyl-5-phenyl-2H-1, 4-benzodiazepin-2-one.
- Differin® (adapalene) cream, 0.1%, contains adapalene 0.1% in an aqueous cream emulsion consisting of carbomer 934P, cyclomethicone, edetate disodium, glycerin, methyl glucose sesquistearate, methyl paraben, PEG-20 methyl glucose sesquistearate, phenoxyethanol, propyl paraben, purified water, squalane, and trolamine.
- Dilaudid suppositories (for rectal administration) contain 3 mg hydromorphone hydrochloride in a cocoa butter base with silicon dioxide.
- Dinoprostone vaginal insert is a thin, flat polymeric slab, which is rectangular in shape with rounded corners contained within the pouch of an off-white knitted polyester retrieval system. Each slab is buff colored, semitransparent, and contains 10 mg of dinoprostone in a hydrogel insert. An integral part of the knitted polyester retrieval system is a long tape designed to aid retrieval at the end of the dosing interval or earlier if clinically indicated. The finished product is a controlled-release formulation, which has been found to release dinoprostone in vivo at a rate of approximately 0.3 mg/h. Each insert contains 10 mg of dinoprostone in 241 mg of a cross-linked polyethylene oxide/urethane polymer which is a semiopaque, beige-colored, flat rectangular slab measuring 29 mm × 9.5 mm × 0.8 mm in thickness. The insert and its retrieval system, made of polyester yarn, are nontoxic and when placed in a moist environment absorb water, swell, and release dinoprostone.
- Diprolene® ointment contains betamethasone dipropionate. Each gram of Diprolene ointment 0.05% contains 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in Actibase®, an optimized vehicle of propylene glycol, propylene glycol stearate (55% monoester), white wax, and white petrolatum.
- Diprolene AF cream, 0.05%, contains betamethasone dipropionate. Each gram of Diprolene AF cream 0.05% contains 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in an emollient cream base of purified water, USP; chlorocresol; propylene glycol, USP; white petrolatum, USP; white wax, NF; cyclomethicone; sorbitol solution, USP; glyceryl oleate/propylene glycol; ceteareth-30; carbomer 940, NF; and sodium hydroxide.
- Diprolene gel contains betamethasone dipropionate. Each gram of Diprolene gel contains 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone),

in an augmented gel base of purified water, USP; propylene glycol, USP; carbomer 940, NF; and sodium hydroxide, NF or R. May also contain phosphoric acid, NF, to adjust the pH to approximately 4.5.

- Diprolene lotion contains betamethasone dipropionate. Each gram of Diprolene lotion 0.05% contains 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in a lotion base of purified water; isopropyl alcohol (30%); hydroxypropyl cellulose; propylene glycol; sodium phosphate monobasic monohydrate R; phosphoric acid used to adjust the pH to 4.5.
- Diprosone cream, 0.05%, contains betamethasone dipropionate. Each gram of Diprosone cream 0.05% contains 0.643 mg betamethasone dipropionate, USP (equivalent to 0.5 mg betamethasone), in a hydrophilic emollient cream consisting of purified water, USP; mineral oil, USP; white petrolatum, USP; ceteareth-30; cetearyl alcohol 70/30 (7.2%); sodium phosphate monobasic monohydrate R; and phosphoric acid, NF; chlorocresol and propylene glycol, USP as preservatives. May also contain sodium hydroxide R to adjust pH to approximately 5.
- Dovonex® (calcipotriene ointment) ointment, 0.005%, contains calcipotriene 50 μg/g in an ointment base of dibasic sodium phosphate, edetate disodium, mineral oil, petrolatum, propylene glycol, tocopherol, steareth-2, and water. Dovonex (calcipotriene cream) cream, 0.005%, contains calcipotriene monohydrate, a synthetic vitamin D_3 derivative, for topical dermatological use. Calcipotriene monohydrate is a white or off-white crystalline substance. Dovonex cream contains calcipotriene monohydrate equivalent to 50 μg/g anhydrous calcipotriene in a cream base of cetearyl alcohol, ceteth-20, diazolidinyl urea, dichlorobenzyl alcohol, dibasic sodium phosphate, edetate disodium, glycerin, mineral oil, petrolatum, and water.
- Duac® topical cel contains clindamycin phosphate, equivalent to 1% clindamycin, and 5% benzoyl peroxide. Each gram of Duac topical gel contains 10 mg (1%) clindamycin, as phosphate and 50 mg (5%) benzoyl peroxide in a base consisting of carbomer 940, dimethicone, disodium lauryl sulfosuccinate, edetate disodium, glycerin, silicon dioxide, methyl paraben, poloxamer, purified water, and sodium hydroxide.
- Duac topical gel contains clindamycin phosphate, equivalent to 1% clindamycin, and 5% benzoyl peroxide. Each gram of Duac topical gel contains 10 mg (1%) clindamycin, as phosphate, and 50 mg (5%) benzoyl peroxide in a base consisting of carbomer 940, dimethicone, disodium lauryl sulfosuccinate, edetate disodium, glycerin, silicon dioxide, methyl paraben, poloxamer, purified water, and sodium hydroxide.
- Efudex cream is a topical preparation containing the fluorinated pyrimidine 5-fluorouracil. Efudex cream contains 5% fluorouracil in a vanishing cream base consisting of white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60, and parabens (methyl and propyl).
- Elidel® (pimecrolimus) cream, 1%, contains the compound pimecrolimus. Each gram of Elidel cream, 1%, contains 10 mg of pimecrolimus in a whitish cream base of benzyl alcohol, cetyl alcohol, citric acid, mono- and diglycerides, oleyl alcohol, propylene glycol, sodium cetostearyl sulphate, sodium hydroxide, stearyl alcohol, triglycerides, and water.
- Elocon® (mometasone furoate cream) cream, 0.1%, contains mometasone furoate, USP, for dermatologic use. Each gram of Elocon cream 0.1% contains 1 mg mometasone furoate, USP, in a cream base of hexylene glycol, phosphoric acid, propylene glycol stearate (55% monoester), stearyl alcohol and ceteareth-20, titanium dioxide, aluminum starch octenylsuccinate (gamma irradiated), white wax, white petrolatum, and purified water.
- Elocon (mometasone furoate ointment, USP) ointment, 0.1%, contains mometasone furoate, USP, for dermatologic use. Each gram contains 1 mg mometasone furoate, USP, in an ointment base of hexylene glycol, phosphoric acid, propylene glycol stearate (55% monoester), white wax, white petrolatum, and purified water.
- Elocon (mometasone furoate topical solution) lotion, 0.1%, contains mometasone furoate, USP, for dermatologic use. Each gram of Elocon lotion, 0.1%, contains 1 mg mometasone furoate, USP, in a lotion base of isopropyl alcohol (40%), propylene glycol, hydroxypropyl cellulose, sodium phosphate monobasic monohydrate R, and water. May also contain phosphoric acid used to adjust the pH to approximately 4.5.
- Elspar (asparaginase), the specific activity of Elspar is at least 225 IU/mg of protein and each vial contains 10000 IU of asparaginase and 80 mg of mannitol, an inactive ingredient, as a sterile, white lyophilized plug or powder for intravenous or intramuscular injection after reconstitution.
- Erygel® topical gel contains erythromycin. Each gram of Erygel topical gel contains 20 mg of erythromycin, USP, in a base of alcohol 92% and hydroxypropyl cellulose.
- EstroGel® (estradiol gel) contains 0.06% estradiol in an absorptive hydroalcoholic gel base formulated to provide a controlled release of the active ingredient. An EstroGel unit dose of 1.25 g contains 0.75 mg of estradiol. The active component of the transdermal gel is estradiol. The remaining components of the gel (purified water, alcohol, triethanolamine, and carbomer 934P) are pharmacologically inactive.
- Evoclin (clindamycin phosphate) foam, 1%, a topical antibiotic in a foam vehicle, contains clindamycin phosphate, USP, at a concentration equivalent to 10 mg clindamycin per gram in a vehicle consisting of cetyl alcohol, dehydrated alcohol (ethanol 58%), polysorbate 60, potassium hydroxide, propylene glycol, purified water, and stearyl alcohol, pressurized with a hydrocarbon (propane/butane) propellant.
- Finacea® (azelaic acid) gel, 15%, each gram of Finacea gel, 15%, contains 0.15 g azelaic acid (15% w/w) as the active ingredient in an aqueous gel base containing benzoic acid (as a preservative), disodium-EDTA, lecithin, medium-chain triglycerides, polyacrylic acid, polysorbate 80, propylene glycol, purified water, and sodium hydroxide to adjust pH.
- Gynazole 1® (butoconazole nitrate) vaginal cream, 2%, contains butoconazole nitrate 2%, an imidazole derivative with antifungal activity. Gynazole 1 contains 2% butoconazole nitrate in a cream of edetate disodium, glyceryl monoisostearate, methyl paraben, mineral oil, polyglyceryl-3 oleate, propylene glycol, propyl paraben, colloidal silicon dioxide, sorbitol solution, purified water, and microcrystalline wax.
- Gynazole 1 (butoconazole nitrate) vaginal cream, 2%, contains butoconazole nitrate 2%. Gynazole 1 contains 2% butoconazole nitrate in a cream of edetate disodium, glyceryl monoisostearate, methyl paraben, mineral oil, polyglyceryl-3 oleate, propylene glycol, propyl paraben, colloidal silicon dioxide, sorbitol solution, purified water, and microcrystalline wax.
- Hydrocortisone, 1%, inactive ingredients: BHA, carboxymethylcellulose sodium, cetyl alcohol, citric acid,

edetate disodium, glycerin, glyceryl oleate, glyceryl stearate, lanolin, methyl paraben, petrolatum, propyl gallate, propylene glycol, propyl paraben, simethicone, sodium benzoate, sodium lauryl sulfate, stearyl alcohol, water, xanthan gum.

- Indocin suppositories for rectal use contain 50 mg of indomethacin and the following inactive ingredients: butylated hydroxyanisole, butylated hydroxytoluene, edetic acid, glycerin, polyethylene glycol 3350, polyethylene glycol 8000, and sodium chloride.
- Klaron® (sodium sulfacetamide lotion) lotion, 10%, contains 100 mg of sodium sulfacetamide in a vehicle consisting of purified water; propylene glycol; lauramide DEA (and) diethanolamine; polyethylene glycol 400, monolaurate; hydroxyethyl cellulose; sodium chloride; sodium metabisulfite; methyl paraben; xanthan gum; EDTA; and simethicone.
- Loprox® gel (ciclopirox), 0.77%, each gram of Loprox gel contains 7.70 mg of ciclopirox in a gel consisting of purified water USP, isopropyl alcohol USP, octyldodecanol NF, dimethicone copolyol 190, carbomer 980, sodium hydroxide NF, and docusate sodium USP. Loprox gel is a white slightly fluid gel.
- Lotrimin cream contains 10 mg clotrimazole, USP, in a vanishing cream base of benzyl alcohol NF (1%), cetearyl alcohol 70/30 (10%), cetyl esters wax NF, octyldodecanol NF, polysorbate 60 NF, sorbitan monostearate NF, and purified water USP.
- Lotrisone cream and lotion contain combinations of clotrimazole and betamethasone dipropionate. Each gram of Lotrisone cream contains 10 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in a hydrophilic cream consisting of purified water, mineral oil, white petrolatum, cetyl alcohol plus stearyl alcohol, ceteareth-30, propylene glycol, sodium phosphate monobasic monohydrate, and phosphoric acid; benzyl alcohol as preservative.
- Lotrisone lotion contains 10 mg clotrimazole and 0.643 mg betamethasone dipropionate (equivalent to 0.5 mg betamethasone) in a hydrophilic base of purified water, mineral oil, white petrolatum, cetyl alcohol plus stearyl alcohol, ceteareth-30, propylene glycol, sodium phosphate monobasic monohydrate, and phosphoric acid; benzyl alcohol as a preservative. Lotrisone lotion may contain sodium hydroxide.
- Lustra-Ultra™, USP 4%, other ingredients (Lustra®): purified water USP, phenyl trimethicone, glycerin 99% USP, glyceryl stearate (and) PEG-100 stearate, alcohol, cetyl alcohol NF, cyclopentasiloxane (and) polysilicone-11, linoleic acid, glycolic acid, polyacrylamide (and) c13-14 isoparaffin (and) laureth-7, cetearyl alcohol (and) ceteareth-20, triethanolamine 99% USP, tocopheryl acetate USP, hydrogenated lecithin, phenoxyethanol, magnesium 1-ascorbyl phosphate NF, benzyl alcohol NF, dimethiconol, sodium metabisulfite NF, sodium citrate USP, disodium EDTA USP, butylated hydroxytoluene, vitamin E USP, carbomer NF, fragrance. Other ingredients (Lustra-AF®): purified water USP, octyl methoxycinnamate, glycerin 99% USP, phenyl trimethicone, glyceryl stearate (and) PEG-100 stearate, cetyl alcohol NF, alcohol, avobenzone, cyclopentasiloxane (and) polysilicone-11, linoleic acid, glycolic acid, polyacrylamide (and) C 13-14 isoparaffin (and) laureth-7, cetearyl alcohol (and) ceteareth-20, triethanolamine 99% USP, hydrogenated lecithin, tocopheryl acetate USP, phenoxyethanol, benzyl alcohol NF, magnesium 1-ascorbyl phosphate NF, dimethiconol, sodium metabisulfite NF, sodium citrate USP, disodium EDTA USP, butylated hydroxytoluene, vitamin E USP, carbomer NF, fragrance. Other ingredients (Lustra-Ultra): purified water USP, octinoxate USP, propylene glycol USP, cetyl alcohol NF, glyceryl stearate (and) PEG-100 stearate, avobenzone USP, cyclomethicone NF, cetearyl glucoside, capric caprylic triglyceride, microcrystalline wax NF, dimethicone NF, magnesium ascorbyl phosphate, polysorbate 20 NF, xanthan gum NF, retinol, sodium metabisulfite NF, methyl paraben NF, disodium EDTA USP, propyl paraben NF, vitamin E USP
- Luxiq contains betamethasone valerate, USP. Each gram of Luxiq contains 1.2 mg betamethasone valerate, USP, in a hydroalcoholic, thermolabile foam. The foam also contains cetyl alcohol, citric acid, ethanol (60.4%), polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol and is dispensed from an aluminum can pressurized with a hydrocarbon propellant (propane/butane).
- Mederma® is a topical gel for scar treatment. Ingredients: water (purified), PEG-4, *Allium cepa* (onion) bulb extract, xanthan gum, allantoin, fragrance, methyl paraben, sorbic acid.
- Menostar, estradiol transdermal system, is designed to provide nominal in vivo delivery of 14 μg 17(beta)-estradiol per day continuously upon application to intact skin. The period of use is 7 days. The transdermal system has a contact surface area of 3.25 cm^2 and contains 1 mg of estradiol USP. The Menostar transdermal system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyethylene film and (2) an acrylate adhesive matrix containing estradiol USP. A protective liner (3) of siliconized or fluoropolymer-coated polyester film is attached to the adhesive surface and must be removed before the transdermal system can be used. The active component of the transdermal system is 17(beta)-estradiol. The remaining components of the transdermal system (acrylate copolymer adhesive, fatty acid esters, and polyethylene backing) are pharmacologically inactive.
- Mentax® cream, 1%, contains the synthetic antifungal agent, butenafine hydrochloride. Each gram of Mentax cream, 1%, contains 10 mg of butenafine HCl in a white cream base of purified water USP, propylene glycol dicaprylate, glycerin USP, cetyl alcohol NF, glyceryl monostearate SE, white petrolatum USP, stearic acid NF, polyoxyethylene (23) cetyl ether, benzyl alcohol NF, diethanolamine NF, and sodium benzoate NF.
- Metrogel-Vaginal is the intravaginal dosage form of the synthetic antibacterial agent, metronidazole, USP, at a concentration of 0.75%. Metrogel-Vaginal is a gelled, purified water solution containing metronidazole at a concentration of 7.5 mg/g (0.75%). The gel is formulated at pH 4. The gel also contains carbomer 934P, edetate disodium, methyl paraben, propyl paraben, propylene glycol, and sodium hydroxide. Each applicator full of 5 g of vaginal gel contains approximately 37.5 mg of metronidazole.
- Naftin® cream, 1%, contains naftifine hydrochloride 1%. Inactive ingredients: benzyl alcohol, cetyl alcohol, cetyl esters wax, isopropyl myristate, polysorbate 60, purified water, sodium hydroxide, sorbitan monostearate, and stearyl alcohol. Hydrochloric acid may be added to adjust pH.
- Naftin gel, 1%, contains naftifine hydrochloride. Naftin gel, 1%, is for topical use only. Active ingredient: naftifine hydrochloride, 1%. Inactive ingredients: polysorbate 80,

carbomer 934P, diisopropanolamine, edetate disodium, alcohol (52% v/v), and purified water.

- Nitro-Dur (nitroglycerin) transdermal infusion system is a flat unit designed to provide continuous controlled release of nitroglycerin through intact skin. The rate of release of nitroglycerin is linearly dependent upon the area of the applied system; each square centimeter of applied system delivers approximately 0.02 mg of nitroglycerin per hour. Thus, the 5-, 10-, 15-, 20-, 30-, and 40-cm^2 systems deliver approximately 0.1, 0.2, 0.3, 0.4, 0.6, and 0.8 mg of nitroglycerin per hour respectively. The remainder of the nitroglycerin in each system serves as a reservoir and is not delivered in normal use. After 12 hours, for example, each system has delivered approximately 6% of its original content of nitroglycerin. The Nitro-Dur transdermal system contains nitroglycerin in acrylic-based polymer adhesives with a resinous cross-linking agent to provide a continuous source of active ingredient. Each unit is sealed in a paper polyethylene-foil pouch.
- Noritate® (metronidazole cream) cream, 1%, is an emollient cream; each gram contains 10 mg micronized metronidazole USP, in a base of purified water USP, stearic acid NF, glyceryl monostearate NF, glycerin USP, methyl paraben NF, trolamine NF, and propyl paraben NF.
- Olux foam contains clobetasol propionate, USP. Each gram of Olux Foam contains 0.5 mg clobetasol propionate, USP, in thermolabile foam, which consists of cetyl alcohol, citric acid, ethanol (60%), polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol. Olux foam is dispensed from an aluminum can pressurized with a hydrocarbon propellant (propane/butane).
- Ovide lotion contains 0.005 g of malathion per milliliter in a vehicle of isopropyl alcohol (78%), terpineol, dipentene, and pine needle oil.
- Oxistat cream and lotion, Oxistat cream contains 10 mg of oxiconazole per gram of cream in a white to off-white opaque cream base of purified water USP, white petrolatum USP, stearyl alcohol NF, propylene glycol USP, polysorbate 60 NF, cetyl alcohol NF, and benzoic acid USP 0.2% as a preservative. Oxistat lotion contains 10 mg of oxiconazole per gram of lotion in a white to off-white opaque lotion base of purified water USP, white petrolatum USP, stearyl alcohol NF, propylene glycol USP, polysorbate 60 NF, cetyl alcohol NF, and benzoic acid USP 0.2% as a preservative.
- Oxytrol (oxybutynin) transdermal system is designed to deliver oxybutynin continuously and consistently over a 3- to 4-day interval after application to intact skin. Oxytrol is available as a 39 cm^2 system containing 36 mg of oxybutynin. Oxytrol has a nominal in vivo delivery rate of 3.9 mg oxybutynin per day through skin of average permeability (interindividual variation in skin permeability is approximately 20%).
- Panafil ointment contains papain, USP (not less than 405, 900 USP units of activity based on Lot I0C389 per gram of ointment), urea, USP 10%, and chlorophyllin copper complex sodium USP 0.5% in a hydrophilic base composed of boric acid, chlorobutanol (anhydrous) as a preservative, polyoxyl 40 stearate, propylene glycol, purified water, sodium borate, sorbitan monostearate, stearyl alcohol, and white petrolatum.
- Pandel cream contains hydrocortisone probutate. Each gram of Pandel (hydrocortisone probutate cream) cream, 0.1%, contains 1 mg of hydrocortisone probutate in a cream base of propylene glycol, white petrolatum, light mineral oil, stearyl alcohol, polysorbate 60, sorbitan monostearate, glyceryl monostearate, PEG-20 stearate, glyceryl stearate SE, methyl paraben, butylparaben, citric acid, sodium citrate anhydrous, and purified water.
- Permethrin lotion, each fluid ounce contains active ingredient: permethrin 280 mg (1%). Inactive ingredients: balsam fir Canada, cetyl alcohol, citric acid, FD&C yellow No. 6, fragrance, hydrolyzed animal protein, hydroxyethyl cellulose, polyoxyethylene 10 cetyl ether, propylene glycol, stearalkonium chloride, water, isopropyl alcohol 5.6 g (20%), methyl paraben 56 mg (0.2%), and propyl paraben 22 mg (0.08%).
- Premarin®, each gram of Premarin (conjugated estrogens) vaginal cream contains 0.625 mg conjugated estrogens, USP, in a nonliquefying base containing cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, benzyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil. Premarin vaginal cream is applied intravaginally. Premarin (conjugated estrogens) vaginal cream contains a mixture of conjugated estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of material derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17-alpha-dihydroequilin, 17-alpha-estradiol, and 17-beta-dihydroequilin.
- Preparation H is available in ointment, cream, gel, and suppository product forms. The ointment contains petrolatum, 71.9%, mineral oil, 14%, shark liver, oil 3% and phenylephrine HCl, 0.25%. The maximum strength cream contains white petrolatum, 15%, glycerin, 14.4%, pramoxine HCl, 1%, and phenylephrine HCl, 0.25%. The suppositories contain cocoa butter, 85.5%, shark liver oil, 3%, and phenylephrine HCl, 0.25%. The cooling gel contains phenylephrine HCl, 0.25%, and witch hazel, 50%. Inactive ingredients: ointment–benzoic acid, BHA, BHT, corn oil, glycerin, lanolin, lanolin alcohol, methyl paraben, paraffin, propyl paraben, thyme oil, tocopherol, water, wax. maximum strength cream: aloe barbadensis leaf extract, BHA, carboxymethylcellulose sodium, cetyl alcohol, citric acid, edetate disodium, glyceryl stearate, laureth-23, methyl paraben, mineral oil, panthenol, propyl gallate, propylene glycol, propyl paraben, purified water, sodium benzoate, steareth-2, steareth-20, stearyl alcohol, tocopherol, vitamin E, xanthan gum. Suppositories: methyl paraben, propyl paraben, starch. Cooling gel: aloe barbadensis gel, benzophenone-4, edetate disodium, hydroxyethyl cellulose, methyl paraben, polysorbate 80, propylene glycol, propyl paraben, sodium citrate, vitamin E, water
- Prochieve® (progesterone gel) is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single-use, one-piece polyethylene vaginal applicators. The carrier vehicle is an oil-in-water emulsion containing the water-swellable, but insoluble, polymer, polycarbophil. The progesterone is partially soluble in both the oil and water phase of the vehicle, with the majority of the progesterone existing as a suspension. Physically, Prochieve has the appearance of a soft, white to off-white gel. The active ingredient, progesterone, is present in either a 4% or an 8% concentration (w/w). Progesterone exists in two polymorphic forms. Form 1, which is the form used in Prochieve, exists as white orthorhombic prisms with a melting point of 127°C to 131°C. Each applicator delivers 1.125 g of Prochieve gel containing either 45 mg (4% gel) or 90 mg (8% gel) of progesterone in

a base containing glycerin, mineral oil, polycarbophil, carbomer 934P, hydrogenated palm oil glyceride, sorbic acid, purified water and may contain sodium hydroxide. Form 2, which is not used in pharmaceutical dosage forms is thermodynamically unstable.

- Proctofoam®-HC (hydrocortisone acetate, 1%, and pramoxine hydrochloride, 1%) is a topical aerosol foam for anal use containing hydrocortisone acetate, 1%, and pramoxine hydrochloride, 1%, in a hydrophilic base containing cetyl alcohol, emulsifying wax, methyl paraben, polyoxyethylene-10-stearyl ether, propylene glycol, propyl paraben, purified water, trolamine, and inert propellants: isobutane and propane.
- Protopic (tacrolimus) ointment contains (w/w) either 0.03% or 0.1% of tacrolimus in a base of mineral oil, paraffin, propylene carbonate, white petrolatum, and white wax.
- Psoriatec (anthralin cream, 1%, USP) is a smooth yellow cream containing 1% anthralin USP in an aqueous cream base of glyceryl monolaurate, glyceryl monomyristate, citric acid, sodium hydroxide, and purified water.
- Rosac cream, each gram of Rosac® cream with sunscreens contains 100 mg of sodium sulfacetamide and 50 mg of sulfur in a cream containing avobenzone, benzyl alcohol, C12-15 alkyl benzoate, cetostearyl alcohol, dimethicone, edetate disodium, emulsifying wax, monobasic sodium phosphate, octinoxate, propylene glycol, purified water, sodium thiosulfate, steareth-2, steareth-21.
- Sulfamylon cream is a soft, white, nonstaining, water-miscible, anti-infective cream for topical administration to burn wounds. Each gram of Sulfamylon cream contains mafenide acetate equivalent to 85 mg of the base. The cream vehicle consists of cetyl alcohol, stearyl alcohol, cetyl esters wax, polyoxyl 40 stearate, polyoxyl 8 stearate, glycerin, and water, with methyl paraben, propyl paraben, sodium metabisulfite, and edetate disodium as preservatives.
- Temovate (clobetasol propionate cream and ointment) cream contains clobetasol propionate 0.5 mg/g in a cream base of propylene glycol, glyceryl monostearate, cetostearyl alcohol, glyceryl stearate, PEG-100 stearate, white wax, chlorocresol, sodium citrate, citric acid monohydrate, and purified water. Temovate ointment contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, sorbitan sesquioleate, and white petrolatum.
- Temovate (clobetasol propionate gel) contains clobetasol propionate 0.5 mg/g in a base of propylene glycol, carbomer 934P, sodium hydroxide, and purified water.
- Temovate (clobetasol propionate scalp application) contains clobetasol propionate 0.5 mg/g in a base of purified water, isopropyl alcohol (39.3%), carbomer 934P, and sodium hydroxide.
- Testim® (testosterone gel) is a clear to translucent hydroalcoholic topical gel containing 1% testosterone. Testim provides continuous transdermal delivery of testosterone for 24 hours, following a single application to intact, clean, dry skin of the shoulders and upper arms. The active pharmacological ingredient in Testim is testosterone.
- Vivelle® (estradiol transdermal system) contains estradiol in a multipolymeric adhesive. The system is designed to release estradiol continuously upon application to intact skin. Five systems are available to provide nominal in vivo delivery of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via skin of average permeability. Each corresponding system having an active surface area of 7.25, 11.0, 14.5, 22.0, or 29.0 cm^2 contains 2.17, 3.28, 4.33, 6.57, or 8.66 mg of estradiol USP respectively. The composition of the systems per unit area is identical. The Vivelle system comprises three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent flexible film consisting of an ethylene vinyl alcohol copolymer film, a polyurethane film, urethane polymer, and epoxy resin; (2) an adhesive formulation containing estradiol USP, acrylic adhesive, polyisobutylene, ethylene vinyl acetate copolymer, 1,3-butylene glycol, styrene-butadiene rubber, oleic acid NF, lecithin, propylene glycol, bentonite NF, mineral oil USP, and dipropylene glycol; and (3) a polyester release liner that is attached to the adhesive surface and must be removed before the system can be used. The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.
- Thera-Gesic, active ingredients: methyl salicylate 25%, menthol 4%. Inactive ingredients: aloe vera, carbomer 980, dimethicone, glycerin, methyl paraben, propyl paraben, sodium lauryl sulfate, trolamine, water.
- Topicort® LP (desoximetasone) cream, 0.05%, Topicort (desoximetasone) cream, 0.25%, Topicort (desoximetasone) gel, 0.05%, and Topicort (desoximetasone) ointment, 0.25%, contain the active synthetic corticosteroid desoximetasone. Each gram of Topicort LP cream, 0.05%, contains 0.5 mg of desoximetasone in an emollient cream base consisting of white petrolatum, purified water, isopropyl myristate, lanolin alcohols, mineral oil, cetostearyl alcohol, and edetate disodium. Each gram of Topicort cream, 0.25%, contains 2.5 mg of desoximetasone in an emollient cream base consisting of white petrolatum, purified water, isopropyl myristate, lanolin alcohols, mineral oil, and cetostearyl alcohol. Each gram of Topicort gel, 0.05%, contains 0.5 mg of desoximetasone in a gel base consisting of purified water, docusate sodium, edetate disodium, isopropyl myristate, carbomer 940, trolamine, and SDAG-3, 95% alcohol. Each gram of Topicort ointment, 0.25%, contains 2.5 mg of desoximetasone in an ointment base consisting of white petrolatum and fractionated coconut oil.
- Tri-Luma® cream (fluocinolone acetonide, 0.01%, hydroquinone, 4%, tretinoin, 0.05%) contains fluocinolone acetonide, USP, hydroquinone, USP, and tretinoin, USP, in a hydrophilic cream base for topical application. Each gram of Tri-Luma cream contains active ingredients: fluocinolone acetonide, 0.01% (0.1 mg), hydroquinone, 4% (40 mg), and tretinoin, 0.05% (0.5 mg). Inactive ingredients: butylated hydroxytoluene, cetyl alcohol, citric acid, glycerin, glyceryl stearate, magnesium aluminum silicate, methyl gluceth-10, methyl paraben, PEG-100 stearate, propyl paraben, purified water, sodium metabisulfite, stearic acid, and stearyl alcohol.
- U-Kera™ is a keratolytic emollient, which is a gentle, yet potent, tissue softener for nails and/or skin. Each gram of U-Kera contains urea USP (40%), purified water USP, light mineral oil NF, white petrolatum USP, glycolic acid, propylene glycol USP, trolamine NF, glyceryl stearate SE, cetyl alcohol NF, L-arginine USP, and xanthan gum NF.
- Vanos™ (fluocinonide) cream, 0.1%, 1 mg micronized fluocinonide in a cream base of propylene glycol USP, dimethyl isosorbide, glyceryl stearate (and) PEG-100 stearate, glyceryl monostearate NF, purified water USP, Carbopol 980 NF, diisopropanolamine, and citric acid USP.
- Vicks® VapoRub® active ingredients: camphor, 4.8%, eucalyptus oil, 1.2%, menthol, 2.6%.
- Vivelle-Dot® (estradiol transdermal system) contains estradiol in a multipolymeric adhesive. The system is designed to release estradiol continuously upon application

to intact skin. Five dosage strengths of Vivelle-Dot are available to provide nominal in vivo delivery rates of 0.025, 0.0375, 0.05, 0.075, or 0.1 mg of estradiol per day via the skin. Each corresponding system has an active surface area of 2.5, 3.75, 5.0, 7.5, or 10.0 cm^2 and contains 0.39, 0.585, 0.78, 1.17, or 1.56 mg of estradiol USP respectively. The composition of the systems per unit area is identical. Vivelle-Dot is comprised of three layers. Proceeding from the visible surface toward the surface attached to the skin, these layers are (1) a translucent polyolefin film; (2) an adhesive formulation containing estradiol, acrylic adhesive, silicone adhesive, oleyl alcohol, NF, povidone, USP, and dipropylene glycol; and (3) a polyester release liner which is attached to the adhesive surface and must be removed before the system can be used. The active component of the system is estradiol. The remaining components of the system are pharmacologically inactive.

- Zovirax ointment, 5%, contains 50 mg of acyclovir in a polyethylene glycol (PEG) base. Zovirax cream, 5%, is a formulation for topical administration. Each gram of Zovirax cream, 5%, contains 50 mg of acyclovir and the following inactive ingredients: cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, and white petrolatum.

Index

Pharmaceutical Science

about the book...

The fourth volume in the series covers the techniques and technologies involved in the preparation of semisolid products such as ointments, creams, gels, suppositories, and special topical dosage forms. Drug manufacturers need a thorough understanding of the specific requirements that regulatory agencies impose on the formulation and efficacy determination of drugs contained in these formulations.

Highlights from ***Semisolid Products, Volume Four*** include:
- coverage of over 350 formulations
- valuable information on the difficult area of compliance
- changes to approved new drug applications and abbreviated new drug applications
- the evolving guidelines of ICH and when to conduct a regulatory review

about the author...

SARFARAZ K. NIAZI is Consultant, Pharmaceutical Scientist, Inc., Deerfield, Illinois, USA. Dr. Niazi has over 35 years of worldwide experience in managing multidisciplinary research; he has been teaching and conducting research in the field of pharmaceutical and biotechnology sciences and has published over 100 research articles, dozens of books, both technical and literary including several textbooks. He is a recipient of several research recognition awards. He is a licensed practitioner of patent law before the US Patent and Trademark Office and serves the global pharmaceutical and biotechnology industry in the transition of research ideas into useful technology. Dr. Niazi holds several major US and worldwide patents for his inventions and writes in the fields of philosophy, sociology, rhetoric, and poetry; he is the author of the first book on clinical pharmacokinetics and the largest work on pharmaceutical manufacturing formulations and also on the manufacturing of therapeutic proteins. He has extensive experience in global management of research in healthcare systems.

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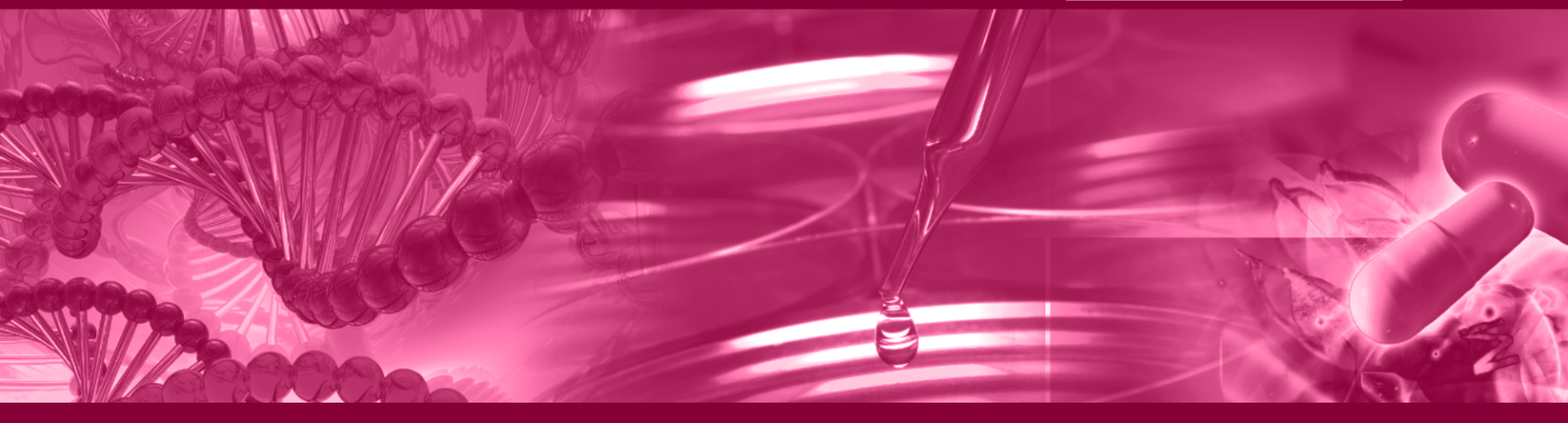

VOLUME FIVE

Second Edition

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Over-the-Counter Products

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Handbook of Pharmaceutical Manufacturing Formulations Second Edition

Volume Series

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to the memory of Dean Allen I. White

Preface to the Series—Second Edition

The science and the art of pharmaceutical formulation keeps evolving as new materials, methods, and machines become readily available to produce more reliable, stable, and release-controlled formulations. At the same time, globalization of sourcing of raw and finished pharmaceuticals brings challenges to regulatory authorities and results in more frequent revisions to the current good manufacturing practices, regulatory approval dossier requirements, and the growing need for cost optimization. Since the publication of the first edition of this book, a lot has changed in all of these areas of importance to pharmaceutical manufacturers. The second edition builds on the dynamic nature of the science and art of formulations and provides an evermore useful handbook that should be highly welcomed by the industry, the regulatory authorities, as well as the teaching institutions.

The first edition of this book was a great success as it brought under one umbrella the myriad of choices available to formulators. The readers were very responsive and communicated with me frequently pointing out to the weaknesses as well as the strengths of the book. The second edition totally revised attempts to achieve these by making major changes to the text, some of which include:

1. Complete, revised errors corrected and subject matter reorganized for easy reference. Whereas this series has six volumes differentiated on the basis of the type of dosage form and a separate inclusion of the U.S. OTC products, ideally the entire collection is needed to benefit from the myriad of topics relating to formulations, regulatory compliance, and dossier preparation.
2. Total number of pages is increased from 1684 to 2726.
3. Total number of formulations is expanded by about 30% with many newly approved formulations.
4. Novel formulations are now provided for a variety of drugs; these data are collected from the massive intellectual property data and suggest toward the future trend of formulations. While some of these formulations may not have been approved in the United States or Europe, these do provide additional choices, particularly for the NDA preparation. As always, it is the responsibility of the manufacturer to assure that the intellectual property rights are not violated.
5. A significant change in this edition is the inclusion of commercial products; while most of this information is culled out from the open source such as the FOIA (http://www.fda.gov/foi/default.htm), I have made attempts to reconstruct the critical portions of it based on what I call the generally acceptable standards. The drug companies are advised to assure that any intellectual property rights are not violated and this applies to all information contained in this book. The freedom of information act (FOIA) is an extremely useful conduit for reliable information and manufacturers are strongly urged to make use of this information. Whereas this information is provided free of charge, the process of obtaining the information may be cumbersome, in which case, commercial sources of these databases can prove useful, particularly for the non-U.S. companies.
6. Also included are the new Good Manufacturing Guidelines (2007) with amendments (2008) for the United States and similar updates for European Union and WHO; it is strongly urged that the companies discontinue using all old documents as there are significant changes in the revised form, and many of them are likely to reduce the cost of GMP compliance.
7. Details on design of clean rooms is a new entry that will be of great use to sterile product manufacturers; whereas the design and flow of personnel and material flow is of critical nature, regulatory agencies view these differently and the manufacturer is advised always to comply with most stringent requirements.
8. Addition of a self-auditing template in each volume of the series. While the cGMP compliance is a complex issue and the requirements diversified across the globe, the basic compliance remains universal. I have chosen the European Union guidelines (as these are more in tune with the ICH) to prepare a self-audit module that I recommend that every manufacturer adopt as a routine to assure GMP compliance. In most instances reading the template by those responsible for compliance with keep them sensitive to the needs of GMP.
9. OTC products cross-referenced in other volumes where appropriate. This was necessary since the regulatory authorities worldwide define this class of drug differently. It is important to iterate that regardless of the prescription or the OTC status of a product, the requirements for compliance with the cGMP apply equally.
10. OTC monograph status is a new section added to the OTC volume and this should allow manufacturers to chose appropriate formulations that may not require a filing with the regulatory agencies; it is important to iterate that an approved OTC monograph includes details of formulation including the types and quantities of active drug and excipients, labeling, and presentation. To qualify the exemption, the manufacturer must comply with the monograph in its entirety. However, subtle modifications that are merely cosmetic in nature and where there is an evidence that the modification will not affect the safety and efficacy of the products can be made but require prior approval of the regulatory agencies and generally these approvals are granted.
11. Expanded discussion on critical factors in the manufacturing of formulations provided; from basic shortcuts to smart modifications now extend to all dosage forms. Pharmaceutical compounding is one of the oldest professions and whereas the art of formulations has been

relegated to more objective parameters, the art nevertheless remains. An experienced formulator, like an artist, would know what goes with what and why; he avoids the pitfalls and stays with conservative choices. These sections of the book present advice that is time tested, although it may appear random at times; this is intended for experienced formulators.

12. Expanded details on critical steps in the manufacturing processes provided but to keep the size of the book manageable, and these are included for prototype formulations. The reader is advised to browse through similar formulations to gain more insight. Where multiple formulations are provided for the same drug, it intended to show the variety of possibilities in formulating a drug and whereas it pertains to a single drug, the basic formulation practices can be extended to many drugs of same class or even of diversified classes. Readers have often requested that more details be provided in the Manufacturing Direction sections. Whereas sufficient details are provided, this is restricted to prototype formulations to keep the size of the book manageable and to reduce redundancy.
13. Addition of a listing of approved excipients and the level allowed by regulatory authorities. This new section allows formulators a clear choice on which excipients to choose; the excipients are reported in each volume pertaining to the formulation type covered. The listing is drawn from the FDA-approved entities. For the developers of an ANDA, it is critical that the level of excipients be kept within the range generally approved to avoid large expense in justifying any unapproved level. The only category for which the listing is not provided separately is the OTC volume since it contains many dosage forms and the reader is referred to dosage form–specific title of the series. The choice of excipients forms keeps increasing with many new choices that can provide many special release characteristics to the dosage forms. Choosing correct excipients is thus a tedious exercise and requires sophisticated multivariate statistical analysis. Whereas the formulator may choose any number of novel or classical components, it is important to know the levels of excipients that are generally allowed in various formulations to reduce the cost of redundant exercises; I have therefore included, as an appendix to each volume, a list of all excipients that are currently approved by the U.S. FDA along their appropriate levels. I suggest that a formulator consult this table before deciding on which level of excipient to use; it does not mean that the excipient cannot be used outside this range but it obviates the need for a validation and lengthy justification studies in the submission of NDAs.
14. Expanded section on bioequivalence submission was required to highlight the recent changes in these requirements. New entries include a comprehensive listing of bioequivalence protocols in abbreviated form as approved by the U.S. FDA; these descriptions are provided in each volume where pertinent. To receive approval for an ANDA, an applicant must generally demonstrate, among other things, equivalence of the active ingredient, dosage form, strength, route of administration and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. Bioequivalent drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 U.S.C. 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320. The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-specific BE studies, the U.S. FDA will be issuing product-specific BE recommendations (www.fda.gov/cder/ogd/index.htm). To make this vital information available, an appendix to each volume includes a summary of all currently approved products by the U.S. FDA where a recommendation on conducting bioequivalence studies is made available by the U.S. FDA. When filing an NDA or an ANDA, the filer is faced with the choice of defending the methods used to justify the bioavailability or bioequivalence data. The U.S. FDA now allows application for waiver of bioequivalence requirement; a new chapter on this topic has been added along with details of the dissolution tests, where applicable, approved for various dosage forms.
15. Dissolution testing requirements are included for all dosage forms where this testing is required by the FDA. Surrogate testing to prove efficacy and compliance is getting more acceptance at regulatory agencies; in my experience, a well-designed dissolution test is the best measure of continuous compliance. Coupled with chapters on waivers of bioequivalence testing, this information on dissolution testing should be great value to all manufacturers; it is recommended that manufacturers develop their own in-house specifications, more stringent than those allowed in these listings and the USP.
16. Best-selling products (top 200 prescription products) are identified with an asterisk and a brand name where applicable; in all instances, composition of these products is provided and formulation of generic equivalents. Despite the vast expansion of pharmaceutical sales and shifting of categories of blockbuster drugs, basic drugs affecting gastrointestinal tract, vascular system, and brain remain most widely prescribed.
17. Updated list of approved coloring agents in the United States, Canada, European Union, and Japan is included to allow manufactures to design products for worldwide distribution.
18. Tablet-coating formulations that meet worldwide requirements of color selection are included in the Volume 1 (compressed solids) and Volume 5 (OTC) because these represent the products often coated.
19. Guidelines on preparing regulatory filings are now dispersed throughout the series depending on where these guidelines are more crucial. However, the reader would, as before, need access to all volumes to benefit from the advice and guidelines provided.

As always, comments and criticism from the readers are welcomed and these can be sent to me at Niazi@pharmsci.com or Niazi@niazi.com. I would try to respond to any inquiries requiring clarification of the information enclosed in these volumes.

I would like to express deep gratitude to Sherri R. Niziolek and Michelle Schmitt-DeBonis at Informa, the publisher of

this work, for seeing an immediate value to the readers in publishing the second edition of this book and allowing me enough time to prepare this work. The diligent editing and composing staff at Informa, particularly Joseph Stubenrauch, Baljinder Kaur and others are highly appreciated. Regardless, all errors and omissions remain altogether mine.

In the first edition, I had dedicated each volume to one of my mentors; the second edition continues the dedication to these great teachers.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois, U.S.A.

Preface to the Series—First Edition

No industry in the world is more highly regulated than the pharmaceutical industry because of potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity (amortized over the cost of all molecules racing) to final regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. In the year 2004, it is anticipated that the industry will spend about $20 billion on research and development. The generic market of drugs as the new entities come off patent is one of the fastest growing segments of the pharmaceutical industry, with every major multinational company having a significant presence in this field.

Whereas many stages of new drug development are inherently constrained with time, the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced with appropriate knowledge by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the first major attempt to consolidate the available knowledge about formulations in a comprehensive, and by nature a rather voluminous, presentation.

The book is divided into six volumes, based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and OTC products. The separation of OTC products, even though they may easily fall into one of the other five categories, is made to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of product, and of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of products into these six categories.

Each volume includes a description of regulatory filing techniques for the formulations described. Also included are the current regulatory guidelines on cGMP compliance specific to the dosage form. Advice is offered on how to scale up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and cut the race to file short by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a close paradigm when it comes to selecting formulations—"not invented here" perhaps reigns in the mind of many seasoned formulations scientists subconsciously when they prefer to choose only a certain platform for development. It is expected that with the quick review of possibilities available to formulate made available in this book, scientists will benefit from the experience of others.

For the teachers of formulation sciences, this series offers a wealth of information. Whether it is a selection of a preservative system or the choice of a disintegrant, the series offers a wide choice to study and rationalize.

Many have assisted me in the development of this work that has taken years to compile, and I thank scores of my graduate students and colleagues for their help. A work of this size cannot be produced without errors, although I hope that these errors do not distract the reader from the utility of the book. I would sincerely appreciate if readers point out these mistakes for corrections in future editions.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois, U.S.A.

Preface to the Volume—First Edition

The *Handbook of Pharmaceutical Manufacturing Formulations—OTC Drugs* is written for the pharmaceutical scientist and others involved in the regulatory filing and manufacturing of new OTC products. Because of the wide variety of products involved, from those bordering on cosmetics to proton pump inhibitors, the OTC products are manufactured by the most sophisticated global manufacturers as well as small one-room makeshift manufacturing houses.

The OTC products comprise a special category of health-care products in that they can be dispensed without prescription; the rationale being that the use of these products does not expose patients to serious risks associated with side effects even if some misuse or overuse of these products occurs. The OTC category includes three types of products:

Products that require full filing with the U.S. Food and Drug Administration (FDA) for marketing approval (the NDA/NADA or ANDA/ANADA process) including products or compositions not included in the monographs (see below) or administered in controlled release formulations.

Products that do not require filing with the U.S. FDA because they comply with the monographs issued by the U.S. FDA in its Code of Federal Regulations (CFR).

Products that fall under the category of grandfather products which have been in use prior to the 1960s and have not been specifically excluded by the FDA; not all grandfather products fall under the OTC category—only those that are generally regarded as safe (GRAS).

The U.S. FDA provides excellent support through its OTC website (http://www.fda.gov/cder/otc/index.htm) and formulators are highly encouraged to make use of the information available, particularly the updates in the monograph label requirements and withdrawal of approvals of formulations.

With the safety of consumers in mind, the U.S. FDA is in the process of establishing guidelines for all OTC products. Although the U.S. FDA began this work over three decades ago, much remains to be done. The U.S. FDA process begins with the issuance of Proposed Rules; this notification is like a warning (or advice) to the industry that this category of products is now under the U.S. FDA watch. Often years go by before Proposed Rules are published in the Code of Federal Regulations. The Proposed Rules include not only identification of approved active ingredients but also inactive ingredients that are deemed compatible with the active ingredients and safe for consumers. The Proposed Rules are subject to criticism by the industry health-care practitioners and consumers. After receiving these comments over what can be a period of several years, the U.S. FDA issues Final Rules on a specific category of products; these become official on the date of publication in the Code of Federal Regulations. In many cases, however, the U.S. FDA issues subsequent rules either to delay application of Final Rules or to modify the Final Rules if new information has become available.

The Final Rule requirements have primarily been applied to products on the market and a newcomer is well advised to study competitor products for market leaders as ample opportunities are available to innovate these products. Examples include the Tylenol® Hot Therapy products and loratidine tablets that dissolve in the mouth and do not require water. I foresee more such products entering into the ever-competitive OTC market.

It is imperative that any prospective entry into the OTC market should begin with a thorough consultation of the Final Rules; an examination of Proposed Rules and notifications to issue Proposed Rules is also helpful in determining what rules are about to become Final Rules. Reviewing the discussions about Proposed Rules that have affected their finalization can be very helpful in understanding the relevant issues of safety, efficacy, and labeling. Because the marketing of OTC products requires a large investment in marketing efforts, it is prudent to develop a clear understanding of the legality of formulations and claims made in the initial phases of product development.

A large number of products on the market today are not covered by the U.S. FDA monographs but does that make them legitimate? This is the often-asked question. The U.S. FDA has limited resources to tackle everything that is out there on the market. When emergencies arise, however, the U.S. FDA reacts immediately as it did in the case of phenylpropanolamine, pseudoephedrine, and recently, kava kava. Here are some broad guidelines adopted by the U.S. FDA for the most commonly abused categories of products:

No treatments are approved for hair growth except for minoxidil.

No treatments are approved for enhancing sexual performance except for sildenafil citrate (and that only in MED).

The few treatments approved for weight loss include olristat phentermine and sibutramine (phenylpropanolamine is no longer a recommended compound).

It is noteworthy that the U.S. FDA does not differentiate between botanical products and chemical-based products. If a product bears an efficacy claim, it must be governed by the U.S. FDA rules; however, a product that falls into a drug category that makes nutritional claims falls under a food category with its own set of detailed rules. Vitamins and minerals fall under food labeling guidelines; however, a single-entity vitamin product with specific claims to treat or ameliorate a disease is a drug product. These definitions do not necessarily coincide with the rulings of regulatory authorities worldwide. In many countries nutritional products are controlled as drugs and require prescriptions; these same products would be considered nonprescription items in the United States. On the other hand, a number of highly active drugs are available without prescription in many countries such as the Traditional Chinese Medicine (TCM) in China and Ayurvedic and Unani medicines in South Asia.

A reclassification of a drug to OTC status can be requested by drug manufacturers. Recent examples of such a prescription-to-OTC switch include ibuprofen (200 mg), ranitidine hydrochloride (75 mg), and loratidine (10 mg). Note that specific strengths, not necessarily the chemical entity itself, are made OTC. In other words, it is not necessary to have an official monograph to secure OTC status for a drug. The decision to request reclassification of a drug as OTC is always a well-calculated business decision. Generally, drugs with an OTC status will not qualify for medical reimbursement by insurance companies or federal assistance programs in the United States. This can substantially reduce sales of the product; on the other hand, ease of availability to a greater number of patients can easily compensate for this loss. The most lucrative opportunities arise when one strength is made OTC while other strengths remain available by prescription only.

It is noteworthy that the decision to allow a switch from prescription to OTC by the U.S. FDA is primarily driven by the side effects or toxicity of the drug. For example, in Australia a Roche request for a prescription-to-OTC switch for its weight-loss drug orlistat (Xenical®) was recently turned down because of extensive side effects associated with the use of Xenical. The drug itself is very safe as it does not enter the body and acts only locally to partially block absorption of fat. The unabsorbed fat produces many gastrointestinal symptoms which though temporary were sufficient to disallow the status switch. Obviously, Roche would have been best advised to develop an OTC formulation with fewer side effects before requesting this switch. (In the case of orlistat, the solution was simple as described in U.S. Patent No. 6,251,421 by this author wherein combining orlistat with a natural fiber reduced the side effects by 70%.)

The OTC category of products represents a wide range of dosage forms. These formulations have much in common with their prescription counterparts but are presented in this volume of the *Handbook of Pharmaceutical Manufacturing Formulations* because of the development approach taken, labeling considerations, and support available from suppliers of ingredients in designing these products. Because the consumer is inevitably involved in the selection of these products, packaging considerations are much more important than in the prescription category of products. Additional considerations include ease of administration, palatability, and stability in storage as consumers are likely to keep leftovers around for a long time. Additionally, price constraints often make it difficult to enjoy some freedom of choice in formulations, especially if the innovator company faces the competition of house brands. All of these considerations taken together make the OTC category one that should be presented in a single volume of this series of books.

Formulating OTC products is generally easier than formulating prescription products if the product is described in U.S. FDA monographs (either as Proposed Rules or Final Rules); such formulations become merely an exercise in mechanics. Whereas a manufacturer is not bound by these rules, complying with them reduces the costs and time involved securing approval from regulatory authorities. The multibillion-dollar market of OTC products has attracted major chemical suppliers to develop support ingredients that are much easier to use; they have also developed typical formulations for hundreds of these products.

The most notable industry leaders include

Amerchol,
American Colloid,
Aqualon,
BASF,
BF Goodrich,
Calgon,
Colorcon,
Croda,
Dow Corning,
FMC,
Gattefose,
General Electric,
Henkel,
Hormel,
Huls America,
ICI Americas,
Inolex,
International Sourcing,
International Specialty,
Laboratoires Serobioligique,
Lonza,
NIPA,
PPG Industries,
R.I.T.A.,
Reheis,
Rheox,
Rhone-Poulenc,
Rohm and Haas,
Southern Clay,
Sutton, and
Vanderbilt.

The formulations recommended by these and other companies have acquired almost a universal appeal; throughout this book you will find formulations recommended by these laboratories, as acknowledged by the listing of a brand name in the formula. The best way to connect to these companies is to search the Internet for contact information; it is no longer necessary to reproduce such information here. Whereas many companies prefer to use generic components in the dosage form, it has been found that the use of proprietary components can indeed reduce costs in the long run.

The choice of color is a highly sensitive issue in the formulation of OTC products; only FDC colors are allowed. Whereas there is a great need to make the products attractive and appealing, the choices of safe colors are dwindling quickly, such as for red colors. The formulator is encouraged to review the status of approved colors around the world before committing to a specific color.

Many OTC solid dosage forms are available in coated form. Sugar coatings have yielded to film coatings, and this book contains a large number of sugar-coating, seal-coating, subcoating, film-coating, and polish-coating formulations that can be easily adapted to various dosage form sizes. The use of organic solvent-based coatings has become prohibitive because of environment considerations, but in those cases where formulations are extremely sensitive to moisture, organic coatings may still offer a valid choice. A few companies offer ready-made coating formulations, and these are worth considering. The Appendix to this book includes a large number of formulations of coatings of solid dosage forms. A keen formulator will have no difficulty based on these formulations in adopting a coating system that will provide the necessary protection and offer esthetic appeal as well. Solid dosage forms are coated for many reasons, including masking the taste, making them easier to swallow, and providing protection against the environment.

Stability considerations remain paramount, and the data in the final packaging must be evaluated carefully before

adjusting formulae for excesses; in this book, most formulations are provided without this consideration. A strip or blister dosage form is more popular around the world, but the plastic bottle is the most popular final form in the United States.

The development of OTC products is similar to the development of prescription dosage forms; as a result, cGMP and Good Laboratory Practice (GLP) considerations apply equally. The first chapter describes in greater detail the cGMP considerations. An appendix to chapter 1 provides a comprehensive checklist of items to review to ensure that a manufacturing facility is in compliance with cGMP standards. Appropriate identification is made in this checklist of those items that comply with EC guidelines. The U.S. FDA guidelines are available from the U.S. FDA website: http://www.fda.gov. The World Health Organization (WHO) provides GMP guidelines that are less stringent than those of the U.S. FDA and EC, and formulators should be aware of the fact that all of these are simply guidelines. One should be fully cognizant of the fact that no agencies are bound by these guidelines, particularly the U.S. FDA. Manufacturers cannot take refuge in the defense that they have complied with these guidelines. It is further worthwhile remembering that all of these guidelines are continuously revised, and the "c" in the cGMP does refer to current.

The second chapter deals with the most popular category of dosage forms encountered in OTC offerings—solids. Issues specific to manufacturing of these dosage forms are described from a practical viewpoint, indicating the problem areas frequently encountered in manufacturing practice.

The third chapter deals with liquids and suspensions and includes, like the chapter above, practical advice on how to bring manufacturing practices into compliance with regulatory requirements.

The fourth chapter offers highlights of cleaning validation, a topic often ignored by OTC manufacturers as not being significant because of the safety of ingredients used. It is true that the same stringent standards may not apply, but compliance with cleaning standards and validation of processes go a long way toward ensuring overall compliance.

The first four chapters were drawn from the advice which the U.S. FDA gives to its inspectors before they inspect a manufacturer. The CFR includes complete details of what is considered acceptable by the U.S. FDA; this advice is of a practical nature, and I find it to be extremely helpful in enhancing awareness of the guidelines of regulatory authorities. It is noteworthy that EC guidelines, particularly in light of the harmonization of specifications, are somewhat identical to the U.S. FDA guidelines; in chapter 1, specific references are made to EC guidelines. The Appendix includes formulations of coating solutions; these should prove useful for the pharmaceutical formulation teams.

The formulations in this book generally fall into three categories. Some formulations are presented in greater detail, including indications of where quality assurance (QA)/quality control (QC) sampling is to be done and describing the tooling and in-process and finished product specifications. The other extreme is a mere listing of components with a bare minimum of manufacturing methods. This was necessary for two reasons: first, to contain the size of this book, and second, to keep from presenting superfluous information, as formulators would eventually adopt such a formula to their own delivery forms. Also, at times the various strengths are merely achieved through adjustment of dosage size, so it was considered unnecessary to reproduce manufacturing steps where they are obvious.

The primary source of these formulations is publicly available knowledge about formulae that have proven to provide stable products. No representation is made that these formulations meet U.S. FDA monographs or any other regulatory guidelines for safety of inert ingredients. The formulator is advised to determine guideline compliance before adopting any of the formulations given in this book. Those interested in obtaining detailed information about these formulations are encouraged to contact the author at http://www.pharmsci.com. Because of the wide variety of sources from which the information has been gathered in the book, the format of formulations also varies. For example, in some instances scale is provided, whereas in others a percentage by weight is described. In still other instances, quantities for a specific batch size are provided. Obviously, it would be desirable to convert these formulations into a uniform format, but the task would be daunting and inevitably would lead to inclusion of errors. Professional formulators should not encounter any difficulty in adapting these formulations to their own system.

As mentioned before, not all formulations contain the required overages for stability considerations and losses during manufacturing; formulators are expected to develop these based on the final packaging chosen for the product. The author would appreciate being notified of any special problems encountered in adopting these formulations or of any errors (niazi@pharmsci.com). Whereas much care has gone into ensuring the accuracy of quantities and proper identification of ingredients, such errors shall remain in a work as large as that presented here.

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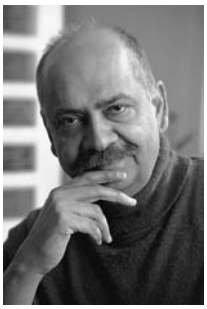

Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 35 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents in the field of drug and dosage form delivery systems; he is also licensed to practice law before the U.S. Patent and Trademark Office. Having formulated hundreds of products from the most popular consumer entries to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science and art of formulating and regulatory filings of investigational new drugs (INDs) and new drug applications (NDAs). Dr. Niazi advises the pharmaceutical industry internationally on issues related to formulations, cGMP compliance, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (http://www.pharmsci.com). He can be contacted at Niazi@pharmsci.com.

Contents

Part I

Regulatory Guidance

1

EU Guidelines to Good Manufacturing Practice: Medicinal Products for Human and Veterinary Use

INTRODUCTION

Document History	
The *first edition* of the guide was published, including an Annex on the manufacture of sterile medicinal products.	1989
The *second edition* was published; implementing Commission Directives 91/356 of June 13, 1991 and 91/412 of July 23, 1991 laying down the principles and guidelines on good manufacturing practice for medicinal products for human use as well as for veterinary medicinal products. The second edition also included 12 additional annexes.	January 1992
An update of legal references was made. In the meantime, the guide is updated as needed on the Web site of the European Commission, several additional Annexes added.	August 2004
Restructuring of GMP guide, consisting of part I for medicinal products for human and veterinary use and part II for active substances used as starting materials, implementing Directives 2004/27/EC and 2004/28/EC. The current guide includes 17 Annexes, the former Annex 18 being replaced.	October 2005
Implementation of ICH Q9 guideline as GMP Annex 20	March 2008

The pharmaceutical industry of the European Union maintains high standards of quality assurance in the development, manufacture, and control of medicinal products. A system of marketing authorizations ensures that all medicinal products are assessed by a competent authority to ensure compliance with contemporary requirements of safety, quality, and efficacy. A system of manufacturing authorizations ensures that all products authorized on the European market are manufactured only by authorized manufacturers, whose activities are regularly inspected by the competent authorities. Manufacturing authorizations are required by all pharmaceutical manufacturers in the European Community whether the products are sold within or outside the community.

Two directives laying down principles and guidelines of good manufacturing practice (GMP) for medicinal products were adopted by the Commission. Directive 2003/94/EC applies to medicinal products for human use and Directive 91/412/EEC for veterinary use. Detailed guidelines in accordance with those principles are published in the *Guide to Good Manufacturing Practice*, which will be used in assessing applications for manufacturing authorizations and as a basis for inspection of manufacturers of medicinal products.

The principles of GMP and the detailed guidelines are applicable to all operations which require the authorization referred to in Article 40 of Directive 2001/83/EC and in Article 44 of Directive 2001/82/EC, as amended by Directives 2004/27/EC and 2004/28/EC, respectively. They are also relevant for all other large scale pharmaceutical manufacturing processes, such as that undertaken in hospitals, and for the preparation of products for use in clinical trials.

All member states and the industry agreed that the GMP requirements applicable to the manufacture of veterinary medicinal products are the same as those applicable to the manufacture of medicinal products for human use. Certain detailed adjustments to the GMP guidelines are set out in two annexes specific to veterinary medicinal products and to immunologic veterinary medicinal products.

The guide is presented in two parts of basic requirements and specific annexes. Part I covers GMP principles for the manufacture of medicinal products. Part II covers GMP for active substances used as starting materials.

Chapters of part I on "basic requirements" are headed by principles as defined in Directives 2003/94/EC and 91/412/EEC. Chapter 1 on Quality Management outlines the fundamental concept of quality assurance as applied to the manufacture of medicinal products. Thereafter, each chapter has a principle outlining the quality assurance objectives of that chapter and a text which provides sufficient detail for manufacturers to be made aware of the essential matters to be considered when implementing the principle.

Part II was newly established on the basis of a guideline developed on the level of ICH and published as ICH Q7 a on "active pharmaceutical ingredients," which was implemented as GMP Annex 18 for voluntary application in 2001. According to the revised Article 47 and Article 51, respectively, of the Directive 2001/83/EC and Directive 2001/82/EC, as amended, detailed guidelines on the principles of GMP for active substances used as starting materials shall be adopted and published by the Commission. The former Annex 18 has been replaced by the new part II of the GMP guide, which has an extended application both for the human and the veterinary sector.

In addition to the general matters of Good Manufacturing Practice outlined in part I and II, a series of annexes providing detail about specific areas of activity is included. For some manufacturing processes, different annexes will apply simultaneously (e.g., Annex on Sterile Preparations and on Radiopharmaceuticals and/or on Biological Medicinal Products).

GMP part I, Chapter 1 on Quality Management, has been revised to include aspects of quality risk management within the quality system framework. In future revisions of

the guide, the opportunity will be taken to introduce quality risk management elements when appropriate.

The new GMP Annex 20, which corresponds to the ICH Q9 guideline, provides guidance on a systematic approach to quality risk management leading to compliance with GMP and other quality requirements. It includes principles to be used and options for processes, methods, and tools, which may be used when applying a formal quality risk management approach. While the GMP guide is primarily addressed to manufacturers, the ICH Q9 guideline, has relevance for other quality guidelines and includes specific sections for regulatory agencies. However, for reasons of coherence and completeness the ICH Q9 guideline has been transferred completely into GMP Annex 20.

A glossary of some terms used in the guide has been incorporated after the annexes.

The guide is not intended to cover security aspects for the personnel engaged in manufacture. This may be particularly important in the manufacture of certain medicinal products such as highly active, biological, and radioactive medicinal products. However, those aspects are governed by other provisions of Community or National Law.

Throughout the guide, it is assumed that the requirements of the Marketing Authorization relating to the safety, quality, and efficacy of the products are systematically incorporated into all the manufacturing, control and release for sale arrangements of the holder of the Manufacturing Authorization.

The manufacture of medicinal products has for many years taken place in accordance with guidelines for Good Manufacturing Practice and the manufacture of medicinal products is not governed by CEN/ISO standards. Harmonized standards as adopted by the European Standardization Organizations CEN/ISO may be used at industry's discretion as a tool for implementing a quality system in the pharmaceutical sector. The CEN/ISO standards have been considered but the terminology of these standards has not been implemented in this edition. It is recognized that there are acceptable methods, other than those described in the guide, which are capable of achieving the principles of Quality Assurance. The guide is not intended to place any restraint upon the development of any new concepts or new technologies which have been validated and which provide a level of Quality Assurance at least equivalent to those set out in this guide. With its principles, methods, and tools, Annex 20 provides a systematic approach, which may be used to demonstrate such equivalence.

The GMP guide will be regularly revised. Revisions will be made publicly available on the Web site of the European Commission (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev4.htm).

PART I CHAPTER 1: QUALITY MANAGEMENT

Principle

The holder of a Manufacturing Authorization must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorization, and do not place patients at risk due to inadequate safety, quality, or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment by staff in many different departments and at all levels within the company, by the company's suppliers, and by the distributors. To achieve the quality objective reliably, there must be a comprehensively designed and correctly implemented system of Quality Assurance incorporating Good Manufacturing Practice, Quality Control, and Quality Risk Management. It should be fully documented and its effectiveness monitored. All parts of the Quality Assurance System should be adequately resourced with competent personnel, and suitable and sufficient premises, equipment, and facilities. There are additional legal responsibilities for the holder of the Manufacturing Authorization and for the Qualified Person(s).

The basic concepts of Quality Assurance, Good Manufacturing Practice, Quality Control, and Quality Risk Management are interrelated. They are described here in order to emphasize their relationships and their fundamental importance to the production and control of medicinal products.

Quality Assurance

1.1 Quality Assurance is a wide-ranging concept, which covers all matters, which individually or collectively influence the quality of a product. It is the sum total of the organized arrangements made with the objective of ensuring that medicinal products are of the quality required for their intended use. Quality Assurance therefore incorporates Good Manufacturing Practice plus other factors outside the scope of this guide.

The system of Quality Assurance appropriate for the manufacture of medicinal products should ensure that

(i) medicinal products are designed and developed in a way that takes account of the requirements of GMP;
(ii) production and control operations are clearly specified and GMP adopted;
(iii) managerial responsibilities are clearly specified;
(iv) arrangements are made for the manufacture, supply, and use of the correct starting and packaging materials;
(v) all necessary controls on intermediate products, and any other in-process controls and validations are carried out;
(vi) the finished product is correctly processed and checked, according to the defined procedures;
(vii) medicinal products are not sold or supplied before a Qualified Person has certified that each production batch has been produced and controlled in accordance with the requirements of the Marketing Authorization and any other regulations relevant to the production, control, and release of medicinal products;
(viii) satisfactory arrangements exist to ensure, as far as possible, that the medicinal products are stored, distributed, and subsequently handled so that quality is maintained throughout their shelf life; and
(ix) there is a procedure for Self-Inspection and/or quality audit, which regularly appraises the effectiveness and applicability of the Quality Assurance system.

Good Manufacturing Practice for Medicinal Products

1.2 GMP is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the Marketing Authorization or product specification.

Good Manufacturing Practice is concerned with both production and quality control. The basic requirements of GMP are that

(i) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;
(ii) critical steps of manufacturing processes and significant changes to the process are validated;
(iii) all necessary facilities for GMP are provided including
    appropriately qualified and trained personnel,
    adequate premises and space,
    suitable equipment and services,
    correct materials, containers and labels,
    approved procedures and instructions, and
    suitable storage and transport
(iv) instructions and procedures are written in an instructional form in clear and unambiguous language, specifically applicable to the facilities provided;
(v) operators are trained to carry out procedures correctly;
(vi) records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. Any significant deviations are fully recorded and investigated;
(vii) records of manufacture including distribution which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
(viii) the distribution (wholesaling) of the products minimizes any risk to their quality;
(ix) a system is available to recall any batch of product, from sale or supply; and
(x) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products and to prevent reoccurrence.

Quality Control

1.3 Quality Control is that part of Good Manufacturing Practice which is concerned with sampling, specifications, and testing, and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their quality has been judged to be satisfactory.

The basic requirements of Quality Control are that

(i) adequate facilities, trained personnel, and approved procedures are available for sampling, inspecting and testing starting materials, packaging materials, intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes;
(ii) samples of starting materials, packaging materials, intermediate products, bulk products, and finished products are taken by personnel and by methods approved by Quality Control;
(iii) test methods are validated;
(iv) records are made, manually and/or by recording instruments, which demonstrate that all the required sampling, inspecting, and testing procedures were actually carried out. Any deviations are fully recorded and investigated;
(v) the finished products contain active ingredients complying with the qualitative and quantitative composition of the Marketing Authorization, are of the purity required, and are enclosed within their proper containers and correctly labeled;
(vi) records are made of the results of inspection and that testing of materials, intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and evaluation of relevant production documentation and an assessment of deviations from specified procedures;
(vii) no batch of product is released for sale or supply prior to certification by a Qualified Person that it is in accordance with the requirements of the relevant authorizations; and
(viii) sufficient reference samples of starting materials and products are retained to permit future examination of the product if necessary and that the product is retained in its final pack unless exceptionally large packs are produced.

Product Quality Review

1.4 Regular periodic or rolling quality reviews of all licensed medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of current specifications for both starting materials and finished product to highlight any trends, and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews, and should include at least

(i) a review of starting materials including packaging materials used in the product, especially those from new sources;
(ii) a review of critical in-process controls and finished product results;
(iii) a review of all batches that failed to meet established specification(s) and their investigation;
(iv) a review of all significant deviations or nonconformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken;
(v) a review of all changes carried out to the processes or analytical methods;
(vi) a review of Marketing Authorization variations submitted/granted/refused, including those for third country (export only) dossiers;
(vii) a review of the results of the stability monitoring program and any adverse trends;
(viii) a review of all quality-related returns, complaints, and recalls and the investigations performed at the time;
(ix) a review of adequacy of any other previous product process or equipment corrective actions;
(x) for new marketing authorizations and variations to marketing authorizations, a review of postmarketing commitments;

(xi) the qualification status of relevant equipment and utilities, for example, HVAC, water, compressed gases,; and
(xii) a review of any contractual arrangements as defined in Chapter 7 to ensure that they are up to date.

The manufacturer and marketing authorization holder should evaluate the results of this review, where different, and an assessment made of whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventative actions should be completed in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self-inspection. Quality reviews may be grouped by product type, for example, solid dosage forms, liquid dosage forms, sterile products, and so on, where scientifically justified.

Where the marketing authorization holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The Qualified Person responsible for final batch certification together with the marketing authorization holder should ensure that the quality review is performed in a timely manner and is accurate.

Quality Risk Management

1.5 Quality Risk Management is a systematic process for the assessment, control, communication, and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

1.6 The Quality Risk Management system should ensure that: the evaluation of the risk to quality is based on scientific knowledge, experience with the process, and ultimately links to the protection of the patient; and the level of effort, formality, and documentation of the quality risk management process is commensurate with the level of risk.

CHAPTER 2: PERSONNEL

Principle

The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture of medicinal products relies upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks which are the responsibility of the manufacturer. Individual responsibilities should be clearly understood by the individuals and recorded. All personnel should be aware of the principles of Good Manufacturing Practice that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs.

General

2.1 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive as to present any risk to quality.

2.2 The manufacturer must have an organization chart. People in responsible positions should have specific duties recorded in written job descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of those personnel concerned with the application of Good Manufacturing Practice.

Key Personnel

2.3 Key Personnel include the head of Production, the head of Quality Control, and if at least one of these persons is not responsible for the duties described in Article 51 of Directive 2001/83/EC1, the Qualified Person(s) designated for the purpose. Normally, key posts should be occupied by full-time personnel. The heads of Production and Quality Control must be independent from each other. In large organizations, it may be necessary to delegate some of the functions listed in 2.5, 2.6, and 2.7.

2.4 The duties of the Qualified Person(s) are fully described in Article 51 of Directive 2001/83/EC, and can be summarized as follows:

(a) For medicinal products manufactured within the European Community, a Qualified Person must ensure that each batch has been produced and tested/checked in accordance with the directives and the marketing authorization (2).
(b) For medicinal products manufactured outside the European Community, a Qualified Person must ensure that each imported batch has undergone, in the importing country, the testing specified in paragraph 1(b) of Article 51; Article 55 of Directive 2001/82/EC (2) According to Directive 75/319/EEC (now codified Directive 2001/83/EC) and the Ruling (Case 247/81) of the Court of Justice of the European Communities, medicinal products which have been properly controlled in the EU by a Qualified Person do not have to be recontrolled or rechecked in any other member state of the community.
(c) a Qualified Person must certify in a register or equivalent document, as operations are carried out and before any release, that each production batch satisfies the provisions of Article 51. The persons responsible for these duties must meet the qualification requirements laid down in Article 49(3) of the same Directive, they shall be permanently and continuously at the disposal of the holder of the Manufacturing Authorization to carry out their responsibilities. Their responsibilities may be delegated, but only to other Qualified Person(s).

2.5 The head of the Production Department generally has the following responsibilities:

i. to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
ii. to approve the instructions relating to production operations and to ensure their strict implementation;
iii. to ensure that the production records are evaluated and signed by an authorized person before they are sent to the Quality Control Department;
iv. to check the maintenance of his department, premises, and equipment;
v. to ensure that the appropriate validations are done; and
vi. to ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

2.6 The head of the Quality Control Department generally has the following responsibilities:
   i. to approve or reject, as he sees fit, starting materials, packaging materials, and intermediate, bulk, and finished products;
   ii. to evaluate batch records;
   iii. to ensure that all necessary testing is carried out;
   iv. to approve specifications, sampling instructions, test methods, and other Quality Control procedures;
   v. to approve and monitor any contract analysts;
   vi. to check the maintenance of his department, premises, and equipment;
   vii. to ensure that the appropriate validations are done; and
   viii. to ensure that the required initial and continuing training of his department personnel is carried out and adapted according to need.

   Other duties of the Quality Control Department are summarized in Chapter 6.

2.7 The heads of Production and Quality Control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, subject to any national regulations:
   - the authorization of written procedures and other documents, including amendments;
   - the monitoring and control of the manufacturing environment;
   - plant hygiene;
   - process validation;
   - training;
   - the approval and monitoring of suppliers of materials;
   - the approval and monitoring of contract manufacturers;
   - the designation and monitoring of storage conditions for materials and products;
   - the retention of records;
   - the monitoring of compliance with the requirements of Good Manufacturing Practice; and
   - the inspection, investigation, and taking of samples, in order to monitor factors which may affect product quality.

Training

2.8 The manufacturer should provide training for all the personnel whose duties take them into production areas or into control laboratories (including the technical, maintenance, and cleaning personnel), and for other personnel whose activities could affect the quality of the product.

2.9 Besides the basic training on the theory and practice of Good Manufacturing Practice, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness should be periodically assessed. Training programs should be available, approved by either the head of Production or the head of Quality Control, as appropriate. Training records should be kept.

2.10 Personnel working in areas where contamination is a hazard, for example, clean areas or areas where highly active, toxic, infectious, or sensitizing materials are handled, should be given specific training.

2.11 Visitors or untrained personnel should, preferably, not be taken into the production and quality control areas. If this is unavoidable, they should be given information in advance, particularly about personal hygiene and the prescribed protective clothing. They should be closely supervised.

2.12 The concept of Quality Assurance and all the measures capable of improving its understanding and implementation should be fully discussed during the training sessions.

Personnel Hygiene

2.13 Detailed hygiene programs should be established and adapted to the different needs within the factory. They should include procedures relating to the health, hygiene practices, and clothing of personnel. These procedures should be understood and followed in a very strict way by every person whose duties take him into the production and control areas. Hygiene programs should be promoted by management and widely discussed during training sessions.

2.14 All personnel should receive medical examination upon recruitment. It must be the manufacturer's responsibility that there are instructions ensuring that health conditions that can be of relevance to the quality of products come to the manufacturer's knowledge. After the first medical examination, examinations should be carried out when necessary for the work and personal health.

2.15 Steps should be taken to ensure as far as is practicable that no person affected by an infectious disease or having open lesions on the exposed surface of the body is engaged in the manufacture of medicinal products.

2.16 Every person entering the manufacturing areas should wear protective garments appropriate to the operations to be carried out.

2.17 Eating, drinking, chewing or smoking, or the storage of food, drink, smoking materials, or personal medication in the production and storage areas should be prohibited. In general, any unhygienic practice within the manufacturing areas or in any other area where the product might be adversely affected, should be forbidden.

2.18 Direct contact should be avoided between the operator's hands and the exposed product as well as with any part of the equipment that comes into contact with the products.

2.19 Personnel should be instructed to use the hand-washing facilities.

2.20 Any specific requirements for the manufacture of special groups of products, for example sterile preparations, are covered in the Annexes.

CHAPTER 3: PREMISES AND EQUIPMENT

Principle

Premises and equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. Their layout and design must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build up of dust or dirt and, in general, any adverse effect on the quality of products.

Premises

General

3.1 Premises should be situated in an environment which, when considered together with measures to protect the

manufacture, presents minimal risk of causing contamination of materials or products.

3.2 Premises should be carefully maintained, ensuring that repair and maintenance operations do not present any hazard to the quality of products. They should be cleaned and, where applicable, disinfected according to detailed written procedures.

3.3 Lighting, temperature, humidity, and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the medicinal products during their manufacture and storage, or the accurate functioning of equipment.

3.4 Premises should be designed and equipped so as to afford maximum protection against the entry of insects or other animals.

3.5 Steps should be taken in order to prevent the entry of unauthorized people. Production, storage, and quality control areas should not be used as a right of way by personnel who do not work in them.

Production Area

3.6 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular medicinal products, such as highly sensitizing materials (e.g., penicillins) or biological preparations (e.g., from live microorganisms). The production of certain additional products, such as certain antibiotics, certain hormones, certain cytotoxics, certain highly active drugs, and nonmedicinal products should not be conducted in the same facilities. For those products, in exceptional cases, the principle of campaign working in the same facilities can be accepted provided that specific precautions are taken and the necessary validations are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of medicinal products.

3.7 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

3.8 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different medicinal products or their components, to avoid cross-contamination and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

3.9 Where starting and primary packaging materials, intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors, and ceilings) should be smooth, free from cracks and open joints, and should not shed particulate matter and should permit easy and effective cleaning and, if necessary, disinfection.

3.10 Pipework, light fittings, ventilation points, and other services should be designed and sited to avoid the creation of recesses which are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

3.11 Drains should be of adequate size, and have trapped gullies. Open channels should be avoided where possible, but if necessary, they should be shallow to facilitate cleaning and disinfection.

3.12 Production areas should be effectively ventilated, with air control facilities (including temperature and, where necessary, humidity, and filtration) appropriate both to the products handled, to the operations undertaken within them and to the external environment.

3.13 Weighing of starting materials usually should be carried out in a separate weighing room designed for that use.

3.14 In cases where dust is generated (e.g., during sampling, weighing, mixing and processing operations, packaging of dry products), specific provisions should be taken to avoid cross- contamination and facilitate cleaning.

3.15 Premises for the packaging of medicinal products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

3.16 Production areas should be well lit, particularly where visual controls are carried out.

3.17 In-process controls may be carried out within the production area provided they do not carry any risk for the production.

Storage Areas

3.18 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products: starting and packaging materials, intermediate, bulk, and finished products, products in quarantine, released, rejected, returned, or recalled.

3.19 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g., temperature, humidity) these should be provided, checked, and monitored.

3.20 Receiving and dispatch bays should protect materials and products from the weather. Reception areas should be designed and equipped to allow containers of incoming materials to be cleaned where necessary before storage.

3.21 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

3.22 There should normally be a separate sampling area for starting materials. lf sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.

3.23 Segregated areas should be provided for the storage of rejected, recalled, or returned materials or products.

3.24 Highly active materials or products should be stored in safe and secure areas.

3.25 Printed packaging materials are considered critical to the conformity of the medicinal product and special attention should be paid to the safe and secure storage of these materials.

Quality Control Areas

3.26 Normally, Quality Control laboratories should be separated from production areas. This is particularly important for laboratories for the control of biologicals, microbiologicals, and radioisotopes, which should also be separated from each other.

3.27 Control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples and records.

3.28 Separate rooms may be necessary to protect sensitive instruments from vibration, electrical interference, humidity, and so on.
3.29 Special requirements are needed in laboratories handling particular substances, such as biological or radioactive samples.

Ancillary Areas

3.30 Rest and refreshment rooms should be separate from other areas.
3.31 Facilities for changing clothes, washing, and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not directly communicate with production or storage areas.
3.32 Maintenance workshops should as far as possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.
3.33 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air handling facilities.

Equipment

3.34 Manufacturing equipment should be designed, located, and maintained to suit its intended purpose.
3.35 Repair and maintenance operations should not present any hazard to the quality of the products.
3.36 Manufacturing equipment should be designed so that it can be easily and thoroughly cleaned. It should be cleaned according to detailed and written procedures and stored only in a clean and dry condition.
3.37 Washing and cleaning equipment should be chosen and used in order not to be a source of contamination.
3.38 Equipment should be installed in such a way as to prevent any risk of error or of contamination.
3.39 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to such an extent that it will affect the quality of the product and thus present any hazard.
3.40 Balances and measuring equipment of an appropriate range and precision should be available for production and control operations.
3.41 Measuring, weighing, recording, and control equipment should be calibrated and checked at defined intervals by appropriate methods. Adequate records of such tests should be maintained.
3.42 Fixed pipework should be clearly labeled to indicate the contents and, where applicable, the direction of flow.
3.43 Distilled, deionized, and, where appropriate, other water pipes should be sanitized according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.
3.44 Defective equipment should, if possible, be removed from production and quality control areas, or at least be clearly labeled as defective.

CHAPTER 4: DOCUMENTATION

Principle

Good documentation constitutes an essential part of the quality assurance system. Clearly written documentation prevents errors from spoken communication and permits tracing of batch history. Specifications, Manufacturing Formulae and instructions, procedures, and records must be free from errors and available in writing. The legibility of documents is of paramount importance.

General

4.1 *Specifications* describe in detail the requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.
Manufacturing Formulae, Processing, and Packaging Instructions state all the starting materials used and lay down all processing and packaging operations.
Procedures give directions for performing certain operations for example, cleaning, clothing, environmental control, sampling, testing, equipment operation.
Records provide a history of each batch of product, including its distribution, and also of all other relevant circumstances pertinent to the quality of the final product.
4.2 Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorization dossiers.
4.3 Documents should be approved, signed, and dated by appropriate and authorized persons.
4.4 Documents should have unambiguous contents; title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.
4.5 Documents should be regularly reviewed and kept up-to-date. When a document has been revised, systems should be operated to prevent inadvertent use of superseded documents.
4.6 Documents should not be handwritten; although, where documents require the entry of data, these entries may be made in clear, legible, and indelible handwriting. Sufficient space should be provided for such entries.
4.7 Any alteration made to the entry on a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.
4.8 The records should be made or completed at the time each action is taken and in such a way that all significant activities concerning the manufacture of medicinal products are traceable. They should be retained for at least 1 year after the expiry date of the finished product.
4.9 Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data processing methods, only authorized persons should be able to enter or modify data in the computer and there should be a record of changes and deletions; access should be restricted by passwords or other means and the result of entry of critical data should be independently checked. Batch records electronically stored should be protected by back-up transfer on magnetic tape, microfilm, paper, or other means. It is particularly important that the data are readily available throughout the period of retention.

4.10 There should be appropriately authorized and dated specifications for starting and packaging materials, and finished products; where appropriate, they should be also available for intermediate or bulk products.

Specifications for Starting and Packaging Materials

4.11 Specifications for starting and primary or printed packaging materials should include, if applicable:

- a description of the materials, including
  - the designated name and the internal code reference;
  - the reference, if any, to a pharmacopoeia monograph;
  - the approved suppliers and, if possible, the original producer of the products;
- (a) specimen of printed materials; (b) directions for sampling and testing or reference to procedures; (c) qualitative and quantitative requirements with acceptance limits; and (d) storage conditions and precautions;
- the maximum period of storage before reexamination.

Specifications for Intermediate and Bulk Products

4.12 Specifications for intermediate and bulk products should be available if these are purchased or dispatched, or if data obtained from intermediate products are used for the evaluation of the finished product. The specifications should be similar to specifications for starting materials or for finished products, as appropriate.

Specifications for Finished Products

4.13 Specifications for finished products should include (a) the designated name of the product and the code reference where applicable; (b) the formula or a reference; (c) a description of the pharmaceutical form and package details; (d) directions for sampling and testing or a reference to procedures; (e) the qualitative and quantitative requirements, with the acceptance limits; (f) the storage conditions and any special handling precautions, where applicable; and (g) the shelf life.

Manufacturing Formula and Processing Instructions

Formally authorized Manufacturing Formula and Processing Instructions should exist for each product and batch size to be manufactured. They are often combined in one document.

4.14 The Manufacturing Formula should include (a) the name of the product, with a product reference code relating to its specification; (b) a description of the pharmaceutical form, strength of the product, and batch size; (c) a list of all starting materials to be used, with the amount of each, described using the designated name and a reference which is unique to that material; mention should be made of any substance that may disappear in the course of processing; and (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable.

4.15 The Processing Instructions should include

a) a statement of the processing location and the principal equipment to be used;
b) the methods, or reference to the methods, to be used for preparing the critical equipment (e.g., cleaning, assembling, calibrating, sterilizing);
c) detailed stepwise processing instructions (e.g., checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
d) the instructions for any in-process controls with their limits;
e) where necessary, the requirements for bulk storage of the products; including the container, labeling, and special storage conditions where applicable; and
f) any special precautions to be observed.

Packaging Instructions

4.16 There should be formally authorized Packaging Instructions for each product, pack size, and type. These should normally include, or have a reference to, the following:

a) name of the product;
b) description of its pharmaceutical form, and strength where applicable;
c) the pack size expressed in terms of the number, weight, or volume of the product in the final container;
d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes, and types, with the code or reference number relating to the specifications of each packaging material;
e) where appropriate, an example or reproduction of the relevant printed packaging materials, and specimens indicating where to apply batch number references, and shelf life of the product;
f) special precautions to be observed, including a careful examination of the area and equipment in order to ascertain the line clearance before operations begin;
g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used; and
h) details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Records

4.17 A Batch Processing Record should be kept for each batch processed. It should be based on the relevant parts of the currently approved Manufacturing Formula and Processing Instructions. The method of preparation of such records should be designed to avoid transcription errors. The record should carry the number of the batch being manufactured.

Before any processing begins, there should be recorded checks that the equipment and work station are clear of previous products, documents, or materials not required for the planned process, and that equipment is clean and suitable for use.

During processing, the following information should be recorded at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person responsible for the processing operations:

a) the name of the product;
b) dates and times of commencement, of significant intermediate stages and of completion of production;
c) name of the person responsible for each stage of production;
d) initials of the operator of different significant steps of production and, where appropriate, of the person who checked each of these operations (e.g., weighing);
e) the batch number and/or analytical control number as well as the quantities of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);

f) any relevant processing operation or event and major equipment used;
g) a record of the in-process controls and the initials of the person(s) carrying them out, and the results obtained;
h) the product yield obtained at different and pertinent stages of manufacture; and
i) notes on special problems including details, with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions.

Batch Packaging Records

4.18 A Batch Packaging Record should be kept for each batch or part batch processed. It should be based on the relevant parts of the Packaging Instructions and the method of preparation of such records should be designed to avoid transcription errors. The record should carry the batch number and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained.

Before any packaging operation begins, there should be recorded checks that the equipment and work station are clear of previous products, documents, or materials not required for the planned packaging operations, and that equipment is clean and suitable for use.

The following information should be entered at the time each action is taken and, after completion, the record should be dated and signed in agreement by the person(s) responsible for the packaging operations:

a) the name of the product;
b) the date(s) and times of the packaging operations;
c) the name of the responsible person carrying out the packaging operation;
d) the initials of the operators of the different significant steps;
e) records of checks for identity and conformity with the packaging instructions, including the results of in-process controls;
f) details of the packaging operations carried out, including references to equipment and the packaging lines used;
g) whenever possible, samples of printed packaging materials used, including specimens of the batch coding, expiry dating, and any additional overprinting;
h) notes on any special problems or unusual events including details, with signed authorization for any deviation from the Manufacturing Formula and Processing Instructions; and
i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed, or returned to stock and the quantities of obtained product, in order to provide for an adequate reconciliation.

Procedures and Records

Receipt

4.19 There should be written procedures and records for the receipt of each delivery of each starting and primary and printed packaging material.

4.20 The records of the receipts should include (a) the name of the material on the delivery note and the containers; (b) the "in-house" name and/or code of material (if different from a); (c) date of receipt; (d) supplier's name and, if possible, manufacturer's name; (e) manufacturer's batch or reference number; (f) total quantity, and number of containers received; (g) the batch number assigned after receipt; and (h) any relevant comment (e.g., state of the containers).

4.21 There should be written procedures for the internal labeling, quarantine and storage of starting materials, packaging materials, and other materials, as appropriate.

Sampling

4.22 There should be written procedures for sampling, which include the person(s) authorized to take samples, the methods and equipment to be used, the amounts to be taken, and any precautions to be observed to avoid contamination of the material or any deterioration in its quality (see Chapter 6, item 13).

Testing

4.23 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods and equipment to be used. The tests performed should be recorded (see Chapter 6, item 17).

Other

4.24 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by the Qualified Person(s) in accordance with the requirements of Article 51 of Directive 2001/83/EC.[1]

4.25 Records should be maintained of the distribution of each batch of a product in order to facilitate the recall of the batch if necessary.

4.26 There should be written procedures and the associated records of actions taken or conclusions reached, where appropriate, for

- validation;
- equipment assembly and calibration;
- maintenance, cleaning, and sanitation;
- personnel matters including training, clothing, and hygiene;
- environmental monitoring;
- pest control;
- complaints;
- recalls; and
- returns.

4.27 Clear operating procedures should be available for major items of manufacturing and test equipment.

4.28 Log books should be kept for major or critical equipment recording, as appropriate, any validations, calibrations, maintenance, cleaning, or repair operations, including the dates and identity of people who carried these operations out.

4.29 Log books should also record in chronological order the use of major or critical equipment and the areas where the products have been processed.

CHAPTER 5: PRODUCTION

Principle

Production operations must follow clearly defined procedures; they must comply with the principles of Good Manufacturing Practice in order to obtain products of the requisite quality and be in accordance with the relevant manufacturing and marketing authorizations.

General

5.1 Production should be performed and supervised by competent people.

5.2 All handling of materials and products, such as receipt and quarantine, sampling, storage, labeling, dispensing, processing, packaging, and distribution should be done in accordance with written procedures or instructions and, where necessary, recorded.

5.3 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled with the prescribed data.

5.4 Damage to containers and any other problem, which might adversely affect the quality of a material should be investigated, recorded, and reported to the Quality Control Department.

5.5 Incoming materials and finished products should be physically or administratively quarantined immediately after receipt or processing, until they have been released for use or distribution.

5.6 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

5.7 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation.

5.8 Checks on yields, and reconciliation of quantities, should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

5.9 Operations on different products should not be carried out simultaneously or consecutively in the same room unless there is no risk of mix-up or cross-contamination.

5.10 At every stage of processing, products and materials should be protected from microbial and other contamination.

5.11 When working with dry materials and products, special precautions should be taken to prevent the generation and dissemination of dust. This applies particularly to the handling of highly active or sensitizing materials.

5.12 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate rooms used should be labeled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and batch number. Where applicable, this indication should also mention the stage of production and batch number.

5.13 Labels applied to containers, equipment, or premises should be clear, unambiguous, and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colors to indicate status (e.g., quarantined, accepted, rejected, clean).

5.14 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

5.15 Any deviation from instructions or procedures should be avoided as far as possible. lf a deviation occurs, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.

5.16 Access to production premises should be restricted to authorized personnel.

5.17 Normally, the production of nonmedicinal products should be avoided in areas and with the equipment destined for the production of medicinal products.

Prevention of Cross-Contamination in Production

5.18 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, vapors, sprays, or organisms from materials and products in process, from residues on equipment, and from operators clothing. The significance of this risk varies with the type of contaminant and of product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations containing living organisms, certain hormones, cytotoxics, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection, those given in large doses and/or over a long time.

5.19 Cross-contamination should be avoided by appropriate technical or organizational measures, for example

a) production in segregated areas (required for products such as penicillins, live vaccines, live bacterial preparations, and some other biologicals), or by campaign (separation in time) followed by appropriate cleaning;
b) providing appropriate air locks and air extraction;
c) minimizing the risk of contamination caused by recirculation or reentry of untreated or insufficiently treated air;
d) keeping protective clothing inside areas where products with special risk of cross- contamination are processed;
e) using cleaning and decontamination procedures of known effectiveness, as ineffective cleaning of equipment is a common source of cross-contamination;
f) using "closed systems" of production; and
g) testing for residues and use of cleaning status labels on equipment.

5.20 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to set procedures.

Validation

5.21 Validation studies should reinforce Good Manufacturing Practice and be conducted in accordance with defined procedures. Results and conclusions should be recorded.

5.22 When any new manufacturing formula or method of preparation is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to yield a product consistently of the required quality.

5.23 Significant amendments to the manufacturing process, including any change in equipment or materials, which may affect product quality and/or the reproducibility of the process should be validated.

5.24 Processes and procedures should undergo periodic critical revalidation to ensure that they remain capable of achieving the intended results.

Starting Materials

5.25 The purchase of starting materials is an important operation, which should involve staff who have a particular and thorough knowledge of the suppliers.

5.26 Starting materials should only be purchased from approved suppliers named in the relevant specification

and, where possible, directly from the producer. It is recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all aspects of the production and control of the starting material in question, including handling, labeling and packaging requirements, as well as complaints and rejection procedures are discussed with the manufacturer and the supplier.

5.27 For each delivery, the containers should be checked for integrity of package and seal and for correspondence between the delivery note and the supplier's labels.

5.28 lf one material delivery is made up of different batches, each batch must be considered as separate for sampling, testing, and release.

5.29 Starting materials in the storage area should be appropriately labeled (see Chapter 5, item 13). Labels should bear at least the following information:
- the designated name of the product and the internal code reference where applicable;
- a batch number given at receipt;
- where appropriate, the status of the contents (e.g., in quarantine, on test, released, rejected); and
- where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully computerized storage systems are used, all the above information need not necessarily be in a legible form on the label.

5.30 There should be appropriate procedures or measures to assure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified (see Chapter 6, item 13).

5.31 Only starting materials which have been released by the Quality Control Department and which are within their shelf life should be used.

5.32 Starting materials should only be dispensed by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers.

5.33 Each dispensed material and its weight or volume should be independently checked and the check recorded.

5.34 Materials dispensed for each batch should be kept together and conspicuously labeled as such.

Processing Operations: Intermediate and Bulk Products

5.35 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, or documents not required for the current operation.

5.36 Intermediate and bulk products should be kept under appropriate conditions.

5.37 Critical processes should be validated (see "Validation" in this Chapter).

5.38 Any necessary in-process controls and environmental controls should be carried out and recorded.

5.39 Any significant deviation from the expected yield should be recorded and investigated.

Packaging Materials

5.40 The purchase, handling, and control of primary and printed packaging materials shall be accorded attention similar to that given to starting materials.

5.41 Particular attention should be paid to printed materials. They should be stored in adequately secure conditions such as to exclude unauthorized access. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by authorized personnel following an approved and documented procedure.

5.42 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

5.43 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and this disposal recorded.

Packaging Operations

5.44 When setting up a program for the packaging operations, particular attention should be given to minimizing the risk of cross-contamination, mix-ups, or substitutions. Different products should not be packaged in close proximity unless there is physical segregation.

5.45 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines, and other equipment are clean and free from any products, materials, or documents previously used, if these are not required for the current operation. The line clearance should be performed according to an appropriate checklist.

5.46 The name and batch number of the product being handled should be displayed at each packaging station or line.

5.47 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity, and conformity with the Packaging Instructions.

5.48 Containers for filling should be clean before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

5.49 Normally, filling and sealing should be followed as quickly as possible by labeling. lf it is not the case, appropriate procedures should be applied to ensure that no mix-ups or mislabeling can occur.

5.50 The correct performance of any printing operation (e.g., code numbers, expiry dates) to be done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand which should be rechecked at regular intervals.

5.51 Special care should be taken when using cut labels and when overprinting is carried out off-line. Roll feed labels are normally preferable to cut labels, in helping to avoid mix-ups.

5.52 Checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly.

5.53 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

5.54 Online control of the product during packaging should include at least checking the following:
a) general appearance of the packages;
b) whether the packages are complete;
c) whether the correct products and packaging materials are used;
d) whether any overprinting is correct; and
e) correct functioning of line monitors.

Samples taken away from the packaging line should not be returned.

5.55 Products which have been involved in an unusual event should only be reintroduced into the process after special inspection, investigation, and approval by authorized personnel. Detailed record should be kept of this operation.

5.56 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated and satisfactorily accounted for before release.

5.57 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure should be followed if uncoded printed materials are returned to stock.

Finished Products

5.58 Finished products should be held in quarantine until their final release under conditions established by the manufacturer.

5.59 The evaluation of finished products and documentation, which is necessary before release of product for sale are described in Chapter 6, "Quality Control".

5.60 After release, finished products should be stored as usable stock under conditions established by the manufacturer.

Rejected, Recovered, and Returned Materials

5.61 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed. Whatever action is taken should be approved and recorded by authorized personnel.

5.62 The reprocessing of rejected products should be exceptional. It is only permitted if the quality of the final product is not affected, if the specifications are met and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. Record should be kept of the reprocessing.

5.63 The recovery of all or part of earlier batches which conform to the required quality by incorporation into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

5.64 The need for additional testing of any finished product which has been reprocessed, or into which a recovered product has been incorporated, should be considered by the Quality Control Department.

5.65 Products returned from the market and which have left the control of the manufacturer should be destroyed unless without doubt their quality is satisfactory; they may be considered for resale, relabeling, or recovery in a subsequent batch only after they have been critically assessed by the Quality Control Department in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse, although basic chemical reprocessing to recover active ingredient may be possible. Any action taken should be appropriately recorded.

CHAPTER 6: QUALITY CONTROL

Principle

Quality Control is concerned with sampling, specifications and testing as well as the organization, documentation, and release procedures which ensure that the necessary and relevant tests are carried out, and that materials are not released for use, nor products released for sale or supply, until their quality has been judged satisfactory. Quality Control is not confined to laboratory operations, but must be involved in all decisions, which may concern the quality of the product. The independence of Quality Control from Production is considered fundamental to the satisfactory operation of Quality Control. (see also chapter 1).

General

6.1 Each holder of a manufacturing authorization should have a Quality Control Department. This department should be independent from other departments, and under the authority of a person with appropriate qualifications and experience, who has one or several control laboratories at his disposal. Adequate resources must be available to ensure that all the Quality Control arrangements are effectively and reliably carried out.

6.2 The principal duties of the head of Quality Control are summarized in Chapter 2. The Quality Control Department as a whole will also have other duties, such as to establish, validate, and implement all quality control procedures, keep the reference samples of materials and products, ensure the correct labeling of containers of materials and products, ensure the monitoring of the stability of the products, participate in the investigation of complaints related to the quality of the product, and so on. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

6.3 Finished product assessment should embrace all relevant factors, including production conditions, results of in-process testing, a review of manufacturing (including packaging) documentation, compliance with Finished Product Specification, and examination of the final finished pack.

6.4 Quality Control personnel should have access to production areas for sampling and investigation as appropriate.

Good Quality Control Laboratory Practice

6.5 Control laboratory premises and equipment should meet the general and specific requirements for Quality Control areas given in Chapter 3.

6.6 The personnel, premises, and equipment in the laboratories should be appropriate to the tasks imposed by the nature and the scale of the manufacturing operations. The use of outside laboratories, in conformity with the principles detailed in Chapter 7, Contract Analysis, can be accepted for particular reasons, but this should be stated in the Quality Control records.

Documentation

6.7 Laboratory documentation should follow the principles given in Chapter 4. An important part of this documentation deals with Quality Control and the following details should be readily available to the Quality Control Department:

- specifications;
- sampling procedures;
- testing procedures and records (including analytical worksheets and/or laboratory notebooks);
- analytical reports and/or certificates;

- data from environmental monitoring, where required;
- validation records of test methods, where applicable; and
- procedures for and records of the calibration of instruments and maintenance of equipment.

6.8 Any Quality Control documentation relating to a batch record should be retained for 1 year after the expiry date of the batch and at least 5 years after the certification referred to in Article 51(3) of Directive 2001/83/EC.

6.9 For some kinds of data (e.g., analytical tests results, yields, environmental controls), it is recommended that records are kept in a manner permitting trend evaluation.

6.10 In addition to the information, which is part of the batch record, other original data such as laboratory notebooks and/or records should be retained and readily available.

Sampling

6.11 The sample taking should be done in accordance with approved written procedures that describe:

- the method of sampling;
- the equipment to be used;
- the amount of the sample to be taken;
- instructions for any required subdivision of the sample;
- the type and condition of the sample container to be used;
- the identification of containers sampled;
- any special precautions to be observed, especially with regard to the sampling of sterile or noxious materials;
- the storage conditions; and
- instructions for the cleaning and storage of sampling equipment.

6.12 Reference samples should be representative of the batch of materials or products from which they are taken. Other samples may also be taken to monitor the most stressed part of a process (e.g., beginning or end of a process).

6.13 Sample containers should bear a label indicating the contents, with the batch number, the date of sampling and the containers from which samples have been drawn.

6.14 Further guidance on reference and retention samples is given in Annex 19.

Testing

6.15 Analytical methods should be validated. All testing operations described in the marketing authorization should be carried out according to the approved methods.

6.16 The results obtained should be recorded and checked to make sure that they are consistent with each other. Any calculations should be critically examined.

6.17 The tests performed should be recorded and the records should include at least the following data: (a) name of the material or product and, where applicable, dosage form; (b) batch number and, where appropriate, the manufacturer and/or supplier; (c) references to the relevant specifications and testing procedures; (d) test results, including observations and calculations, and reference to any certificates of analysis; (e) dates of testing; (f) initials of the persons who performed the testing; (g) initials of the persons who verified the testing and the calculations, where appropriate; and (h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

6.18 All the in-process controls, including those made in the production area by production personnel, should be performed according to methods approved by Quality Control and the results recorded.

6.19 Special attention should be given to the quality of laboratory reagents, volumetric glassware and solutions, reference standards, and culture media. They should be prepared in accordance with written procedures.

6.20 Laboratory reagents intended for prolonged use should be marked with the preparation date and the signature of the person who prepared them. The expiry date of unstable reagents and culture media should be indicated on the label, together with specific storage conditions. In addition, for volumetric solutions, the last date of standardization and the last current factor should be indicated.

6.21 Where necessary, the date of receipt of any substance used for testing operations (e.g., reagents and reference standards) should be indicated on the container. Instructions for use and storage should be followed. In certain cases, it may be necessary to carry out an identification test and/or other testing of reagent materials upon receipt or before use.

6.22 Animals used for testing components, materials, or products, should, where appropriate, be quarantined before use. They should be maintained and controlled in a manner that assures their suitability for the intended use. They should be identified, and adequate records should be maintained, showing the history of their use.

Ongoing Stability Program

6.23 After marketing, the stability of the medicinal product should be monitored according to a continuous appropriate program that will permit the detection of any stability issue (e.g., changes in levels of impurities or dissolution profile) associated with the formulation in the marketed package.

6.24 The purpose of the ongoing stability program is to monitor the product over its shelf life and to determine that the product remains, and can be expected to remain, within specifications under the labeled storage conditions.

6.25 This mainly applies to the medicinal product in the package in which it is sold, but consideration should also be given to the inclusion in the program of bulk product. For example, when the bulk product is stored for a long period before being packaged and/or shipped from a manufacturing site to a packaging site, the impact on the stability of the packaged product should be evaluated and studied under ambient conditions. In addition, consideration should be given to intermediates that are stored and used over prolonged periods. Stability studies on reconstituted product are performed during product development and need not be monitored on an ongoing basis. However, when relevant, the stability of reconstituted product can also be monitored.

6.26 The ongoing stability program should be described in a written protocol following the general rules of Chapter 4 and results formalized as a report. The equipment

used for the ongoing stability program (stability chambers among others) should be qualified and maintained following the general rules of Chapter 3 and Annex 15.

6.27 The protocol for an ongoing stability program should extend to the end of the shelf life period and should include, but not be limited to, the following parameters:
- number of batch(es) per strength and different batch sizes, if applicable;
- relevant physical, chemical, microbiological, and biological test methods;
- acceptance criteria;
- reference to test methods;
- description of the container closure system(s);
- testing intervals (time points);
- description of the conditions of storage (standardized ICH conditions for long-term testing, consistent with the product labeling, should be used); and
- other applicable parameters specific to the medicinal product.

6.28 The protocol for the ongoing stability program can be different from that of the initial long-term stability study as submitted in the marketing authorization dossier provided that this is justified and documented in the protocol (e.g., the frequency of testing, or when updating to ICH recommendations).

6.29 The number of batches and frequency of testing should provide a sufficient amount of data to allow for trend analysis. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every primary packaging type, if relevant, should be included in the stability program (unless none are produced during that year). For products where ongoing stability monitoring would normally require testing using animals and no appropriate alternative, validated techniques are available, the frequency of testing may take account of a risk–benefit approach. The principle of bracketing and matrixing designs may be applied if scientifically justified in the protocol.

6.30 In certain situations, additional batches should be included in the ongoing stability program. For example, an ongoing stability study should be conducted after any significant change or significant deviation to the process or package. Any reworking, reprocessing, or recovery operation should also be considered for inclusion.

6.31 Results of ongoing stability studies should be made available to key personnel and, in particular, to the Qualified Person(s). Where ongoing stability studies are carried out at a site other than the site of manufacture of the bulk or finished product, there should be a written agreement between the parties concerned. Results of ongoing stability studies should be available at the site of manufacture for review by the competent authority.

6.32 Out of specification or significant atypical trends should be investigated. Any confirmed out of specification result, or significant negative trend, should be reported to the relevant competent authorities. The possible impact on batches on the market should be considered in accordance with Chapter 8 of the GMP guide and in consultation with the relevant competent authorities.

6.33 A summary of all the data generated, including any interim conclusions on the program, should be written and maintained. This summary should be subjected to periodic review.

CHAPTER 7: CONTRACT MANUFACTURE AND ANALYSIS

Principle

Contract manufacture and analysis must be correctly defined, agreed and controlled in order to avoid misunderstandings which could result in a product or work of unsatisfactory quality. There must be a written contract between the Contract Giver and the Contract Acceptor which clearly establishes the duties of each party. The contract must clearly state the way in which the Qualified Person releasing each batch of product for sale exercises his full responsibility.

Note: This chapter deals with the responsibilities of manufacturers toward the Competent Authorities of the Member States with respect to the granting of marketing and manufacturing authorizations. It is not intended in any way to affect the respective liability of contract acceptors and contract givers to consumers; this is governed by other provisions of Community and National Law.

General

7.1 There should be a written contract covering the manufacture and/or analysis arranged under contract and any technical arrangements made in connection with it.

7.2 All arrangements for contract manufacture and analysis including any proposed changes in technical or other arrangements should be in accordance with the marketing authorization for the product concerned.

The Contract Giver

7.3 The Contract Giver is responsible for assessing the competence of the Contract Acceptor to carry out successfully the work required and for ensuring by means of the contract that the principles and guidelines of GMP as interpreted in this guide are followed.

7.4 The Contract Giver should provide the Contract Acceptor with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The Contract Giver should ensure that the Contract Acceptor is fully aware of any problems associated with the product or the work, which might pose a hazard to his premises, equipment, personnel, other materials, or other products.

7.5 The Contract Giver should ensure that all processed products and materials delivered to him by the Contract Acceptor comply with their specifications or that the products have been released by a Qualified Person.

The Contract Acceptor

7.6 The Contract Acceptor must have adequate premises and equipment, knowledge and experience, and competent personnel to carry out satisfactorily the work ordered by the Contract Giver. Contract manufacture may be undertaken only by a manufacturer who is the holder of a manufacturing authorization.

7.7 The Contract Acceptor should ensure that all products or materials delivered to him are suitable for their intended purpose.

7.8 The Contract Acceptor should not pass to a third party any of the work entrusted to him under the contract without the Contract Giver's prior evaluation and approval of the arrangements. Arrangements made between the Contract Acceptor and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original Contract Giver and Contract Acceptor.

7.9 The Contract Acceptor should refrain from any activity, which may adversely affect the quality of the product manufactured and/or analyzed for the Contract Giver.

The Contract

7.10 A contract should be drawn up between the Contract Giver and the Contract Acceptor which specifies their respective responsibilities relating to the manufacture and control of the product. Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis, and Good Manufacturing Practice. All arrangements for manufacture and analysis must be in accordance with the marketing authorization and agreed by both parties.

7.11 The contract should specify the way in which the Qualified Person releasing the batch for sale ensures that each batch has been manufactured and checked for compliance with the requirements of Marketing Authorization.

7.12 The contract should describe clearly who is responsible for purchasing materials, testing and releasing materials, undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the Contract Acceptor should take samples at the premises of the manufacturer.

7.13 Manufacturing, analytical and distribution records, and reference samples should be kept by, or be available to, the Contract Giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the Contract Giver.

7.14 The contract should permit the Contract Giver to visit the facilities of the Contract Acceptor.

7.15 In the case of contract analysis, the Contract Acceptor should understand that he is subject to Inspection by the competent Authorities.

CHAPTER 8: COMPLAINTS AND PRODUCT RECALL

Principle

All complaints and other information concerning potentially defective products must be reviewed carefully according to written procedures. In order to provide for all contingencies, and in accordance with Article 117 of Directive 2001/83/EC and Article 84 of Directive 2001/82/EC, a system should be designed to recall, if necessary, promptly and effectively products known or suspected to be defective from the market.

Complaints

8.1 A person should be designated responsible for handling the complaints and deciding the measures to be taken together with sufficient supporting staff to assist him. If this person is not the Qualified Person, the latter should be made aware of any complaint, investigation, or recall.

8.2 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.

8.3 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for Quality Control should normally be involved in the study of such problems.

8.4 If a product defect is discovered or suspected in a batch, consideration should be given to checking other batches in order to determine whether they are also affected. In particular, other batches which may contain reworks of the defective batch should be investigated.

8.5 All the decisions and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.

8.6 Complaints records should be reviewed regularly for any indication of specific or recurring problems requiring attention and possibly the recall of marketed products.

8.7 Special attention should be given to establishing whether a complaint was caused because of counterfeiting.

8.8 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, detection of counterfeiting, or any other serious quality problems with a product

Recalls

8.9 A person should be designated as responsible for execution and coordination of recalls and should be supported by sufficient staff to handle all the aspects of the recalls with the appropriate degree of urgency. This responsible person should normally be independent of the sales and marketing organization. If this person is not the Qualified Person, the latter should be made aware of any recall operation.

8.10 There should be established written procedures, regularly checked and updated when necessary, in order to organize any recall activity.

8.11 Recall operations should be capable of being initiated promptly and at any time.

8.12 All Competent Authorities of all countries to which products may have been distributed should be informed promptly if products are intended to be recalled because they are, or are suspected of being defective.

8.13 The distribution records should be readily available to the person(s) responsible for recalls, and should contain sufficient information on wholesalers and directly supplied customers (with addresses, phone, and/or fax numbers inside and outside working hours, batches, and amounts delivered), including those for exported products and medical samples.

8.14 Recalled products should be identified and stored separately in a secure area while awaiting a decision on their fate.

8.15 The progress of the recall process should be recorded and a final report issued, including a reconciliation between the delivered and recovered quantities of the products.

8.16 The effectiveness of the arrangements for recalls should be evaluated regularly.

2

EDQM Certification

The European legislation does not require mandatory routine GMP inspections for active substance manufacturers. Responsibility for using only active substances that have been manufactured in accordance with good manufacturing practice is placed on the holders of a manufacturing authorization. Art. 111 Directive 2001/83/EC (Art. 80 Directive 2001/82/EC for veterinary medicinal products), however makes provision for GMP inspections of active substance manufacturing sites to be carried out at the request of the manufacturer itself. The request for the inspection should be made to the EEA competent authority where the site is located or, in case of sites located in third countries, to a competent authority where the active substance is used as a starting material in the manufacture of medicinal products. If this is not the case, any EEA authority can be approached. There is no guarantee that such a request will be fulfilled, as the competent authorities need to balance such requests with other priorities. It should also be borne in mind that an inspection does not replace the responsibility of the manufacturing authorization holder using the active substance in question as a starting material and will not be accepted alone as adequate assurance that the manufacturing authorization holder has fulfilled its responsibilities.

Manufacturing authorization holders sometimes confuse the role of inspectorates with their own obligations but nevertheless, when inspection reports or GMP certificates issued by EEA, MRA partners, or other recognized authorities are available; these can provide useful information to manufacturing authorization holders. However, these alone cannot fulfill the statutory obligations of the manufacturing authorization holder or the requirements of section 5.25 of the GMP Guide, but the results of inspections, may be used together with other supporting information in a risk-based approach by the manufacturer in establishing priorities for its own audit program of active substance suppliers.

A GMP certificate is a certificate issued, following a GMP inspection, by the competent authority responsible for carrying out the inspection, to confirm the GMP compliance status of the inspected site. GMP certificates are site specific, but can be restricted to particular activities depending on the scope of the inspection (e.g., manufacturing activities related to a specific product). Directives 2001/82/EC and 2001/83/EC, as amended state that after every GMP inspection, and within 90 days of the inspection, a GMP certificate shall be issued to a manufacturer, if the outcome of the inspection shows that the manufacturer complies with GMP.

CMPs are product specific certificates, issued by the competent authority that granted the marketing authorization (EMEA issues CMPs on behalf of the European Commission for centrally authorized products), in the context of the WHO certification scheme on the quality of pharmaceutical products moving in international commerce, to confirm the marketing authorization status of the products. These certificates also confirm the GMP compliance status of the manufacturing site(s). CMPs are mainly used by companies to support applications to export their pharmaceutical products to countries with less developed regulatory systems.

CEPs are certificates issued by the European Directorate for the Quality of Medicines (EDQM) to confirm that a certain active substance is produced according to the requirements of the relevant monograph of the European Pharmacopoeia or of the monograph on TSE. CEPs can be used by companies when submitting an application for marketing authorization, and replaces much of the documentation required for the active substance in the marketing authorization dossier. GMP inspections of active substance manufacturers can be requested by EDQM in the context of the CEP certification scheme.

EMEA does not perform inspections; they are carried out on its behalf by the national competent authorities of the member states of the EEA, in connection with products under the centralized marketing authorization procedure. The competent authority responsible for carrying out the inspection issues the GMP certificate, or makes an entry of noncompliance into the EudraGMP Database.

The EDQM allows raw material manufacturers to submit and secure approval for their active pharmaceutical ingredients besides the approval of the finished products; such approvals are not available in the jurisdictions of the FDA. Given below is submission requirement that can be used by the manufacturers to audit for the quality of the API in those instances where such certificates and/or DMF are not available.

I.2.3.S DRUG SUBSTANCE

A.2.3.S.1 General Information

Use of the substance: *Route(s) of administration, maximum daily dose.*

Commercialization history: *Summarize the history based on the table in application form.*

Declarations: Summarize the declarations appended to the application form:

- *Manufacture of the substance in accordance with ICH Q7A GMP rules*
- *Commitment by the manufacturer to keep the proposed holder informed of any changes to the documentation*
- *If applicable: manufacturer's authorization for X to act as representative*
- *Willingness to be inspected (holder, manufacturers)*
- *Nonuse/use of materials of human or animal origin in the process*

1.2.3.S.1.1 Nomenclature

(a) *Recommended International Nonproprietary name (INN)*
(b) *Chemical name(s)*
(c) *Company or laboratory code*

(d) *Other nonproprietary name(s) (e.g., national name, USAN, BAN)*
(e) *CAS No.: Molecular Formula MW*

1.2.3.S.1.2 General Properties
Give summarized data on

(a) *Physical description (e.g., appearance, color, physical state. . .)*
(b) *Physical form (e.g., polymorphic form, solvate, hydrate): to be commented especially if requested as grade*
(c) *Solubility and other properties as necessary*
(d) *Particle size: for example, nonmicronized, micronized, or any grade claimed as subtitle*

2.3.S.2 Manufacture
2.3.S.2.1 Manufacturer(s) (Name, Manufacturer) and Sites Involved in the Entire Process
Give the name, address, and responsibility of each manufacturer, including contractors and manufacturer and each proposed production site or facility involved in manufacture.

2.3.S.2.2 Description of Manufacturing Process and Process Controls
(a) *Give a brief narrative step-by-step description of the manufacturing process(es) and provide reference to detailed description in the documentation. Confirm the maximum batch size*
(b) *If applicable, summarize alternate processes and give a short explanation of their use*
(c) *Comment shortly on recovery of materials (solvents, reagents, and mother liquor) together with reprocessing steps and give a brief justification*

2.3.S.2.3 Control of Materials
(I) Starting material(s)
  (a) *Give summarized specifications (including impurities profile) including their justification based on studies of carryover.*
    NB: If starting material is obtained by fermentation or is from herbal origin, summarize the information related to the nature of this material.
(II) Reagents and solvents
  Summarize the quality and controls of the materials (e.g., raw materials, solvents pure, and/or recovered, reagents, catalysts) used in the manufacture of the drug substance.

2.3.S.2.4 Controls of Critical Steps and Intermediates
Summary of the controls performed at critical steps of the manufacturing process and on intermediates, compare analytical procedures used for intermediates and final substance.

2.3.S.2.5 Process Validation and/or Evaluation
For aseptic processing and sterilization, only give the summary of process validation and/or evaluation studies.

2.3.S.3 Characterization
2.3.S.3.1 Impurities
(I) Related substances
  (a) *Fill in the following table identifying related substances, their origin, and distinguishing between potential and actual impurities and comparing with impurity section of the monograph*

Chemical Name	Ph.Eur. Impurity	Applicant's Specifications	Ph.Eur. Specifications	Origin	Levels Found	LOD of the Method	LOQ of the Method

  (b) Justify these specifications based on *data observed for impurities in relevant batches*
  (c) *Discuss briefly about the* suitability of the monograph *to control the potential impurities present in the substance (residual starting materials, reactants, and reagents etc.)*
  (d) Specific discussion on possible genotoxic impurities: *Give a brief discussion on impurities with potential genotoxicity based on the requirements of the guideline*
(II) Residual solvent(s)/reagent(s)/catalyst(s)
  (a) *Fill in the following table*

Solvent/ Reagent/ Catalyst	Used in Step X/Y	Applicant's Limit	ICH Class/ Limit	Levels (PPM)	LOD of the Method	LOQ of the Method

  (b) *Discuss briefly the basis for setting the specification*

2.3.S.4 Control of the Drug Substance
2.3.S.4.1 Specification
Give a table summarizing the proposed specifications.

2.3.S.4.2 Analytical Procedures
(a) *Summarize of the analytical procedures*

2.3.S.4.3 Validation of Analytical Procedures
Give the summary of the validation information for any in-house tests and compare shortly with the method(s) described in the monograph (cross-validation).

2.3.S.4.4 Batch Analyses
(a) *Give a short description of the batches: batch number, batch size date, and site of production*
(b) *Summarize the results for relevant batches (according to specifications and showing equivalence of any alternative supplier, process etc.)*

2.3.S.4.5 Justification of Specification
Justify the drug substance specification

2.3.S.5 Reference Standards or Materials
(a) *Give the source of primary reference standards or reference materials (e.g., Ph.Eur.) for final substance and its impurities where relevant*
(b) *Summarize characterization and evaluation of in-house standards*

2.3.S.6 Container Closure System

(a) *Describe shortly the container closure system(s) for the storage and shipment of the drug substance, as it has to be mentioned on the CEP in case a retest period is requested (i.e.. in a clear and understandable manner)*
(b) *Summarize the specifications (description + identification)*

2.3.S.7 Stability

State retest period claimed for the substance and storage recommendations, if any.

2.3.S.7.1 Stability Summary and Conclusions

(a) *Summarize accelerated and long-term testing (e.g., studies conducted, protocols used, results obtained)*
(b) *Justify of the retest period claimed based on data available*

2.3.S.7.2 Postapproval Stability Protocol and Stability Commitment

Give the stability protocol for commitment batches.

3

GMP Audit Template, EU Guidelines (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm)

		Compliance 1 2 3[a]	Remarks	EU-Guide
1	**PERSONNEL**			
1.1	Qualified personnel available?	☐ ☐ ☐		2.1
1.2	Organization charts available?	☐ ☐ ☐		2.2
1.3	Job descriptions available?	☐ ☐ ☐		2.2
1.4	Responsibilities clearly defined?	☐ ☐ ☐		2.2
	Key personnel			
	Responsible persons designated for			
1.5	• production?	☐ ☐ ☐		2.5
1.6	• quality control?	☐ ☐ ☐		2.6
1.7	Are they independent from each other?	☐ ☐ ☐		2.3
1.8	Are joint functions clearly defined?	☐ ☐ ☐		2.7
1.9	Are the responsible persons working full time?	☐ ☐ ☐		2.3
1.10	Do the responsible persons have the appropriate formation, knowledge, and experience?	☐ ☐ ☐		2.1/2.2
1.11	Do the relevant departments have enough personnel?	☐ ☐ ☐		2.1
	Training			
1.12	Continuous training programs for the production and QC staff?	☐ ☐ ☐		2.8
1.13	Initial job training for all employees?	☐ ☐ ☐		2.9
1.14	Teaching aids (videos, slides, and brochures) available?	☐ ☐ ☐		2.9
1.15	External training courses for the staff?	☐ ☐ ☐		2.9
1.16	Training records?	☐ ☐ ☐		2.9
1.17	Special training in sensitive areas? (sterile prod. and toxic subs.)	☐ ☐ ☐		2.10
1.18	Information for visitors to the manufacturing area?	☐ ☐ ☐		2.11
2	**HYGIENE**			
	Personnel hygiene			
	Detailed written hygiene programs for			
2.1	• clothing?	☐ ☐ ☐		2.13
2.2	• use of washrooms?	☐ ☐ ☐		2.13
2.3	• behavior in production areas?	☐ ☐ ☐		2.13
2.4	Precautions against sick or personnel with open wounds in production?	☐ ☐ ☐		2.14
	Medical examination:			
2.5	• on recruitment?	☐ ☐ ☐		2.15
2.6	• regular reexaminations?	☐ ☐ ☐		2.15

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Duty of notification after			
2.7	• trips to tropical countries?	☐ ☐ ☐		2.15
2.8	• cases of contagious illness in the family?	☐ ☐ ☐		2.15
2.9	Instructions for appropriate working clothes?	☐ ☐ ☐		2.16
2.10	Absence of food and drinks (chewing gum!) in the working area?	☐ ☐ ☐		2.17
2.11	Measures against contact with open product (gloves etc.)?	☐ ☐ ☐		2.18
2.12	Instructions for hand washing in production?	☐ ☐ ☐		2.19
2.13	Change of clothes when entering and leaving the production area?	☐ ☐ ☐		5.19
2.14	Change rooms and toilets easily within reach?	☐ ☐ ☐		3.31
2.15	Toilets and restrooms sufficiently separated from production areas?	☐ ☐ ☐		3.30/3.31
2.16	Workshops separate from production areas?	☐ ☐ ☐		3.32
2.17	Laboratory animal rooms totally segregated from production rooms?	☐ ☐ ☐		3.33
3	**WAREHOUSE**			
	Rooms, general			
3.1	Suitable for the intended use?	☐ ☐ ☐		3
3.2	• adequate size?	☐ ☐ ☐		3
3.3	• clean?	☐ ☐ ☐		3
3.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
3.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
3.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
3.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
3.8	Recording of temperature and humidity?	☐ ☐ ☐		
3.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
3.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
	Type of warehousing:			
3.11	Separation of goods sufficient?	☐ ☐ ☐		3.18
3.12	Provision for different storage temperatures?	☐ ☐ ☐		3.19
3.13	Goods receiving zone weather protected?	☐ ☐ ☐		3.20
3.14	Cleaning zone for incoming goods?	☐ ☐ ☐		3.20
3.15	Separate quarantine area with controlled access?	☐ ☐ ☐		3.21
3.16	Separate, protected sampling area?	☐ ☐ ☐		3.22
	Separate and safe storage of			
3.17	• returned goods?	☐ ☐ ☐		3.23
3.18	• rejected goods?	☐ ☐ ☐		3.23
3.19	Separate and safe storage of highly active, toxic, or dangerous substances?	☐ ☐ ☐		3.24
3.20	Safe storage of narcotics?	☐ ☐ ☐		3.24
3.21	Safe storage of printed packaging materials?	☐ ☐ ☐		3.25
3.22	Security measurements against theft?	☐ ☐ ☐		3.25
3.23	Smoke detectors?	☐ ☐ ☐		3.25
3.24	Fire extinguishing system?	☐ ☐ ☐		3.25

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Operations			
3.25	Reception, sampling, and labeling according to written procedures?	☐ ☐ ☐		5.2
3.26	Is a sampling plan available?	☐ ☐ ☐		suppl. 4
3.27	Cleaning of incoming containers?	☐ ☐ ☐		5.3
3.28	Investigation and recording of damaged deliveries?	☐ ☐ ☐		5.4
3.29	FIFO principle?	☐ ☐ ☐		5.7
3.30	Inventory system?	☐ ☐ ☐		5.8
3.31	The location of materials can be detected at all times?	☐ ☐ ☐		
3.32	Incoming goods: containers and seals intact?	☐ ☐ ☐		5.27
3.33	Incoming goods: conformity with bill of delivery?	☐ ☐ ☐		5.27
	Labeling of incoming containers with			
3.34	• internal name and code?	☐ ☐ ☐		5.29
3.35	• allocated batch number?	☐ ☐ ☐		5.29
3.36	• quarantine status?	☐ ☐ ☐		5.29
3.37	• expiry date or reanalysis date?	☐ ☐ ☐		5.29
3.38	Identity test for each incoming container?	☐ ☐ ☐		5.29
3.39	Are the sampled containers marked?	☐ ☐ ☐		5.30
3.40	Are reference samples taken?	☐ ☐ ☐		5.30
3.41	Safe storage of printed packaging materials?	☐ ☐ ☐		5.41
3.42	Lot tracing of all packaging materials possible?	☐ ☐ ☐		5.42
3.43	Are excessive packaging materials destroyed?	☐ ☐ ☐		5.43
	Release of starting materials by			
	physical/inventory checks on raw materials, packaging materials, and finished goods:			
	Item:	Stocks: Physical:	Stocks: Inventory:	Storage conditions:	
4	**DISPENSING/ASSEMBLING**			
	Rooms, general			
4.1	Suitable for the intended use?	☐ ☐ ☐		3
4.2	• adequate size?	☐ ☐ ☐		3
4.3	• clean?	☐ ☐ ☐		3
4.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
4.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
4.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2

		Compliance 1 2 3[a]	Remarks	EU-Guide
4.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
4.8	Recording of temperature and humidity?	☐ ☐ ☐		
4.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
4.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
4.11	Segregated from production and warehouse?	☐ ☐ ☐		3.13
4.12	Separate weighing cabins?	☐ ☐ ☐		3.13
4.13	Separate AHU for each cabin?	☐ ☐ ☐		3.12
	Air pressure gradient from weighing cabin → corridor:			3.3
4.14	Dust extraction systems available?	☐ ☐ ☐		5.11
	Operations			
4.15	Balances regularly calibrated?	☐ ☐ ☐		3.41
4.16	Only pharmaceutical raw materials in this area?	☐ ☐ ☐		5.17
4.17	Check on remains from previous materials before entering of new materials into a weighing cabin?	☐ ☐ ☐		5.9/5.35
4.18	Only one material in one cabin?	☐ ☐ ☐		5.9
4.19	Are dispensed materials correct labeled?	☐ ☐ ☐		5.29
4.20	Only released products in the dispensing?	☐ ☐ ☐		5.31
4.21	Cleaning SOPs for the dispensing?	☐ ☐ ☐		4.28
4.22	Previously dispensed material recorded on weighing protocol?	☐ ☐ ☐		4.8
4.23	Safety measures against mix-up's during assembling (e.g., cage pallets)?	☐ ☐ ☐		5.32/5.34
5	**SOLIDS MANUFACTURING**			
	Field of activity:			
	• Granulation	☐		
	• Compression	☐		
	• Encapsulation	☐		
	• Film and sugar coating	☐		
	• Visual inspection (capsules, tablets, etc.)	☐		
	• Premix (human)	☐		
	Rooms, general			
5.1	Suitable for the intended use?	☐ ☐ ☐		3
5.2	• adequate size?	☐ ☐ ☐		3
5.3	• clean?	☐ ☐ ☐		3
5.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
5.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
5.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
5.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
5.8	Recording of temperature and humidity?	☐ ☐ ☐		
5.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
5.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
5.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6

		Compliance 1 2 3[a]	Remarks	EU-Guide
5.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
5.13	Logical flow of materials?	☐ ☐ ☐		3.7
5.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
5.15	Easy cleaning possible?	☐ ☐ ☐		3.10
5.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
5.17	Appropriate air-handling system?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
5.18	Appropriate dust extraction system?	☐ ☐ ☐		3.14
5.19	Appropriate lighting?	☐ ☐ ☐		3.16
5.20	Separate rest rooms?	☐ ☐ ☐		3.30
5.21	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
5.22	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
5.23	Suitable for the intended use?	☐ ☐ ☐		3.34
5.24	Well maintained?	☐ ☐ ☐		3.34
5.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
5.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
5.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
5.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
5.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
5.30	Calibration records available?	☐ ☐ ☐		3.41
5.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
5.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
5.33	Not functioning equipment in the production area (if yes: clearly marked)?	Y N ☐ ☐ ☐		3.44
5.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
5.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
5.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
5.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
5.38	Check of each single container of the starting materials (contents, weight, and identity)?	☐ ☐ ☐		5.3
5.39	Limits for yields?	☐ ☐ ☐		5.8
5.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
5.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
5.42	Appropriate measures against generation of dust (e.g., closed systems)?	☐ ☐ ☐		5.11
	Correct labeling of containers, materials, equipment, and rooms with			5.12

		Compliance 1 2 3[a]	Remarks	EU-Guide
5.43	• product name and batch no.	☐ ☐ ☐		5.12
5.44	• quarantine status?	☐ ☐ ☐		5.12
5.45	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐		5.14
5.46	Special procedures for the production of antibiotics, hormones, etc.?	☐ ☐ ☐		5.19
5.47	• Campaign production?	☐ ☐ ☐		5.19
5.48	• Special monitoring?	☐ ☐ ☐		5.19
5.49	• Validated decontamination procedure?	☐ ☐ ☐		5.19
5.50	Double check on weight?	☐ ☐ ☐		5.34
5.51	Line clearance before start of production?	☐ ☐ ☐		5.35
5.52	Investigation of deviations in yields?	☐ ☐ ☐		5.39
5.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐		5.62
5.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐		5.63
5.55	Special release procedure (QA) for those batches?	☐ ☐ ☐		5.64
5.56	Use of protective clothing (hair cover, shoes, masks, and gloves)?	☐ ☐ ☐		2.16
5.57	Clothing regulation for visitors?	☐ ☐ ☐		2.11
	IPC			5.38
	Who performs IPC?			
5.58	Are IPC methods approved by QC?	☐ ☐ ☐		6.18
	Performance of IPCs:	During Start-up? Yes No	Frequency / Automatic data recording? Yes No	
	Tablets/Kernels			
5.59	Individual weights	☐ ☐	☐ ☐	
5.60	Disintegration	☐ ☐	☐ ☐	
5.61	Thickness	☐ ☐	☐ ☐	
5.62	Hardness	☐ ☐	☐ ☐	
5.63	Friability/Abrasion	☐ ☐	☐ ☐	
	Sugar-/Film-coated tablets			
5.64	Weights	☐ ☐	☐ ☐	
5.65	Disintegration	☐ ☐	☐ ☐	
5.66	Residual absolute humidity (IR or)	☐ ☐	☐ ☐	
	Capsules			
5.67	Individual weights	☐ ☐	☐ ☐	
5.68	Disintegration	☐ ☐	☐ ☐	
	Validation			
5.69	Validation according to fixed procedures?	☐ ☐ ☐		5.21
5.70	New procedures released only after validation?	☐ ☐ ☐		5.22
	Validation of changes of			
5.71	• processes?	☐ ☐ ☐		5.23
5.72	• starting materials?	☐ ☐ ☐		5.23
5.73	• equipment?	☐ ☐ ☐		5.23

		Compliance 1 2 3[a]	Remarks	EU-Guide
5.74	Revalidation in fixed intervals?	☐ ☐ ☐		5.24
5.75	Procedures for the retrospective validation of old procedures?	☐ ☐ ☐		
6	**LIQUIDS MANUFACTURING**			
	Operations carried out:			
	• Dispensing (if different from solid)	☐ ☐ ☐		
	• Syrups and suspensions	☐ ☐ ☐		
	• Drops	☐ ☐ ☐		
	• Ointment manufacture	☐ ☐ ☐		
	• Ointment filling	☐ ☐ ☐		
	• Ampoule solution manufacture	☐ ☐ ☐		
	• Sterile or aseptic ampoule filling	☐ ☐ ☐		
	• Sterile freeze drying	☐ ☐ ☐		
	• Sterile powder filling	☐ ☐ ☐		
	Rooms, general			
6.1	Suitable for the intended use?	☐ ☐ ☐		3
6.2	• adequate size?	☐ ☐ ☐		3
6.3	• clean?	☐ ☐ ☐		3
6.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
6.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
6.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
6.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
6.8	Recording of temperature and humidity?	☐ ☐ ☐		
6.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
6.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
6.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6
6.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
6.13	Logical flow of materials?	☐ ☐ ☐		3.7
6.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
6.15	Easy cleaning possible?	☐ ☐ ☐		3.10
6.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
6.17	Appropriate air-handling system with filtered air where open products are exposed to the environment?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
6.18	Appropriate lighting?	☐ ☐ ☐		3.16
6.19	Separate rest rooms?	☐ ☐ ☐		3.30
6.20	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
6.21	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
6.22	Suitable for the intended use?	☐ ☐ ☐		3.34
6.23	Well maintained?	☐ ☐ ☐		3.34
6.24	Tanks, containers, pipework, and pumps designed for easy cleaning and sanitation (dead legs!)?	☐ ☐ ☐		Suppl. 2

		Compliance 1 2 3[a]	Remarks	EU-Guide
6.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
6.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
6.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
6.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
6.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
6.30	Calibration records available?	☐ ☐ ☐		3.41
6.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
6.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
6.33	Not functioning equipment in the production area (if yes: clearly marked)?	Y N ☐ ☐ ☐		3.44
6.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
6.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
6.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
6.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
6.38	Check of each single container of the starting materials (contents, weight, and identity)?	☐ ☐ ☐		5.3
6.39	Limits for yields?	☐ ☐ ☐		5.8
6.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
6.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
	Correct labeling of containers, materials, equipment, and rooms with:			5.12
6.42	• product name and batch no.	☐ ☐ ☐		5.12
6.43	• quarantine status?	☐ ☐ ☐		5.12
6.44	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐		5.14
6.45	Special procedures for the production of antibiotics, hormones, etc.?	☐ ☐ ☐		5.19
6.46	• Campaign production?	☐ ☐ ☐		5.19
6.47	• Special monitoring?	☐ ☐ ☐		5.19
6.48	• Validated decontamination procedure?	☐ ☐ ☐		5.19
6.49	Double check on weight?	☐ ☐ ☐		5.34
6.50	Line clearance before start of production?	☐ ☐ ☐		5.35
6.51	Investigation of deviations in yields?	☐ ☐ ☐		5.39
6.52	Specification of max. storage time and storage conditions if products are not immediately filled or packaged?	☐ ☐ ☐		Suppl. 9
6.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐		5.62
6.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐		5.63
6.55	Special release procedure (QA) for those batches?	☐ ☐ ☐		5.64
6.56	Use of protective clothing (hair cover, shoes, masks, and gloves)?	☐ ☐ ☐		2.16
6.57	Clothing regulation for visitors?	☐ ☐ ☐		2.11

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Water			
6.58	Loop system for purified water?	☐ ☐ ☐		Suppl. 4
6.59	Antimicrobial treatment of purified water?	☐ ☐ ☐		Suppl. 4
6.60	Loop system for water for injection?	☐ ☐ ☐		Suppl. 4
	Storage temperature of water for injection:			Suppl. 4
6.61	Loop system constructed to avoid dead legs?	☐ ☐ ☐		Suppl. 4
6.62	Regular microbiological monitoring?	☐ ☐ ☐		Suppl. 4
6.63	Regular endotoxin control?	☐ ☐ ☐		Suppl. 4
	Special requirements for sterile and aseptic products			**Suppl.**
	Rooms and equipment			
6.64	Access of staff and materials to clean areas *only* through air locks?	☐ ☐ ☐		1
6.66	Rooms classified according EC Guide?	☐ ☐ ☐		3
	Classification for products to be sterilized:			
6.67	• Solution preparation (EC: class C, with special precautions class D):	Class:		5
6.68	• Filling (EC: under LF in class C):	Class:		5
	Classification for aseptic products:			
6.69	• Handling of starting materials that can be sterile filtered (EC: class C):	Class:		6
6.70	• Handling of starting materials that cannot be sterile filtered (EC: class A in class B):	Class:		6
6.71	• Handling and filling of bulk (EC: class A in Class B):	Class:		6
6.72	All rooms easy to clean disinfect?	☐ ☐ ☐		17
6.73	Doors, windows, frames, lighting, etc. without edges?	☐ ☐ ☐		18
6.74	Suspended ceilings (if yes: sealed?)?	☐ ☐ ☐		19
6.75	Traps constructed to avoid microb. contamination?	☐ ☐ ☐		21
6.76	Appropriate constructed changing rooms?	☐ ☐ ☐		22
6.77	Measures against opening of both doors of air locks?	☐ ☐ ☐		23
6.78	Overpressure gradient from cleanest areas to others?	☐ ☐ ☐		24
6.79	AHU validated and regularly revalidated?	☐ ☐ ☐		25
6.80	Control instruments for pressure gradient?	☐ ☐ ☐		26
6.81	Warning system for errors in air supply?	☐ ☐ ☐		26
6.82	Recording of pressure gradients?	☐ ☐ ☐		26
6.83	Do conveyor belts leave sterile areas?	☐ ☐ ☐		28
6.84	Maintenance works outside from clean areas possible?	☐ ☐ ☐		28
6.85	Cleaning and disinfection procedure after maintenance works?	☐ ☐ ☐		29
6.86	Regular revalidation of all equipment and systems?	☐ ☐ ☐		30
6.87	Water prepared, circulated, and stored to exclude microb. contamination?	☐ ☐ ☐		31
6.88	Cleaning and disinfection of rooms according to validated SOPs rooms?	☐ ☐ ☐		32
	• Disinfection methods?			
6.89	Microb. monitoring of cleaning and disinfection agents?	☐ ☐ ☐		33

		Compliance 1 2 3[a]	Remarks	EU-Guide
6.90	Microb. monitoring program of production areas?	☐ ☐ ☐		35
6.91	Results recorded and considered for the release?	☐ ☐ ☐		35
	Personnel and hygiene			
6.92	Minimal no. of personnel in clean areas?	☐ ☐ ☐		7
6.93	Special and regular training?	☐ ☐ ☐		8
6.94	Regular medical examinations?	☐ ☐ ☐		10
6.95	Appropriate clean room clothes (material, and design)?	☐ ☐ ☐		12
6.96	Protective clothes worn correctly?	☐ ☐ ☐		12
6.97	Prohibition of cosmetics, jewelery, and watches?	☐ ☐ ☐		13
6.98	New clean room clothes for each working cycle?	☐ ☐ ☐		15
6.99	Appropriate washing and sterilization of clothes?	☐ ☐ ☐		16
	Operations			
6.100	Validation (media filling) in regular intervals?	☐ ☐ ☐		38
	Monitoring of water preparation system, frequency:			
6.101	• microbiological:			40
6.102	• chemical:			40
6.103	• particles:			40
6.104	• endotoxins:			40
6.105	Microbiological monitoring of starting materials?	☐ ☐ ☐		42
6.106	Max. storage times defined for sterilized equipment?	☐ ☐ ☐		45
6.107	Max. storage time defined between solution preparation and filtration?	☐ ☐ ☐		46
6.108	Material transfer to clean areas through double door autoclaves?	☐ ☐ ☐		48
	Sterilization processes			
6.109	All processes validated?	☐ ☐ ☐		50
6.110	Sterilized and nonsterilized materials clearly separated?	☐ ☐ ☐		54
	Trays and boxes clearly labeled with			
6.111	• product name and code	☐ ☐ ☐		54
6.112	• batch no.	☐ ☐ ☐		54
6.113	• status: sterilized or nonsterilized	☐ ☐ ☐		54
	Sterilizers			
6.114	• Recording of temp., pressure, and time?	☐ ☐ ☐		55
6.115	• Coldest point determined?	☐ ☐ ☐		55
6.116	• Independent counter check probe?	☐ ☐ ☐		55
6.117	• Heat-up time for each product determined?	☐ ☐ ☐		56
6.118	• Sterile cooling media?	☐ ☐ ☐		57
6.119	• Tightness tests for vacuum autoclaves?	☐ ☐ ☐		58
6.120	• Clean steam for steam autoclaves?	☐ ☐ ☐		58
6.121	• Circulated air with overpressure?	☐ ☐ ☐		61
6.122	• Recirculated air: sterile filtered?	☐ ☐ ☐		61
6.123	• Ethylene oxide autoclaves: humidity, temp., and time recorded?	☐ ☐ ☐		69
6.124	• Ethylene oxide autoclaves: use of bioindicators?	☐ ☐ ☐		70

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Filtration			
6.125	Double filtration?	☐ ☐ ☐		75
6.126	Integrity testing of filters immediately after use?	☐ ☐ ☐		77
6.127	Are results a part of the batch protocol?	☐ ☐ ☐		77
6.128	Optical control of each single container of ampoules, vials, and infusions?	☐ ☐ ☐		82
	IPC			
6.129	Written IPC procedures and SOPs?	☐ ☐ ☐		
	Particle testing of			
6.130	• rooms	☐ ☐ ☐		
6.131	• primary packaging materials	☐ ☐ ☐		
6.132	• system of warning and action limits?	☐ ☐ ☐		
	Microbiological monitoring of			
6.133	• rooms			
6.134	• personnel			
6.135	• equipment			
6.136	Residual O_2 of ampoules, infusions, and syrups?	☐ ☐ ☐		
6.137	Endotoxin testing of water and packaging materials?	☐ ☐ ☐		
6.138	Calibration of equipment?	☐ ☐ ☐		
6.139	Regular revalidation of equipment?	☐ ☐ ☐		
7	**PACKAGING**			
	Operations carried out: • Blistering • Foil packaging • Filling into tablet glasses • Effervescent packaging • Powder filling • Syrup/drops filling • Ointment filling	 ☐ ☐ ☐ ☐ ☐ ☐ ☐		
	Rooms			
7.1	Suitable for the intended use?	☐ ☐ ☐		3
7.2	• adequate size?	☐ ☐ ☐		3
7.3	• clean?	☐ ☐ ☐		3
7.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
7.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
7.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
7.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
7.8	Recording of temperature and humidity?	☐ ☐ ☐		
7.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
7.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
7.11	Adequate separation of the packaging lines?	☐ ☐ ☐		3.15
	Operations			
7.12	Only *one* product per line?	☐ ☐ ☐		5.44

		Compliance 1 2 3[a]	Remarks	EU-Guide
7.13	Check list for clearance before processing a new product/new batch?	☐ ☐ ☐		5.45
7.14	Adequate labeling of the lines (product name and code)?	☐ ☐ ☐		5.46
7.15	Check of all materials delivered to the line (quantity, identity, conformity with order)?	☐ ☐ ☐		5.47
7.16	Cleaning of primary packaging materials?	☐ ☐ ☐		5.48
7.17	Immediate labeling after filling?	☐ ☐ ☐		5.49
7.18	Careful check of all printing processes (code, and expiry date)?	☐ ☐ ☐		5.50
7.19	Special safety measures for off-line printing?	☐ ☐ ☐		5.51
7.20	Regular checks of all control devices (code reader, counter etc.)?	☐ ☐ ☐		5.52
7.21	Printings clear and durable?	☐ ☐ ☐		5.53
7.22	Balancing of printed packaging materials and bulk?	☐ ☐ ☐		5.56
7.23	Destruction of excessive coded packaging material after completion of an order?	☐ ☐ ☐		5.57
7.24	Are the finished products kept in quarantine until final release?	☐ ☐ ☐		5.58
7.25	Appropriate storage after release?	☐ ☐ ☐		5.60
	IPC			
7.26	Checks on identity of bulk and packaging materials?	☐ ☐ ☐		5.47
	Regular line checks on			
7.27	• aspect of the packages	☐ ☐ ☐		5.54a
7.28	• completeness	☐ ☐ ☐		5.54b
7.29	• conformity of quantity and quality of materials with packaging order	☐ ☐ ☐		5.54c
7.30	• correct imprint	☐ ☐ ☐		5.54d
7.31	• correct function of control devices	☐ ☐ ☐		5.54d
	Are the following IPC checks performed?			
7.32	• Leaking	☐ ☐ ☐		
7.33	• Release torque of screw caps	☐ ☐ ☐		
7.34	• pH, density, drop weight, viscosity, and sedimentation	☐ ☐ ☐		
8	**DOCUMENTATION**			
	Specifications			
8.1	Specifications for raw/packaging materials available?	☐ ☐ ☐		4.10
	Do they include			
8.2	• internal name and code	☐ ☐ ☐		4.11
8.3	• name of supplier and/or manufacturer?	☐ ☐ ☐		4.11
8.4	• reference sample (printed pack. mat.)?	☐ ☐ ☐		4.11
8.5	• sampling procedure?	☐ ☐ ☐		4.11
8.6	• qualitative/quantitative specifications with limits?	☐ ☐ ☐		4.11
8.7	• storage conditions?	☐ ☐ ☐		4.11
8.8	• maximum storage period?	☐ ☐ ☐		4.11
	Goods receiving?			
8.9	Written procedures for the reception of deliveries?	☐ ☐ ☐		4.19

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Do records receipt include			
8.10	• product name on labels and delivery note?	☐ ☐ ☐		4.20
8.11	• internal name and code?	☐ ☐ ☐		4.20
8.12	• receiving date?	☐ ☐ ☐		4.20
8.13	• name of supplier and/or manufacturer?	☐ ☐ ☐		4.20
8.14	• batch number of supplier?	☐ ☐ ☐		4.20
8.15	• total quantity and number of containers?	☐ ☐ ☐		4.20
8.16	• allocated internal batch number?	☐ ☐ ☐		4.20
8.17	SOPs for labeling, quarantine, and storage conditions of all incoming goods available?	☐ ☐ ☐		4.21
	SOPs include			
8.18	• authorized sampling personnel?	☐ ☐ ☐		4.22
8.19	• methods, equipment, and quantities?	☐ ☐ ☐		4.22
8.20	• safety measures?	☐ ☐ ☐		4.22
	Master formulae			
8.21	Are master formulae for each product and batch size available?	☐ ☐ ☐		4.3
8.22	Is the master formula approved and signed by the authorized persons?	☐ ☐ ☐		4.3
	The master formula includes			
8.23	• product name and code?	☐ ☐ ☐		4.14a
8.24	• description of galenical form, dosage, and batch size?	☐ ☐ ☐		4.14b
8.25	• all active ingredients with name, code, and weight?	☐ ☐ ☐		4.14c
8.26	• all excipients used during manufacture with name, code, and weight?	☐ ☐ ☐		4.14c
8.27	• yields with limits?	☐ ☐ ☐		4.14d
	Does the working procedure include			
8.28	• the production line?	☐ ☐ ☐		4.15a
8.29	• equipment to be used?	☐ ☐ ☐		4.15a
8.30	• reference to methods for cleaning, assembling, and calibration of machines?	☐ ☐ ☐		4.15b
8.31	• detailed stepwise manufacturing prescription?	☐ ☐ ☐		4.15c
8.32	• IPCs to be performed with limits?	☐ ☐ ☐		4.15d
8.33	• precautions to be followed?	☐ ☐ ☐		4.15e
8.34	Are batch records kept for each batch processed?	☐ ☐ ☐		4.17
	Do batch records include			
8.35	• protocol of line clearance?	☐ ☐ ☐		4.17
8.36	• name of the product and batch no.?	☐ ☐ ☐		4.17a
8.37	• date and time of start and end of production?	☐ ☐ ☐		4.17b
8.38	• name and initials of responsible workers for each step?	☐ ☐ ☐		4.17c, d
8.39	• batch and analytical no. and actual weight of all starting materials?	☐ ☐ ☐		4.17e
8.40	• equipment used?	☐ ☐ ☐		4.17f
8.41	• results of IPCs with initials of person who carries them out?	☐ ☐ ☐		4.17g
8.42	• yields of the relevant manufacturing steps?	☐ ☐ ☐		4.17h
8.43	• detailed notes on problems and process deviations?	☐ ☐ ☐		4.17i

		Compliance 1 2 3[a]	Remarks	EU-Guide
8.44	Records on reprocessing of batches?	☐ ☐ ☐		
	Packaging instructions			
8.45	Packaging instructions for each product, package size, and presentation?	☐ ☐ ☐		4.16
	Do they include			
8.46	• product name?	☐ ☐ ☐		4.16a
8.47	• description of galenical form and strength?	☐ ☐ ☐		4.16b
8.48	• package size?	☐ ☐ ☐		4.17c
8.49	• list of all packaging materials with code for a standard batch size?	☐ ☐ ☐		4.17d
8.50	• samples of printed packaging materials?	☐ ☐ ☐		4.17e
8.51	• special precautions?	☐ ☐ ☐		4.17f
8.52	• description of the process and equipment?	☐ ☐ ☐		4.17g
8.53	• IPCs to be performed with sampling instruction?	☐ ☐ ☐		4.17h
8.54	Are packaging batch records kept for each batch or part batch?	☐ ☐ ☐		4.18
	Do the packaging batch records include			
8.55	• protocol of line clearance?	☐ ☐ ☐		4.18
8.56	• name of the product?	☐ ☐ ☐		4.18a
8.57	• date and time when operations have been performed?	☐ ☐ ☐		4.18b
8.58	• name of the responsible person?	☐ ☐ ☐		4.18c
8.59	• initials of workers carrying out operations?	☐ ☐ ☐		4.18d
8.60	• notes on identity checks and conformity with packaging instructions?	☐ ☐ ☐		4.18e
8.61	• results of IPCs	☐ ☐ ☐		4.18e
8.62	• details of operations and equipment used?	☐ ☐ ☐		4.18f
8.63	• samples of printed packaging materials with codes (MFD, EXP, batch no. etc.)?	☐ ☐ ☐		4.18g
8.64	• record of problems and process deviations?	☐ ☐ ☐		4.18h
8.65	• quantities of packaging materials delivered, used, destroyed, or returned?	☐ ☐ ☐		4.18i
8.66	• no. of packs consumed?	☐ ☐ ☐		4.18j
	Testing			
	Do the written testing procedures include			
8.67	• test methods?	☐ ☐ ☐		4.23
8.68	• equipment for testing?	☐ ☐ ☐		4.23
8.69	Tests documented?	☐ ☐ ☐		4.23
	Others			
8.70	Procedures for release and rejection of materials and finished products?	☐ ☐ ☐		4.24
8.71	Final release by authorized person?	☐ ☐ ☐		4.24
8.72	Records about distribution of each batch?	☐ ☐ ☐		4.25
	Procedures and protocols about			
8.73	• validation?	☐ ☐ ☐		4.26

		Compliance 1 2 3[a]	Remarks	EU-Guide
8.74	• set up and calibration of equipment?	☐ ☐ ☐		4.26
8.75	• maintenance, cleaning, and disinfection?	☐ ☐ ☐		4.26
8.76	• training records?	☐ ☐ ☐		4.26
8.77	• environmental monitoring of production areas?	☐ ☐ ☐		4.26
8.78	• pest control?	☐ ☐ ☐		4.26
8.79	• complaints?	☐ ☐ ☐		4.26
8.80	• recalls?	☐ ☐ ☐		4.26
8.81	• returned goods?	☐ ☐ ☐		4.26
8.82	Instructions for use of manufacturing and testing equipment?	☐ ☐ ☐		4.27
	Log books for major equipment incl. date and name of persons who performed			
8.83	• validation?	☐ ☐ ☐		4.28
8.84	• calibration?	☐ ☐ ☐		4.28
8.85	• maintenance, cleaning, and repair works?	☐ ☐ ☐		4.28
8.86	Chronological records of use of major equipment and manufacturing areas?	☐ ☐ ☐		4.29
9	**QUALITY CONTROL**			**6**
	General requirements			
9.1	Independent QC department available?	☐ ☐ ☐		6.1
9.2	Head of QC well qualified and sufficiently experienced?	☐ ☐ ☐		6.1
9.3	Qualified personnel available?	☐ ☐ ☐		2.1
9.4	Organization charts available?	☐ ☐ ☐		2.2
9.5	Job descriptions available?	☐ ☐ ☐		2.2
9.6	Responsibilities clearly defined?	☐ ☐ ☐		2.2
9.7	Continuous training programs for QC staff?	☐ ☐ ☐		2.2
9.8	Initial job training for all employees?	☐ ☐ ☐		2.9
9.9	Training records?	☐ ☐ ☐		
9.10	QC personnel admitted to the production rooms for sampling etc.?	☐ ☐ ☐		
	QC laboratories			
9.11	Suitable for the intended use?	☐ ☐ ☐		3.26
9.12	Laboratories of adequate size?	☐ ☐ ☐		3.26
9.13	Appropriate level of maintenance?	☐ ☐ ☐		3.1
9.14	Adequate separation from the production area?	☐ ☐ ☐		3.26
9.15	Controlled access of authorized personnel only?	☐ ☐ ☐		3.5
9.16	Special laboratory to handle biological samples available?	☐ ☐ ☐		3.29
9.17	Special laboratory to handle radioactive material available?	☐ ☐ ☐		3.29
9.18	Separate recreation rooms for the personnel available?	☐ ☐ ☐		3.30
9.19	Animal laboratories present?	☐ ☐ ☐		3.33
9.20	Animal laboratories separated from other areas?	☐ ☐ ☐		3.33
9.21	Animal laboratories equipped with a separate air-handling system?	☐ ☐ ☐		3.33

		Compliance 1 2 3[a]	Remarks	EU-Guide
	QC Documentation			
9.22	Do procedures exist for • self inspection? • release or rejection of products or raw material? • product complaints? • product recalls? • local stability testing? • storage of reference samples? • validation of analytical procedures?	 ☐		
9.23	Specifications available for • raw materials? • bulk products? • packaging materials?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.7
9.24	Analytical procedures for every product?	☐ ☐ ☐		
9.25	Are Basel methods followed?	☐ ☐ ☐		
9.26	Validation of locally developed test methods?	☐ ☐ ☐		
9.27	Sampling procedures available for • raw materials? • bulk products? • packaging materials?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.7
9.28	Suppliers certificates available?	☐ ☐ ☐		6.7
9.29	Calibration program for analytical instruments installed?	☐ ☐ ☐		6.7
9.30	Maintenance program for analytical instruments?	☐ ☐ ☐		6.7
9.31	Retention system for QC records?	☐ ☐ ☐		6.8
9.32	Batch documents stored for expiry + 1 year or 5 years (EEC 75/319, article 22) minimum?	☐ ☐ ☐		6.8
9.33	Are original data like notebooks stored in addition to the batch documents?	☐ ☐ ☐		6.10
9.34	Can the original data be traced back easily and quickly from the analytical report number or batch number?	☐ ☐ ☐		6.10
9.35	Are trend analyses being performed for • analytical results? • yields? • environmental monitoring data?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.9
	Sampling			
9.36	Written procedures for taking samples?	☐ ☐ ☐		6.11
9.37	Do procedures define • method of sampling? • necessary equipment? • quantity of the sample? • subdivision of the sample? • sample container? • labeling of samples? • storage conditions? • cleaning and storage of sampling equipment? • identification of containers sampled	 ☐		
9.38	Are samples representative for the batch they are taken from (sampling plan)?	☐ ☐ ☐		6.12
9.39	Are critical steps being surveilled and validated by additional sampling (e.g., beginning or end of a process).	☐ ☐ ☐		6.12

		Compliance 1 2 3[a]	Remarks	EU-Guide
9.40	Sample containers labeled with • name of the content • batch number • date of sampling • batch containers sampled	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.13
9.41	Are samples taken by QC/QA?	☐ ☐ ☐		
9.42	Reference samples retained for validity +1 year?	☐ ☐ ☐		6.14
9.43	Storage of reference samples under the recommended storage conditions?	☐ ☐ ☐		6.14
9.44	Finished products stored in the final packaging?	☐ ☐ ☐		6.14
9.45	Quantity of the reference sample makes 1 (better 2) complete reanalysis possible?	☐ ☐ ☐		6.14
9.46	Sample room secure?	☐ ☐ ☐		
9.47	Sample room neatly organized and not overcrowded?	☐ ☐ ☐		
	Testing			
9.48	Are the applied analytical methods validated?	☐ ☐ ☐		6.15
9.49	Analytical methods in compliance with the registration?	☐ ☐ ☐		6.16
9.50	Are all results recorded and checked for correctness?	☐ ☐ ☐		6.16
9.51	Are all calculations checked?	☐ ☐ ☐		6.16
9.52	Do the testing protocols contain • name and galenical form of material? • batch number? • supplier if applicable? • specification reference? • method reference? • analytical results? • reference to analytical certificates? • date of the analysis? • name of the analyst? • name of the person verifying the data? • statement of release or rejection? • date and sign of the release person?	 ☐		6.17
9.53	Are all IPC methods in production approved by QC?	☐ ☐ ☐		6.18
9.54	Are written methods available for the preparation of reagents and volumetric solutions?	☐ ☐ ☐		6.19
9.55	Is a record maintained of standardization of volumetric solutions?	☐ ☐ ☐		6.2
9.56	Are reagents for prolonged use labeled with • date of the preparation? • sign of the preparator?	 ☐ ☐ ☐ ☐ ☐ ☐		6.20
9.57	Are unstable reagents labeled with • expiry date? • storage conditions?	 ☐ ☐ ☐ ☐ ☐ ☐		6.20
9.58	Are volumetric solutions labeled with • the last date of standardization? • last current factor?	 ☐ ☐ ☐ ☐ ☐ ☐		6.20
9.59	Are reference standards labeled with • name and potency • suppliers reference • date of receipt • date of expiry	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.21

		Compliance 1 2 3[a]	Remarks	EU-Guide
9.60	Are reference standards stored properly and under the control of a designated person?	☐ ☐ ☐		
9.61	Are animals used for testing of components, materials, or products • quarantined before use? • checked for suitability? • Are records maintained showing the history of their use?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		
10	**COMPLAINTS AND PRODUCT RECALLS**			**8**
	Complaints			8.1
10.1	Does a written complaint procedure exist?	☐ ☐ ☐		8.2
10.2	Are product complaints carefully reviewed?	☐ ☐ ☐		8.1
10.3	Is a person designated to handle complaints and to decide on measures to be taken?	☐ ☐ ☐		8.1
10.4	Is each complaint concerning a product recorded with all original details?	☐ ☐ ☐		8.3
10.5	Are product complaints thoroughly investigated?	☐ ☐ ☐		8.3
10.6	Is a responsible person of QC involved in the study?	☐ ☐ ☐		8.3
10.7	Is it considered that other batches might be concerned as well?	☐ ☐ ☐		8.4
10.8	Are decisions and measures as a result recorded?	☐ ☐ ☐		8.5
10.9	Is this record added to the corresponding batch documents?	☐ ☐ ☐		8.5
10.10	Are the complaint records regularly revised with respect to specific or recurring problems?	☐ ☐ ☐		8.6
10.11	Are the authorities informed of serious quality problems with a product?	☐ ☐ ☐		8.7
	Recalls			8.8
10.12	Does a written recall procedure exist?	☐ ☐ ☐		8.9
10.13	Is a person nominated responsible for the execution and coordination of a recall?	☐ ☐ ☐		8.8
10.14	Responsible person independent of the marketing and sales organization?	☐ ☐ ☐		8.8
10.15	Are the competent authorities informed of an imminent recall?	☐ ☐ ☐		8.11
10.16	Does the person responsible for a recall have access to the distribution records?	☐ ☐ ☐		8.12
10.17	Do the distribution records contain sufficient information on customers with • addresses? • phone numbers inside or outside working hours? • batches and amounts delivered? • medical samples?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		8.12
10.18	Are recalled products stored separately in a secure area?	☐ ☐ ☐		8.13
10.19	Is a final record made including a reconciliation between the delivered and recovered quantities?	☐ ☐ ☐		8.14
10.20	Is the effectiveness of the arrangements for recalls checked critically from time to time?	☐ ☐ ☐		8.15
11	**SELF-INSPECTION**			**9**
11.1	Does a self-inspection procedure exist which defines frequency and program?	☐ ☐ ☐		9.1
11.2	Are self-inspections carried out to check compliance with GMP rules?	☐ ☐ ☐		9.1

		Compliance 1 2 3[a]	Remarks	EU-Guide
11.3	Are self-inspections conducted in an independent and detailed way? by designated competent persons from the company or external experts?	☐ ☐ ☐ ☐ ☐ ☐		9.2
11.4	Are self-inspections recorded?	☐ ☐ ☐		9.3
11.5	Do reports contain • the observations made during a self-inspection? • proposals for corrective measures?	☐ ☐ ☐ ☐ ☐ ☐		9.3
11.6	Are actions subsequently taken recorded?	☐ ☐ ☐		9.3
12	**CONTRACT MANUFACTURE AND ANALYSIS**			**7**
12.1	Written contract between contract giver and contract acceptor available?	☐ ☐ ☐		7.1
12.2	Are responsibilities and duties clearly defined?	☐ ☐ ☐		7
12.3	All arrangements in accordance with the marketing authorization of the product concerned?	☐ ☐ ☐		7.2
	The contract giver			
12.4	Competence of the acceptor to carry out the work successful and according to GMP assessed?	☐ ☐ ☐		7.3
12.5	Acceptor provided with all the information necessary to carry out the contract work?	☐ ☐ ☐		7.4
12.6	Acceptor informed of safety aspects?	☐ ☐ ☐		7.4
12.7	Conformance of products supplied by the acceptor ensured?	☐ ☐ ☐		7.5
12.8	Product released by a qualified person on the acceptor's side?	☐ ☐ ☐		7.5
	The contract acceptor			
12.9	Does the acceptor have • adequate premises and equipment? • knowledge and experience? • competent personnel? • a manufacturing authorization?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.6
12.10	Does the acceptor ensure that all products or materials delivered to him are suitable?	☐ ☐ ☐		7.7
12.11	There must be no work passed to a third party without the permission of the giver.	☐ ☐ ☐		7.8
12.12	If a third party is involved it must have the necessary manufacturing and analytical information.	☐ ☐ ☐		7.8
	The contract			
12.13	Does the written contract specify the responsibilities?	☐ ☐ ☐		7.10
12.14	Have technical aspects been drawn up by competent persons?	☐ ☐ ☐		7.10
12.15	Release of material and check for compliance with the marketing authorization defined?	☐ ☐ ☐		7.11
12.16	Is defined who is responsible for • purchasing of materials? • IPC controls • testing and release of materials? • manufacturing and quality control? • sampling? • storage of batch documentation?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.12
12.17	Are manufacturing, analytical, and distribution records available to the contract giver?	☐ ☐ ☐		7.13
12.18	Contract permits the giver to visit the facilities of the acceptor?	☐ ☐ ☐		7.14

		Compliance 1 2 3[a]	Remarks	EU-Guide
12.19	In the case of contract analysis: Does the contract acceptor understand that he is subject to inspection by the competent authorities?	☐ ☐ ☐		7.15
13	**AUDIT OF SUPPLIERS**			**2.7**
13.1	Supplier audits performed for • excipients? • active substances? • packaging material?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		

[a] 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (or Drug Substance)—Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Air lock—An enclosed space with two or more doors, which is interposed between two or more rooms, for example, of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An air lock is designed for use either by people or for goods and/or equipment.

API Starting Material—A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in house. API Starting Materials are normally of defined chemical properties and structure.

Authorized Person—The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested, and approved for release in compliance with the laws and regulations in force in that country.

Batch (or Lot)—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of subbatches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Batch Number (or Lot Number)—A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records and corresponding certificates of analysis, and so on.

Batch Records—All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bioburden—The level and type (e.g., objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates, or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Bulk Product—Any product that has completed all processing stages up to, but not including, final packaging.

Calibration—The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Clean Area—An area with defined environmental control of particulate and microbial contamination, constructed, and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Computer System—A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions. A process or operation integrated with a computer system.

Consignment (or delivery)—The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Contamination—The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, and storage or transport.

Contract Manufacturer—A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical—Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Critical Operation—An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Cross-Contamination—Contamination of a material or product with another material or product. Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Deviation—Departure from an approved instruction or established standard.

Drug (Medicinal) Product—The dosage form in the final immediate packaging intended for marketing. (Reference Q1A).

Drug Substance—See Active Pharmaceutical Ingredient.

Expiry Date (or Expiration Date)—The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf-life specifications if stored under defined conditions, and after which it should not be used.

Finished Product—A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.

Impurity—Any component present in the intermediate or API that is not the desired entity.

Impurity Profile—A description of the identified and unidentified impurities present in an API.

In-process Control—Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate—A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Large-Volume Parenterals—Sterile solutions intended for parenteral application with a volume of 100 mL or more in one container of the finished dosage form.

Lot—See Batch.

Lot Number—See Batch Number.

Manufacture—All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Manufacturer—A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of pharmaceuticals.

Marketing Authorization (Product License, Registration Certificate)—A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling, and shelf life.

Master Formula—A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master Record—A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Material—A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother Liquor—The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It may be used for further processing.

Packaging—All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

Packaging Material—Any material intended to protect an intermediate or API during storage and transport. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical Product—Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Procedure—A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids—Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g. filter aid, activated carbon, and so on).

Process Control—See In-Process Control.

Production—All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, and labeling and relabeling, to completion of the finished product.

Qualification—Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)—The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)—Checking or testing that specifications are met.

Quality Unit(s)—An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine—The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Raw Material—A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reconciliation—A comparison between the theoretical quantity and the actual quantity.

Recovery—The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

Reference Standard, Primary—A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity.

Reference Standard, Secondary—A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing—Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet pre-determined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and preapproved as part of the marketing authorization.

Retest Date—The date when a material should be reexamined to ensure that it is still suitable for use.

Reworking—Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not preapproved as part of the marketing authorization.

Self-Contained Area—Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well-established procedures, controls, and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

Signature (Signed)—See definition for signed.

Signed (Signature)—The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent—An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification—A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Standard Operating Procedure (SOP)—An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g., equipment operation, maintenance, and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting Material—Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Validation—A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity, or system actually leads to the expected results (see also qualification).

Validation Protocol—A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected—The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical—The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

4

WHO Good Manufacturing Guidelines

QUALITY MANAGEMENT IN THE DRUG INDUSTRY: PHILOSOPHY AND ESSENTIAL ELEMENTS

The WHO provides GMP guidelines and also offers a program of GMP compliance certification. One of the most valuable document is the WHO Technical Report 908, which is available at http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=46. In addition, the WHO offers many very useful GMP training programs (http://healthtech.who.int/pq/trainingresources/pq_pres/gmptraining/GMPBasicTraining.htm) that can be of great benefit to companies who may not have access to the inspections by the U.S. FDA or EMEA. It is important to know that the U.S. FDA inspection triggers only when there is an application pending for marketing authorization in the United States, whereas the European as well as the WHO GMP audits can be invited otherwise.

To assure that the interpretation of the WHO guidelines is properly understood, an appendix to this guideline includes the glossary of terms used.

Also included at the end of the chapter is a description of the various types of inspections that the WHO offers. It is important to know that WHO will offer inspections regardless of the status of marketing authorization applications; most manufacturers will request these inspections in anticipation of participation in the WHO Essential Drugs Program and register as certified suppliers that will qualify the manufacturer to bid on various WHO-sponsored drug purchase programs.

In the drug industry at large, quality management is usually defined as the aspect of management function that determines and implements the "quality policy," that is, the overall intention and direction of an organization regarding quality, as formally expressed and authorized by top management. The basic elements of quality management are as follows:

- An appropriate infrastructure or "quality system," encompassing the organizational structure, procedures, processes, and resources.
- Systematic actions necessary to ensure adequate confidence that a product (or service) will satisfy given requirements for quality. The totality of these actions is termed "quality assurance."

Within an organization, quality assurance serves as a management tool. In contractual situations, quality assurance also serves to generate confidence in the supplier.

The concepts of quality assurance, GMP, and quality control are interrelated aspects of quality management. They are described here in order to emphasize their relationship and their fundamental importance to the production and control of pharmaceutical products.

1. QUALITY ASSURANCE

1.1 Principle. "Quality assurance" is a wide-ranging concept covering all matters that individually or collectively influence the quality of a product. It is the totality of the arrangements made with the object of ensuring that pharmaceutical products are of the quality required for their intended use. Quality assurance therefore incorporates GMP and other factors, including those outside the scope of this guide such as product design and development.

1.2 The system of quality assurance appropriate to the manufacture of pharmaceutical products should ensure that

(a) pharmaceutical products are designed and developed in a way that takes account of the requirements of GMP and other associated codes such as those of good laboratory practice (GLP) 1 and good clinical practice (GCP);

(b) production and control operations are clearly specified in a written form and GMP requirements are adopted;

(c) managerial responsibilities are clearly specified in job descriptions;

(d) arrangements are made for the manufacture, supply, and use of the correct starting and packaging materials;

(e) all necessary controls on starting materials, intermediate products, and bulk products and other in-process controls, calibrations, and validations are carried out;

(f) the finished product is correctly processed and checked, according to the defined procedures;

(g) pharmaceutical products are not sold or supplied before the authorized persons (see also sections 9.11 and 9.12) have certified that each production batch has been produced and controlled in accordance with the requirements of the marketing authorization and any other regulations relevant to the production, control, and release of pharmaceutical products;

(h) satisfactory arrangements exist to ensure, as far as possible, that the pharmaceutical products are stored by the manufacturer, distributed, and subsequently handled so that quality is maintained throughout their shelf life;

(i) there is a procedure for self-inspection and/or quality audit that regularly appraises the effectiveness and applicability of the quality assurance system;

(j) deviations are reported, investigated, and recorded;

(k) there is a system for approving changes that may have an impact on product quality; and

(l) regular evaluations of the quality of pharmaceutical products should be conducted with the objective of verifying the consistency of the process and ensuring its continuous improvement.

1.3 The manufacturer must assume responsibility for the quality of the pharmaceutical products to ensure that they are fit for their intended use, comply with the requirements of the marketing authorization and do not place patients at risk due to inadequate safety, quality, or efficacy. The attainment of this quality objective is the responsibility of senior management and requires the participation and commitment of staff in many different departments and at all levels within the company, the company's suppliers, and the distributors. To achieve the quality objective reliably, there must be a comprehensively designed and correctly implemented system of quality assurance incorporating GMP and quality control. It should be fully documented and its effectiveness monitored. All parts of the quality assurance system should be adequately staffed with competent personnel, and should have suitable and sufficient premises, equipment, and facilities.

2. GMPs FOR PHARMACEUTICAL PRODUCTS

2.1 Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. GMPs are aimed primarily at diminishing the risks inherent in any pharmaceutical production. Such risks are essentially of two types: cross-contamination (in particular of unexpected contaminants) and mix-ups (confusion) caused by, for example, false labels being put on containers. Under GMP

(a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;
(b) qualification and validation are performed;
(c) all necessary resources are provided, including
  (i) appropriately qualified and trained personnel;
  (ii) adequate premises and space;
  (iii) suitable equipment and services;
  (iv) appropriate materials, containers, and labels;
  (v) approved procedures and instructions;
  (vi) suitable storage and transport; and
  (vii) adequate personnel, laboratories, and equipment for in-process controls;
(d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided;
(e) operators are trained to carry out procedures correctly;
(f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have, in fact, been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated;
(g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
(h) the proper storage and distribution of the products minimize any risk to their quality;
(i) a system is available to recall any batch of product from sale or supply;
(j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.

3. SANITATION AND HYGIENE

3.1 A high level of sanitation and hygiene should be practiced in every aspect of the manufacture of drug products. The scope of sanitation and hygiene covers personnel, premises, equipment and apparatus, production materials and containers, products for cleaning and disinfection, and anything that could become a source of contamination to the product. Potential sources of contamination should be eliminated through an integrated comprehensive program of sanitation and hygiene. (For personal hygiene see section 11, and for sanitation see section 12, "Premises".)

4. QUALIFICATION AND VALIDATION

4.1 In accordance with GMP, each pharmaceutical company should identify what qualification and validation work is required to prove that the critical aspects of their particular operation are controlled.
4.2 The key elements of a qualification and validation program of a company should be clearly defined and documented in a validation master plan.
4.3 Qualification and validation should establish and provide documentary evidence that
(a) the premises, supporting utilities, equipment, and processes have been designed in accordance with the requirements for GMP (design qualification or DQ);
(b) the premises, supporting utilities, and equipment have been built and installed in compliance with their design specifications (installation qualification or IQ);
(c) the premises, supporting utilities, and equipment operate in accordance with their design specifications (operational qualification or OQ);
(d) a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (process validation, or PV, also called performance qualification, or PQ).
4.4 Any aspect of operation, including significant changes to the premises, facilities, equipment, or processes, which may affect the quality of the product, directly or indirectly, should be qualified and validated.
4.5 Qualification and validation should not be considered as one-off exercises. An ongoing program should follow their first implementation and should be based on an annual review.
4.6 The commitment to maintain continued validation status should be stated in the relevant company documentation, such as the quality manual or validation master plan.
4.7 The responsibility of performing validation should be clearly defined.
4.8 Validation studies are an essential part of GMP and should be conducted in accordance with predefined and approved protocols.
4.9 A written report summarizing the results recorded and the conclusions reached should be prepared and stored.

4.10 Processes and procedures should be established on the basis of the results of the validation performed.
4.11 It is of critical importance that particular attention is paid to the validation of analytical test methods, automated systems, and cleaning procedures.

5. COMPLAINTS

5.1 Principle. All complaints and other information concerning potentially defective products should be carefully reviewed according to written procedures and the corrective action should be taken.
5.2 A person responsible for handling the complaints and deciding the measures to be taken should be designated, together with sufficient supporting staff to assist him or her. If this person is different from the authorized person, the latter should be made aware of any complaint, investigation, or recall.
5.3 There should be written procedures describing the action to be taken, including the need to consider a recall, in the case of a complaint concerning a possible product defect.
5.4 Special attention should be given to establish whether a complaint was caused because of counterfeiting.
5.5 Any complaint concerning a product defect should be recorded with all the original details and thoroughly investigated. The person responsible for quality control should normally be involved in the review of such investigations.
5.6 If a product defect is discovered or suspected in a batch, consideration should be given to whether other batches should be checked in order to determine whether they are also affected. In particular, other batches that may contain reprocessed product from the defective batch should be investigated.
5.7 Where necessary, appropriate follow-up action, possibly including product recall, should be taken after investigation and evaluation of the complaint.
5.8 All decisions made and measures taken as a result of a complaint should be recorded and referenced to the corresponding batch records.
5.9 Complaints records should be regularly reviewed for any indication of specific or recurring problems that require attention and might justify the recall of marketed products.
5.10 The competent authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, counterfeiting, or any other serious quality problems with a product.

6. PRODUCT RECALLS

6.1 Principle. There should be a system to recall from the market, promptly and effectively, products known or suspected to be defective.
6.2 The authorized person should be responsible for the execution and coordination of recalls. He or she should have sufficient staff to handle all aspects of the recalls with the appropriate degree of urgency.
6.3 There should be established written procedures, which are regularly reviewed and updated, for the organization of any recall activity. Recall operations should be capable of being initiated promptly down to the required level in the distribution chain.
6.4 An instruction should be included in the written procedures to store recalled products in a secure segregated area while their fate is decided.
6.5 All competent authorities of all countries to which a given product has been distributed should be promptly informed of any intention to recall the product because it is, or is suspected of being, defective.
6.6 The distribution records should be readily available to the authorized person, and they should contain sufficient information on wholesalers and directly supplied customers (including, for exported products, those who have received samples for clinical tests and medical samples) to permit an effective recall.
6.7 The progress of the recall process should be monitored and recorded. Records should include the disposition of the product. A final report should be issued, including a reconciliation between the delivered and recovered quantities of the products.
6.8 The effectiveness of the arrangements for recalls should be tested and evaluated from time to time.

7. CONTRACT PRODUCTION AND ANALYSIS

7.1 Principle. Contract production and analysis must be correctly defined, agreed, and controlled in order to avoid misunderstandings that could result in a product or work or analysis of unsatisfactory quality.

General

7.2 All arrangements for contract manufacture and analysis, including any proposed changes in technical or other arrangements, should be in accordance with the marketing authorization for the product concerned.
7.3 The contract should permit the contract giver to audit the facilities of the contract accepter.
7.4 In the case of contract analysis, the final approval for release must be given by the authorized person.

The Contract Giver

7.5 The contract giver is responsible for assessing the competence of the contract accepter in successfully carrying out the work or tests required, for approval for contract activities, and for ensuring by means of the contract that the principles of GMP described in this guide are followed.
7.6 The contract giver should provide the contract accepter with all the information necessary to carry out the contracted operations correctly in accordance with the marketing authorization and any other legal requirements. The contract giver should ensure that the contract accepter is fully aware of any problems associated with the product, work, or tests that might pose a hazard to premises, equipment, personnel, other materials, or other products.
7.7 The contract giver should ensure that all processed products and materials delivered by the contract accepter comply with their specifications or that the product has been released by the authorized person.

The Contract Accepter

7.8 The contract accepter must have adequate premises, equipment, knowledge, and experience and competent personnel to carry out satisfactorily the work ordered by the contract giver. Contract manufacture may be

undertaken only by a manufacturer who holds a manufacturing authorization.

7.9 The contract accepter should not pass to a third party any of the work entrusted to him or her under the contract without the contract giver's prior evaluation and approval of the arrangements. Arrangements made between the contract accepter and any third party should ensure that the manufacturing and analytical information is made available in the same way as between the original contract giver and contract accepter.

7.10 The contract accepter should refrain from any activity that may adversely affect the quality of the product manufactured and/or analyzed for the contract giver.

The Contract

7.11 There must be a written contract between the contract giver and the contract accepter which clearly establishes the responsibilities of each party.

7.12 The contract must clearly state the way in which the authorized person, in releasing each batch of product for sale or issuing the certificate of analysis, exercises his or her full responsibility and ensures that each batch has been manufactured in, and checked for, compliance with the requirements of the marketing authorization.

7.13 Technical aspects of the contract should be drawn up by competent persons suitably knowledgeable in pharmaceutical technology, analysis, and GMP.

7.14 All arrangements for production and analysis must be in accordance with the marketing authorization and agreed by both parties.

7.15 The contract should describe clearly who is responsible for purchasing, testing, and releasing materials and for undertaking production and quality controls, including in-process controls, and who has responsibility for sampling and analysis. In the case of contract analysis, the contract should state whether or not the contract accepter should take samples at the premises of the manufacturer.

7.16 Manufacturing, analytical, distribution records and reference samples should be kept by, or be available to, the contract giver. Any records relevant to assessing the quality of a product in the event of complaints or a suspected defect must be accessible and specified in the defect/recall procedures of the contract giver.

7.17 The contract should describe the handling of starting materials, intermediate and bulk products, and finished products if they are rejected. It should also describe the procedure to be followed if the contract analysis shows that the tested product must be rejected.

8. SELF-INSPECTION AND QUALITY AUDITS

8.1 Principle. The purpose of self-inspection is to evaluate the manufacturer's compliance with GMP in all aspects of production and quality control. The self-inspection program should be designed to detect any shortcomings in the implementation of GMP and to recommend the necessary corrective actions. Self-inspections should be performed routinely, and may be, in addition, performed on special occasions, for example, in the case of product recalls or repeated rejections, or when an inspection by the health authorities is announced. The team responsible for self-inspection should consist of personnel who can evaluate the implementation of GMP objectively. All recommendations for corrective action should be implemented. The procedure for self-inspection should be documented, and there should be an effective follow-up program.

Items for Self-Inspection

8.2 Written instructions for self-inspection should be established to provide a minimum and uniform standard of requirements. These may include questionnaires on GMP requirements covering at least the following items:

(a) Personnel
(b) Premises including personnel facilities
(c) Maintenance of buildings and equipment
(d) Storage of starting materials and finished products
(e) Equipment
(f) Production and in-process controls
(g) Quality control
(h) Documentation
(i) Sanitation and hygiene
(j) Validation and revalidation programs
(k) Calibration of instruments or measurement systems
(l) Recall procedures
(m) Complaints management
(n) Labels control
(o) Results of previous self-inspections and any corrective steps taken

Self-Inspection Team

8.3 Management should appoint a self-inspection team consisting of experts in their respective fields and familiar with GMP. The members of the team may be appointed from inside or outside the company.

Frequency of Self-Inspection

8.4 The frequency at which self-inspections are conducted may depend on company requirements but should preferably be at least once a year. The frequency should be stated in the procedure.

Self-Inspection Report

8.5 A report should be made at the completion of a self-inspection. The report should include

(a) self-inspection results,
(b) evaluation and conclusions, and
(c) recommended corrective actions.

Follow-Up Action

8.6 There should be an effective follow-up program. The company management should evaluate both the self-inspection report and the corrective actions as necessary.

Quality Audit

8.7 It may be useful to supplement self-inspections with a quality audit. A quality audit consists of an examination and assessment of all or part of a quality system with the specific purpose of improving it. A quality audit is usually conducted by outside or independent specialists or a team designated by the management for this purpose. Such audits may also be extended to suppliers and contractors (see section 7, "Contract Production and Analysis").

Suppliers' Audits and Approval

8.8 The person responsible for quality control should have responsibility together with other relevant departments

for approving suppliers who can reliably supply starting and packaging materials that meet established specifications.

8.9 Before suppliers are approved and included in the approved suppliers' list or specifications, they should be evaluated. The evaluation should take into account a supplier's history and the nature of the materials to be supplied. If an audit is required, it should determine the supplier's ability to conform with GMP standards.

9. PERSONNEL

9.1 Principle. The establishment and maintenance of a satisfactory system of quality assurance and the correct manufacture and control of pharmaceutical products and active ingredients rely upon people. For this reason, there must be sufficient qualified personnel to carry out all the tasks for which the manufacturer is responsible. Individual responsibilities should be clearly defined and understood by the persons concerned and recorded as written descriptions.

General

9.2 The manufacturer should have an adequate number of personnel with the necessary qualifications and practical experience. The responsibilities placed on any one individual should not be so extensive so as to present any risk to quality.

9.3 All responsible staff should have their specific duties recorded in written descriptions and adequate authority to carry out their responsibilities. Their duties may be delegated to designated deputies of a satisfactory qualification level. There should be no gaps or unexplained overlaps in the responsibilities of personnel concerned with the application of GMP. The manufacturer should have an organization chart.

9.4 All personnel should be aware of the principles of GMP that affect them and receive initial and continuing training, including hygiene instructions, relevant to their needs. All personnel should be motivated to support the establishment and maintenance of high-quality standards.

9.5 Steps should be taken to prevent unauthorized people from entering production, storage, and quality control areas. Personnel who do not work in these areas should not use them as a passageway.

Key Personnel

9.6 Key personnel include the head of production, the head of quality control, and the authorized person. Normally, key posts should be occupied by full-time personnel. The heads of production and quality control should be independent of each other. In large organizations, it may be necessary to delegate some of the functions; however, the responsibility cannot be delegated.

9.7 Key personnel responsible for supervising the manufacture and quality control of pharmaceutical products should possess the qualifications of a scientific education and practical experience required by national legislation. Their education should include the study of an appropriate combination of

(a) chemistry (analytical or organic) or biochemistry,
(b) chemical engineering,
(c) microbiology,
(d) pharmaceutical sciences and technology,
(e) pharmacology and toxicology,
(f) physiology, and
(g) other related sciences.

They should also have adequate practical experience in the manufacture and quality assurance of pharmaceutical products. In order to gain such experience, a preparatory period may be required, during which they should exercise their duties under professional guidance. The scientific education and practical experience of experts should be such as to enable them to exercise independent professional judgment, based on the application of scientific principles and understanding to the practical problems encountered in the manufacture and quality control of pharmaceutical products.

9.8 The heads of the production and quality control generally have some shared, or jointly exercised, responsibilities relating to quality. These may include, depending on national regulations,

(a) to ensure that products are produced and stored according to the appropriate documentation in order to obtain the required quality;
(b) to approve the instructions relating to production operations, including the in-process controls, and to ensure their strict implementation;
(c) to ensure that the production records are evaluated and signed by a designated person;
(d) to check the maintenance of the department, premises, and equipment;
(e) to ensure that the appropriate process validations and calibrations of control equipment are performed and recorded and the reports made available; and
(f) to ensure that the required initial and continuing training of production personnel is carried out and adapted according to need.

9.9 The head of the production generally has the following responsibilities:

(a) authorization of written procedures and other documents, including amendments;
(b) monitoring and control of the manufacturing environment;
(c) plant hygiene;
(d) process validation and calibration of analytical apparatus;
(e) training, including the application and principles of quality assurance;
(f) approval and monitoring of suppliers of materials;
(g) approval and monitoring of contract manufacturers;
(h) designation and monitoring of storage conditions for materials and products;
(i) performance and evaluation of in-process controls;
(j) retention of records;
(k) monitoring of compliance with GMP requirements; and
(l) inspection, investigation, and taking of samples in order to monitor factors that may affect product quality.

9.10 The head of the quality control generally has the following responsibilities:

(a) to approve or reject starting materials, packaging materials, and intermediate, bulk, and finished products in relation to their specifications;
(b) to evaluate batch records;
(c) to ensure that all necessary testing is carried out;

(d) to approve sampling instructions, specifications, test methods, and other quality control procedures;
(e) to approve and monitor analyses carried out under contract;
(f) to check the maintenance of the department, premises, and equipment;
(g) to ensure that the appropriate validations, including those of analytical procedures, and calibrations of control equipment are carried out; and
(h) to ensure that the required initial and continuing training of quality control personnel is carried out and adapted according to need.

Other duties of the quality control are summarized in sections 17.3 and 17.4.

9.11 The authorized person is responsible for compliance with technical or regulatory requirements related to the quality of finished products and the approval of the release of the finished product for sale.

9.12 The authorized person will also be involved in other activities, including
(a) implementation (and, when needed, establishment) of the quality system,
(b) participation in the development of the company's quality manual,
(c) supervision of the regular internal audits or self-inspections,
(d) oversight of the quality control department,
(e) participation in external audit (vendor audit), and
(f) participation in validation programs.

9.13 The function of the approval of the release of a finished batch or a product can be delegated to a designated person with appropriate qualifications and experience who will release the product in accordance with an approved procedure. This is normally done by quality assurance by means of batch review.

9.14 The person responsible for approving a batch for release should always ensure that the following requirements have been met:
(a) The marketing authorization and the manufacturing authorization requirements for the product have been met for the batch concerned.
(b) The principles and guidelines of GMP, as laid down in the guidelines published by WHO, have been followed.
(c) The principal manufacturing and testing processes have been validated, if different.
(d) All the necessary checks and tests have been performed and account taken of the production conditions and manufacturing records.
(e) Any planned changes or deviations in manufacturing or quality control have been notified in accordance with a well-defined reporting system before any product is released. Such changes may need notification to, and approval by, the drug regulatory authority.
(f) Any additional sampling, inspection, tests, and checks have been carried out or initiated, as appropriate, to cover planned changes and deviations.
(g) All necessary production and quality control documentation has been completed and endorsed by supervisors trained in appropriate disciplines.
(h) Appropriate audits, self-inspections, and spot-checks are carried out by experienced and trained staff.
(i) Approval has been given by the head of quality control.
(j) All relevant factors have been considered, including any not specifically associated with the output batch directly under review (e.g., subdivision of output batches from a common input, factors associated with continuous production runs).

10. TRAINING

10.1 The manufacturer should provide training in accordance with a written program for all personnel whose duties take them into manufacturing areas or into control laboratories (including the technical, maintenance, and cleaning personnel) and for other personnel as required.

10.2 Besides basic training on the theory and practice of GMP, newly recruited personnel should receive training appropriate to the duties assigned to them. Continuing training should also be given, and its practical effectiveness periodically assessed. Approved training programs should be available. Training records should be kept.

10.3 Personnel working in areas where contamination is a hazard, for example, clean areas or areas where highly active, toxic, infectious, or sensitizing materials are handled, should be given specific training.

10.4 The concept of quality assurance and all the measures which aid its understanding and implementation should be fully discussed during the training sessions.

10.5 Visitors or untrained personnel should preferably not be taken into the production and quality control areas. If this is unavoidable, they should be given relevant information in advance (particularly about personal hygiene) and the prescribed protective clothing. They should be closely supervised.

10.6 Consultant and contract staff should be qualified for the services they provide. Evidence of this should be included in the training records.

11. PERSONAL HYGIENE

11.1 All personnel, prior to and during employment, as appropriate, should undergo health examinations. Personnel conducting visual inspections should also undergo periodic eye examinations.

11.2 All personnel should be trained in the practices of personal hygiene. A high level of personal hygiene should be observed by all those concerned with manufacturing processes. In particular, personnel should be instructed to wash their hands before entering production areas. Signs to this effect should be posted and instructions observed.

11.3 Any person shown at any time to have an apparent illness or open lesions that may adversely affect the quality of products should not be allowed to handle starting materials, packaging materials, in-process materials, or drug products until the condition is no longer judged to be a risk.

11.4 All employees should be instructed and encouraged to report to their immediate supervisor any conditions (relating to plant, equipment, or personnel) that they consider may adversely affect the products.

11.5 Direct contact should be avoided between the operator's hands and starting materials, primary packaging materials, and intermediate or bulk product.

11.6 To ensure protection of the product from contamination, personnel should wear clean body coverings

appropriate to the duties they perform, including appropriate hair covering. Used clothes, if reusable, should be stored in separate closed containers until properly laundered and, if necessary, disinfected or sterilized.

11.7 Smoking, eating, drinking, chewing, and keeping plants, food, drink, smoking material, and personal medicines should not be permitted in production, laboratory, and storage areas, or in any other areas where they might adversely influence product quality.

11.8 Personal hygiene procedures including the use of protective clothing should apply to all persons entering production areas, whether they are temporary or full-time employees or nonemployees, for example, contractors' employees, visitors, senior managers, and inspectors.

12. PREMISES

12.1 Principle. Premises must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out.

General

12.2 The layout and design of premises must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

12.3 Where dust is generated (e.g., during sampling, weighing, mixing and processing operations, packaging of powder), measures should be taken to avoid cross-contamination and facilitate cleaning.

12.4 Premises should be situated in an environment that, when considered together with measures to protect the manufacturing process, presents minimum risk of causing any contamination of materials or products.

12.5 Premises used for the manufacture of finished products should be suitably designed and constructed to facilitate good sanitation.

12.6 Premises should be carefully maintained, and it should be ensured that repair and maintenance operations do not present any hazard to the quality of products.

12.7 Premises should be cleaned and, where applicable, disinfected according to detailed written procedures. Records should be maintained.

12.8 Electrical supply, lighting, temperature, humidity, and ventilation should be appropriate and such that they do not adversely affect, directly or indirectly, either the pharmaceutical products during their manufacture and storage or the accurate functioning of equipment.

12.9 Premises should be designed and equipped so as to afford maximum protection against the entry of insects, birds, or other animals. There should be a procedure for rodent and pest control.

12.10 Premises should be designed to ensure the logical flow of materials and personnel.

Ancillary Areas

12.11 Rest and refreshment rooms should be separate from manufacturing and control areas.

12.12 Facilities for changing and storing clothes and for washing and toilet purposes should be easily accessible and appropriate for the number of users. Toilets should not communicate directly with production or storage areas.

12.13 Maintenance workshops should if possible be separated from production areas. Whenever parts and tools are stored in the production area, they should be kept in rooms or lockers reserved for that use.

12.14 Animal houses should be well isolated from other areas, with separate entrance (animal access) and air-handling facilities.

Storage Areas

12.15 Storage areas should be of sufficient capacity to allow orderly storage of the various categories of materials and products with proper separation and segregation: starting and packaging materials; intermediates, bulk, and finished products; products in quarantine; and released, rejected, returned, or recalled products.

12.16 Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean, dry, sufficiently lit, and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity), these should be provided, controlled, monitored, and recorded where appropriate.

12.17 Receiving and dispatch bays should be separated and protect materials and products from the weather. Receiving areas should be designed and equipped to allow containers of incoming materials to be cleaned if necessary before storage.

12.18 Where quarantine status is ensured by storage in separate areas, these areas must be clearly marked and their access restricted to authorized personnel. Any system replacing the physical quarantine should give equivalent security.

12.19 Segregation should be provided for the storage of rejected, recalled, or returned materials or products.

12.20 Highly active and radioactive materials, narcotics, other dangerous drugs, and substances presenting special risks of abuse, fire, or explosion should be stored in safe and secure areas.

12.21 Printed packaging materials are considered critical to the conformity of the pharmaceutical product to its labeling and special attention should be paid to sampling and the safe and secure storage of these materials.

12.22 There should normally be a separate sampling area for starting materials. (If sampling is performed in the storage area, it should be conducted in such a way as to prevent contamination or cross-contamination.)

Weighing Areas

12.23 The weighing of starting materials and the estimation of yield by weighing should be carried out in separate weighing areas designed for that use, for example, with provisions for dust control. Such areas may be part of either storage or production areas.

Production Areas

12.24 In order to minimize the risk of a serious medical hazard due to cross-contamination, dedicated and self-contained facilities must be available for the production of particular pharmaceutical products, such as highly sensitizing materials (e.g. penicillins) or biological preparations (e.g. live microorganisms). The production of certain other highly active products, such as some antibiotics, hormones, cytotoxic substances, and certain nonpharmaceutical products, should not be conducted in the same facilities. In exceptional cases, the principle of campaign working in the same facilities

can be accepted provided that specific precautions are taken and the necessary validations (including cleaning validation) are made. The manufacture of technical poisons, such as pesticides and herbicides, should not be allowed in premises used for the manufacture of pharmaceutical products.

12.25 Premises should preferably be laid out in such a way as to allow the production to take place in areas connected in a logical order corresponding to the sequence of the operations and to the requisite cleanliness levels.

12.26 The adequacy of the working and in-process storage space should permit the orderly and logical positioning of equipment and materials so as to minimize the risk of confusion between different pharmaceutical products or their components, to avoid cross-contamination, and to minimize the risk of omission or wrong application of any of the manufacturing or control steps.

12.27 Where starting and primary packaging materials and intermediate or bulk products are exposed to the environment, interior surfaces (walls, floors, and ceilings) should be smooth and free from cracks and open joints, should not shed particulate matter, and should permit easy and effective cleaning and, if necessary, disinfection.

12.28 Pipework, light fittings, ventilation points, and other services should be designed and sited to avoid the creation of recesses that are difficult to clean. As far as possible, for maintenance purposes, they should be accessible from outside the manufacturing areas.

12.29 Drains should be of adequate size and designed and equipped to prevent backflow. Open channels should be avoided where possible, but if they are necessary they should be shallow to facilitate cleaning and disinfection.

12.30 Production areas should be effectively ventilated, with air-control facilities (including filtration of air to a sufficient level to prevent contamination and cross-contamination, as well as control of temperature and, where necessary, humidity) appropriate to the products handled, to the operations undertaken, and to the external environment. These areas should be regularly monitored during both production and nonproduction periods to ensure compliance with their design specifications.

12.31 Premises for the packaging of pharmaceutical products should be specifically designed and laid out so as to avoid mix-ups or cross-contamination.

12.32 Production areas should be well lit, particularly where visual online controls are carried out.

Quality Control Areas

12.33 Quality control laboratories should be separated from production areas. Areas where biological, microbiological, or radioisotope test methods are employed should be separated from each other.

12.34 Quality control laboratories should be designed to suit the operations to be carried out in them. Sufficient space should be given to avoid mix-ups and cross-contamination. There should be adequate suitable storage space for samples, reference standards (if necessary, with cooling), solvents, reagents, and records.

12.35 The design of the laboratories should take into account the suitability of construction materials, prevention of fumes, and ventilation. There should be separate air supply to laboratories and production areas. Separate air-handling units and other provisions are needed for biological, microbiological, and radioisotope laboratories.

12.36 A separate room may be needed for instruments to protect them against electrical interference, vibration, contact with excessive moisture, and other external factors, or where it is necessary to isolate the instruments.

13. EQUIPMENT

13.1 Equipment must be located, designed, constructed, adapted, and maintained to suit the operations to be carried out. The layout and design of equipment must aim to minimize the risk of errors and permit effective cleaning and maintenance in order to avoid cross-contamination, build-up of dust or dirt, and, in general, any adverse effect on the quality of products.

13.2 Equipment should be installed in such a way as to minimize any risk of error or of contamination.

13.3 Fixed pipework should be clearly labeled to indicate the contents and, where applicable, the direction of flow.

13.4 All service pipings and devices should be adequately marked and special attention paid to the provision of noninterchangeable connections or adaptors for dangerous gases and liquids.

13.5 Balances and other measuring equipment of an appropriate range and precision should be available for production and control operations and should be calibrated on a scheduled basis.

13.6 Production equipment should be thoroughly cleaned on a scheduled basis.

13.7 Laboratory equipment and instruments should be suited to the testing procedures undertaken.

13.8 Washing, cleaning, and drying equipment should be chosen and used so as not to be a source of contamination.

13.9 Production equipment should not present any hazard to the products. The parts of the production equipment that come into contact with the product must not be reactive, additive, or absorptive to an extent that would affect the quality of the product.

13.10 Defective equipment should be removed from production and quality control areas. If this is not possible, it should be clearly labeled as defective to prevent use.

13.11 Closed equipment should be used whenever appropriate. Where open equipment is used or equipment is opened, precautions should be taken to minimize contamination.

13.12 Nondedicated equipment should be cleaned according to validated cleaning procedures between production of different pharmaceutical products to prevent cross-contamination.

13.13 Current drawings of critical equipment and support systems should be maintained.

14. MATERIALS

14.1 Principle. The main objective of a pharmaceutical plant is to produce finished products for patients' use from a combination of materials (starting and packaging).

14.2 Materials include starting materials, packaging materials, gases, solvents, process aids, reagents, and labeling materials.

General

14.3 No materials used for operations such as cleaning, lubrication of equipment, and pest control, should come into direct contact with the product. Where possible, such materials should be of a suitable grade (e.g. food grade) to minimize health risks.

14.4 All incoming materials and finished products should be quarantined immediately after receipt or processing, until they are released for use or distribution.

14.5 All materials and products should be stored under the appropriate conditions established by the manufacturer and in an orderly fashion to permit batch segregation and stock rotation by a first-expire, first-out rule.

14.6 Water used in the manufacture of pharmaceutical products should be suitable for its intended use.

Starting Materials

14.7 The purchase of starting materials is an important operation that should involve staff who have a particular and thorough knowledge of the products and suppliers.

14.8 Starting materials should be purchased only from approved suppliers and, where possible, directly from the producer. It is also recommended that the specifications established by the manufacturer for the starting materials be discussed with the suppliers. It is of benefit that all critical aspects of the production and control of the starting material in question, including handling, labeling, and packaging requirements as well as complaints and rejection procedures, are contractually agreed between the manufacturer and the supplier.

14.9 For each consignment, the containers should be checked for at least integrity of package and seal and for correspondence between the order, the delivery note, and the supplier's labels.

14.10 All incoming materials should be checked to ensure that the consignment corresponds to the order. Containers should be cleaned where necessary and labeled, if required, with the prescribed information. Where additional labels are attached to containers, the original information should not be lost.

14.11 Damage to containers and any other problem that might adversely affect the quality of a material should be recorded and reported to the quality control department and investigated.

14.12 If one delivery of material is made up of different batches, each batch must be considered as separate for sampling, testing, and release.

14.13 Starting materials in the storage area should be appropriately labeled. Labels should bear at least the following information:

(a) the designated name of the product and the internal code reference where applicable;
(b) the batch number given by the supplier and, on receipt, the control or batch number given by the manufacturer, if any, documented so as to ensure traceability;
(c) the status of the contents (e.g. on quarantine, on test, released, rejected, returned, recalled); and
(d) where appropriate, an expiry date or a date beyond which retesting is necessary.

When fully validated computerized storage systems are used, not all of the above information need be in a legible form on the label.

14.14 There should be appropriate procedures or measures to ensure the identity of the contents of each container of starting material. Bulk containers from which samples have been drawn should be identified.

14.15 Only starting materials released by the quality control department and within their shelf life should be used.

14.16 Starting materials should be dispensed only by designated persons, following a written procedure, to ensure that the correct materials are accurately weighed or measured into clean and properly labeled containers.

14.17 Each dispensed material and its weight or volume should be independently checked and the check recorded.

14.18 Materials dispensed for each batch of the final product should be kept together and conspicuously labeled as such.

Packaging Materials

14.19 The purchase, handling, and control of primary and printed packaging materials should be as for starting materials.

14.20 Particular attention should be paid to printed packaging materials. They should be stored in secure conditions so as to exclude the possibility of unauthorized access. Roll-feed labels should be used wherever possible. Cut labels and other loose printed materials should be stored and transported in separate closed containers so as to avoid mix-ups. Packaging materials should be issued for use only by designated personnel following an approved and documented procedure.

14.21 Each delivery or batch of printed or primary packaging material should be given a specific reference number or identification mark.

14.22 Outdated or obsolete primary packaging material or printed packaging material should be destroyed and its disposal recorded.

14.23 All products and packaging materials to be used should be checked on delivery to the packaging department for quantity, identity, and conformity with the packaging instructions.

Intermediate and Bulk Products

14.24 Intermediate and bulk products should be kept under appropriate conditions.

14.25 Intermediate and bulk products purchased as such should be handled on receipt as though they were starting materials.

Finished Products

14.26 Finished products should be held in quarantine until their final release, after which they should be stored as usable stock under conditions established by the manufacturer.

14.27 The evaluation of finished products and the documentation necessary for release of a product for sale are described in section 17, "Good Practices in Quality Control".

Rejected, Recovered, Reprocessed, and Reworked Materials

14.28 Rejected materials and products should be clearly marked as such and stored separately in restricted areas. They should either be returned to the suppliers or, where appropriate, reprocessed or destroyed in a

timely manner. Whatever action is taken should be approved by authorized personnel and recorded.

14.29 The reworking or recovery of rejected products should be exceptional. It is permitted only if the quality of the final product is not affected, if the specifications are met, and if it is done in accordance with a defined and authorized procedure after evaluation of the risks involved. A record should be kept of the reworking or recovery. A reworked batch should be given a new batch number.

14.30 The introduction of all or part of earlier batches, conforming to the required quality, into a batch of the same product at a defined stage of manufacture should be authorized beforehand. This recovery should be carried out in accordance with a defined procedure after evaluation of the risks involved, including any possible effect on shelf life. The recovery should be recorded.

14.31 The need for additional testing of any finished product that has been reprocessed, reworked or into which a recovered product has been incorporated, should be considered by the quality control department.

Recalled Products

14.32 Recalled products should be identified and stored separately in a secure area until a decision is taken on their fate. The decision should be made as soon as possible.

Returned Goods

14.33 Products returned from the market should be destroyed unless it is certain that their quality is satisfactory; in such cases they may be considered for resale or relabeling, or alternative action taken only after they have been critically assessed by the quality control function in accordance with a written procedure. The nature of the product, any special storage conditions it requires, its condition and history, and the time elapsed since it was issued should all be taken into account in this assessment. Where any doubt arises over the quality of the product, it should not be considered suitable for reissue or reuse. Any action taken should be appropriately recorded.

Reagents and Culture Media

14.34 There should be records for the receipt and preparation of reagents and culture media.

14.35 Reagents made up in the laboratory should be prepared according to written procedures and appropriately labeled. The label should indicate the concentration, standardization factor, shelf life, the date when restandardization is due, and the storage conditions. The label should be signed and dated by the person preparing the reagent.

14.36 Both positive and negative controls should be applied to verify the suitability of culture media each time they are prepared and used. The size of the inoculum used in positive controls should be appropriate to the sensitivity required.

Reference Standards

14.37 Whenever official reference standards exist, these should preferably be used.

14.38 Official reference standards should be used only for the purpose described in the appropriate monograph.

14.39 Reference standards prepared by the producer should be tested, released, and stored in the same way as official standards. They should be kept under the responsibility of a designated person in a secure area.

14.40 Secondary or working standards may be established by the application of appropriate tests and checks at regular intervals to ensure standardization.

14.41 Reference standards should be properly labeled with at least the following information:
(a) name of the material,
(b) batch or lot number and control number,
(c) date of preparation,
(d) shelf life,
(e) potency, and
(f) storage conditions.

14.42 All in-house reference standards should be standardized against an official reference standard, when available, initially and at regular intervals thereafter.

14.43 All reference standards should be stored and used in a manner that will not adversely affect their quality.

Waste Materials

14.44 Provision should be made for the proper and safe storage of waste materials awaiting disposal. Toxic substances and flammable materials should be stored in suitably designed, separate, enclosed cupboards, as required by national legislation.

14.45 Waste material should not be allowed to accumulate. It should be collected in suitable receptacles for removal to collection points outside the buildings and disposed of safely and in a sanitary manner at regular and frequent intervals.

Miscellaneous

14.46 Rodenticides, insecticides, fumigating agents, and sanitizing materials should not be permitted to contaminate equipment, starting materials, packaging materials, in-process materials, or finished products.

15. DOCUMENTATION

15.1 Principle. Good documentation is an essential part of the quality assurance system and, as such, should exist for all aspects of GMP. Its aims are to define the specifications and procedures for all materials and methods of manufacture and control, to ensure that all personnel concerned with manufacture know what to do and when to do it, to ensure that authorized persons have all the information necessary to decide whether or not to release a batch of a drug for sale, to ensure the existence of documented evidence, traceability, and to provide records and an audit trail that will permit investigation. It ensures the availability of the data needed for validation, review, and statistical analysis. The design and use of documents depend upon the manufacturer. In some cases, some or all of the documents described below may be brought together, but they will usually be separate.

General

15.2 Documents should be designed, prepared, reviewed, and distributed with care. They should comply with the relevant parts of the manufacturing and marketing authorizations.

15.3 Documents should be approved, signed, and dated by the appropriate responsible persons. No document

should be changed without authorization and approval.

15.4 Documents should have unambiguous contents: the title, nature, and purpose should be clearly stated. They should be laid out in an orderly fashion and be easy to check. Reproduced documents should be clear and legible. The reproduction of working documents from master documents must not allow any error to be introduced through the reproduction process.

15.5 Documents should be regularly reviewed and kept up-to-date. When a document has been revised, a system should exist to prevent inadvertent use of the superseded version. Superseded documents should be retained for a specific period of time.

15.6 Where documents require the entry of data, these entries should be clear, legible, and indelible. Sufficient space should be provided for such entries.

15.7 Any alteration made to a document should be signed and dated; the alteration should permit the reading of the original information. Where appropriate, the reason for the alteration should be recorded.

15.8 Records should be made or completed when any action is taken and in such a way that all significant activities concerning the manufacture of pharmaceutical products are traceable. Records should be retained for at least one year after the expiry date of the finished product.

15.9 Data (and records for storage) may be recorded by electronic data-processing systems or by photographic or other reliable means. Master formulae and detailed standard operating procedures relating to the system in use should be available and the accuracy of the records should be checked. If documentation is handled by electronic data-processing methods, only authorized persons should be able to enter or modify data in the computer, and there should be a record of changes and deletions; access should be restricted by passwords or other means and the entry of critical data should be independently checked. Batch records stored electronically should be protected by back-up transfer on magnetic tape, microfilm, paper printouts, or other means. It is particularly important that, during the period of retention, the data are readily available.

Documents Required

Labels

15.10 Labels applied to containers, equipment, or premises should be clear, unambiguous, and in the company's agreed format. It is often helpful in addition to the wording on the labels to use colors to indicate status (e.g., quarantined, accepted, rejected, clean).

15.11 All finished drug products should be identified by labeling, as required by the national legislation, bearing at least the following information:

(a) the name of the drug product;
(b) a list of the active ingredients (if applicable, with the INNs), showing the amount of each present and a statement of the net contents (e.g., number of dosage units, weight, volume);
(c) the batch number assigned by the manufacturer;
(d) the expiry date in an uncoded form;
(e) any special storage conditions or handling precautions that may be necessary;
(f) directions for use, and warnings and precautions that may be necessary; and
(g) the name and address of the manufacturer or the company or the person responsible for placing the product on the market.

15.12 For reference standards, the label and/or accompanying document should indicate potency or concentration, date of manufacture, expiry date, date the closure is first opened, storage conditions, and control number, as appropriate.

Specifications and Testing Procedures

15.13 Testing procedures described in documents should be validated in the context of available facilities and equipment before they are adopted for routine testing.

15.14 There should be appropriately authorized and dated specifications, including tests on identity, content, purity, and quality, for starting and packaging materials and for finished products; where appropriate, they should also be available for intermediate or bulk products. Specifications for water, solvents, and reagents (e.g., acids and bases) used in production should be included.

15.15 Each specification should be approved, signed, and dated, and maintained by quality control, quality assurance unit, or documentation center. Specifications for starting materials, intermediates, and bulk, finished products, and packaging materials are referred to in sections 15.18–15.21.

15.16 Periodic revisions of the specifications may be necessary to comply with new editions of the national pharmacopoeia or other official compendia.

15.17 Pharmacopoeias, reference standards, reference spectra and other reference materials should be available in the quality control laboratory.

Specifications for Starting and Packaging Materials

15.18 Specifications for starting, primary, and printed packaging materials should provide, if applicable, a description of the materials, including

(a) the designated name (if applicable, the INN) and internal code reference,
(b) the reference, if any, to a pharmacopoeial monograph, and
(c) qualitative and quantitative requirements with acceptance limits.

Depending on the company's practice, other data may be added to the specification, such as

(a) the supplier and the original producer of the materials,
(b) a specimen of printed materials,
(c) directions for sampling and testing, or a reference to procedures,
(d) storage conditions and precautions, and
(e) the maximum period of storage before reexamination.

Packaging material should conform to specifications, and should be compatible with the material and/or with the drug product it contains. The material should be examined for compliance with the specification, and for defects as well as for the correctness of identity markings.

15.19 Documents describing testing procedures should state the required frequency for reassaying each starting material, as determined by its stability.

Specifications for Intermediate and Bulk Products

15.20 Specifications for intermediate and bulk products should be available. The specifications should be

similar to specifications for starting materials or for finished products, as appropriate.

Specifications for Finished Products

15.21 Specifications for finished products should include
- (a) the designated name of the product and the code reference, where applicable,
- (b) the designated name(s) of the active ingredient(s) [if applicable, with the INN(s)],
- (c) the formula or a reference to the formula,
- (d) a description of the dosage form and package details,
- (e) directions for sampling and testing or a reference to procedures,
- (f) the qualitative and quantitative requirements, with acceptance limits,
- (g) the storage conditions and precautions, where applicable, and
- (h) the shelf life.

Master Formulae

15.22 A formally authorized master formula should exist for each product and batch size to be manufactured.

15.23 The master formula should include
- (a) the name of the product, with a product reference code relating to its specification;
- (b) a description of the dosage form, strength of the product, and batch size;
- (c) a list of all starting materials to be used (if applicable, with the INNs), with the amount of each, described using the designated name and a reference that is unique to that material (mention should be made of any substance that may disappear in the course of processing);
- (d) a statement of the expected final yield with the acceptable limits, and of relevant intermediate yields, where applicable;
- (e) a statement of the processing location and the principal equipment to be used;
- (f) the methods, or reference to the methods, to be used for preparing and operating the critical equipment, for example, cleaning (especially after a change in product), assembling, calibrating, sterilizing, use;
- (g) detailed stepwise processing instructions (e.g., checks on materials, pretreatments, sequence for adding materials, mixing times, temperatures);
- (h) the instructions for any in-process controls with their limits;
- (i) where necessary, the requirements for storage of the products, including the container, the labeling, and any special storage conditions; and
- (j) any special precautions to be observed.

Packaging Instructions

15.24 Formally authorized packaging instructions should exist for each product, pack size, and type. These should normally include, or make reference to,
- (a) the name of the product;
- (b) a description of its pharmaceutical form, strength, and, where applicable, method of application;
- (c) the pack size expressed in terms of the number, weight, or volume of the product in the final container;
- (d) a complete list of all the packaging materials required for a standard batch size, including quantities, sizes, and types, with the code or reference number relating to the specifications for each packaging material;
- (e) where appropriate, an example or reproduction of the relevant printed packaging materials and specimens, indicating where the batch number and expiry date of the product have been marked;
- (f) special precautions to be observed, including a careful examination of the packaging area and equipment in order to ascertain the line clearance before and after packaging operations;
- (g) a description of the packaging operation, including any significant subsidiary operations, and equipment to be used; and
- (h) details of in-process controls with instructions for sampling and acceptance limits.

Batch Processing Records

15.25 A batch processing record should be kept for each batch processed. It should be based on the relevant parts of the currently approved specifications on the record. The method of preparation of such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)

15.26 Before any processing begins, a check should be made that the equipment and workstation are clear of previous products, documents, or materials not required for the planned process, and that the equipment is clean and suitable for use. This check should be recorded.

15.27 During processing, the following information should be recorded at the time each action is taken, and after completion the record should be dated and signed by the person responsible for the processing operations:
- (a) the name of the product;
- (b) the number of the batch being manufactured;
- (c) dates and times of commencement, of significant intermediate stages, and of completion of production;
- (d) the name of the person responsible for each stage of production;
- (e) the initials of the operator(s) of different significant steps of production and, where appropriate, of the person(s) who checked each of these operations (e.g. weighing);
- (f) the batch number and/or analytical control number and the quantity of each starting material actually weighed (including the batch number and amount of any recovered or reprocessed material added);
- (g) any relevant processing operation or event and the major equipment used;
- (h) the in-process controls performed, the initials of the person(s) carrying them out, and the results obtained;
- (i) the amount of product obtained at different and pertinent stages of manufacture (yield), together with comments or explanations for significant deviations from the expected yield; and
- (j) notes on special problems including details, with signed authorization for any deviation from the master formula.

Batch Packaging Records

15.28 A batch packaging record should be kept for each batch or part batch processed. It should be based on the

relevant parts of the approved packaging instructions, and the method of preparing such records should be designed to avoid errors. (Copying or validated computer programs are recommended. Transcribing from approved documents should be avoided.)

15.29 Before any packaging operation begins, checks should be made that the equipment and workstation are clear of previous products, documents, or materials not required for the planned packaging operations, and that equipment is clean and suitable for use. These checks should be recorded.

15.30 The following information should be recorded at the time each action is taken, and the date and the person responsible should be clearly identified by signature or electronic password:
- (a) the name of the product, the batch number, and the quantity of bulk product to be packed, as well as the batch number and the planned quantity of finished product that will be obtained, the quantity actually obtained, and the reconciliation;
- (b) the date(s) and time(s) of the packaging operations;
- (c) the name of the responsible person carrying out the packaging operation;
- (d) the initials of the operators of the different significant steps;
- (e) the checks made for identity and conformity with the packaging instructions, including the results of in-process controls;
- (f) details of the packaging operations carried out, including references to equipment and the packaging lines used, and, when necessary, the instructions for keeping the product unpacked or a record of returning product that has not been packaged to the storage area;
- (g) whenever possible, samples of the printed packaging materials used, including specimens bearing the approval for the printing of and regular check (where appropriate) of the batch number, expiry date, and any additional overprinting;
- (h) notes on any special problems, including details of any deviation from the packaging instructions, with written authorization by an appropriate person;
- (i) the quantities and reference number or identification of all printed packaging materials and bulk product issued, used, destroyed, or returned to stock and the quantities of product obtained to permit an adequate reconciliation.

Standard Operating Procedures and Records

15.31 Standard operating procedures and associated records of actions taken or, where appropriate, conclusions reached should be available for
- (a) equipment assembly and validation;
- (b) analytical apparatus and calibration;
- (c) maintenance, cleaning, and sanitization;
- (d) personnel matters including qualification, training, clothing, and hygiene;
- (e) environmental monitoring;
- (f) pest control;
- (g) complaints;
- (h) recalls; and
- (i) returns.

15.32 There should be standard operating procedures and records for the receipt of each delivery of starting material and primary and printed packaging material.

15.33 The records of the receipts should include
- (a) the name of the material on the delivery note and the containers,
- (b) the "in-house" name and/or code of the material if different from (a),
- (c) the date of receipt,
- (d) the supplier's name and, if possible, manufacturer's name,
- (e) the manufacturer's batch or reference number,
- (f) the total quantity and number of containers received,
- (g) the batch number assigned after receipt, and
- (h) any relevant comment (e.g. state of the containers).

15.34 There should be standard operating procedures for the internal labeling, quarantine, and storage of starting materials, packaging materials, and other materials, as appropriate.

15.35 Standard operating procedures should be available for each instrument and piece of equipment (e.g., use, calibration, cleaning, maintenance) and placed in close proximity to the equipment.

15.36 There should be standard operating procedures for sampling, which specify the person(s) authorized to take samples.

15.37 The sampling instructions should include
- (a) the method of sampling and the sampling plan;
- (b) the equipment to be used;
- (c) any precautions to be observed to avoid contamination of the material or any deterioration in its quality;
- (d) the amount(s) of sample(s) to be taken;
- (e) instructions for any required subdivision of the sample;
- (f) the type of sample container(s) to be used, and whether they are for aseptic sampling or for normal sampling, and labeling; and
- (g) any specific precautions to be observed, especially in regard to the sampling of sterile or noxious material.

15.38 There should be a standard operating procedure describing the details of the batch (lot) numbering system, with the objective of ensuring that each batch of intermediate, bulk, or finished product is identified with a specific batch number.

15.39 The standard operating procedures for batch numbering that are applied to the processing stage and to the respective packaging stage should be related to each other.

15.40 The standard operating procedure for batch numbering should ensure that the same batch numbers will not be used repeatedly; this applies also to reprocessing.

15.41 Batch-number allocation should be immediately recorded, for example, in a logbook. The record should include at least the date of allocation, product identity, and size of batch.

15.42 There should be written procedures for testing materials and products at different stages of manufacture, describing the methods, and equipment to be used. The tests performed should be recorded.

15.43 Analysis records should include at least the following data:
- (a) the name of the material or product and, where applicable, dosage form;
- (b) the batch number and, where appropriate, the manufacturer and/or supplier;

(c) references to the relevant specifications and testing procedures;
(d) test results, including observations and calculations, and reference to any specifications (limits);
(e) date(s) and reference number(s) of testing;
(f) the initials of the persons who performed the testing;
(g) the date and initials of the persons who verified the testing and the calculations, where appropriate; and
(h) a clear statement of release or rejection (or other status decision) and the dated signature of the designated responsible person.

15.44 Written release and rejection procedures should be available for materials and products, and in particular for the release for sale of the finished product by an authorized person.

15.45 Records should be maintained of the distribution of each batch of a product in order, for example, to facilitate the recall of the batch if necessary.

15.46 Records should be kept for major and critical equipment, as appropriate, of any validations, calibrations, maintenance, cleaning, or repair operations, including dates and the identity of the people who carried these operations out.

15.47 The use of major and critical equipment and the areas where products have been processed should be appropriately recorded in chronological order.

15.48 There should be written procedures assigning responsibility for cleaning and sanitation and describing in sufficient detail the cleaning schedules, methods, equipment and materials to be used, and facilities and equipment to be cleaned. Such written procedures should be followed.

16. GOOD PRACTICES IN PRODUCTION

16.1 Principle. Production operations must follow clearly defined procedures in accordance with manufacturing and marketing authorizations, with the objective of obtaining products of the requisite quality.

General

16.2 All handling of materials and products, such as receipt and cleaning, quarantine, sampling, storage, labeling, dispensing, processing, packaging, and distribution, should be done in accordance with written procedures or instructions and, where necessary, recorded.

16.3 Any deviation from instructions or procedures should be avoided as far as possible. If deviations occur, they should be done in accordance with an approved procedure. The authorization of the deviation should be approved in writing by a designated person, with the involvement of the quality control department, when appropriate.

16.4 Checks on yields and reconciliation of quantities should be carried out as necessary to ensure that there are no discrepancies outside acceptable limits.

16.5 Operations on different products should not be carried out simultaneously or consecutively in the same room or area unless there is no risk of mix-up or cross-contamination.

16.6 At all times during processing, all materials, bulk containers, major items of equipment, and where appropriate, the rooms and packaging lines being used should be labeled or otherwise identified with an indication of the product or material being processed, its strength (where applicable) and the batch number. Where applicable, this indication should also mention the stage of production. In some cases, it may be useful to record also the name of the previous product that has been processed.

16.7 Access to production premises should be restricted to authorized personnel.

16.8 Normally, nonmedicinal products should not be produced in areas or with equipment destined for the production of pharmaceutical products.

16.9 In-process controls are usually performed within the production area. The performance of such in-process controls should not have any negative effect on the quality of the product or another product (e.g., cross-contamination or mix-up).

Prevention of Cross-Contamination and Bacterial Contamination During Production

16.10 When dry materials and products are used in production, special precautions should be taken to prevent the generation and dissemination of dust. Provision should be made for proper air control (e.g., supply and extraction of air of suitable quality).

16.11 Contamination of a starting material or of a product by another material or product must be avoided. This risk of accidental cross-contamination arises from the uncontrolled release of dust, gases, particles, vapors, sprays, or organisms from materials and products in process; from residues on equipment; from intruding insects; and from operators' clothing, skin, etc. The significance of this risk varies with the type of contaminant and of the product being contaminated. Among the most hazardous contaminants are highly sensitizing materials, biological preparations such as living organisms, certain hormones, cytotoxic substances, and other highly active materials. Products in which contamination is likely to be most significant are those administered by injection or applied to open wounds and those given in large doses and/or over a long time.

16.12 Cross-contamination should be avoided by taking appropriate technical or organizational measures, for example,
(a) carrying out production in dedicated and self-contained areas (which may be required for products such as penicillins, live vaccines, live bacterial preparations, and certain other biologicals);
(b) conducting campaign production (separation in time) followed by appropriate cleaning in accordance with a validated cleaning procedure;
(c) providing appropriately designed airlocks, pressure differentials, and air supply and extraction systems;
(d) minimizing the risk of contamination caused by recirculation or reentry of untreated or insufficiently treated air;
(e) wearing protective clothing where products or materials are handled;
(f) using cleaning and decontamination procedures of known effectiveness;
(g) using a "closed system" in production;
(h) testing for residues; and
(i) using cleanliness status labels on equipment.

16.13 Measures to prevent cross-contamination and their effectiveness should be checked periodically according to standard operating procedures.

16.14 Production areas where susceptible products are processed should undergo periodic environmental monitoring (e.g., for microbiological monitoring and particulate matter where appropriate).

Processing Operations

16.15 Before any processing operation is started, steps should be taken to ensure that the work area and equipment are clean and free from any starting materials, products, product residues, labels, or documents not required for the current operation.

16.16 Any necessary in-process controls and environmental controls should be carried out and recorded.

16.17 Means should be instituted of indicating failures of equipment or of services (e.g. water, gas) to equipment. Defective equipment should be withdrawn from use until the defect has been rectified. After use, production equipment should be cleaned without delay according to detailed written procedures and stored under clean and dry conditions in a separate area or in a manner that will prevent contamination.

16.18 Time limits for storage of equipment after cleaning and before use should be stated and based on data.

16.19 Containers for filling should be cleaned before filling. Attention should be given to avoiding and removing any contaminants such as glass fragments and metal particles.

16.20 Any significant deviation from the expected yield should be recorded and investigated.

16.21 Checks should be carried out to ensure that pipelines and other pieces of equipment used for the transportation of products from one area to another are connected in a correct manner.

16.22 Pipes used for conveying distilled or deionized water and, where appropriate, other water pipes should be sanitized and stored according to written procedures that detail the action limits for microbiological contamination and the measures to be taken.

16.23 Measuring, weighing, recording, and control equipment and instruments should be serviced and calibrated at prespecified intervals and records maintained. To ensure satisfactory functioning, instruments should be checked daily or prior to use for performing analytical tests. The date of calibration and servicing and the date when recalibration is due should be clearly indicated, preferably on a label attached to the instrument.

16.24 Repair and maintenance operations should not present any hazard to the quality of the products.

Packaging Operations

16.25 When the program for packaging operations is being set up, particular attention should be given to minimizing the risk of cross-contamination, mix-ups, or substitutions. Different products should not be packaged in close proximity unless there is physical segregation or an alternative system that will provide equal assurance.

16.26 Before packaging operations are begun, steps should be taken to ensure that the work area, packaging lines, printing machines, and other equipment are clean and free from any products, materials, or documents used previously and which are not required for the current operation. The line clearance should be performed according to an appropriate procedure and checklist, and recorded.

16.27 The name and batch number of the product being handled should be displayed at each packaging station or line.

16.28 Normally, filling and sealing should be followed as quickly as possible by labeling. If labeling is delayed, appropriate procedures should be applied to ensure that no mix-ups or mislabeling could occur.

16.29 The correct performance of any printing (e.g., of code numbers or expiry dates) done separately or in the course of the packaging should be checked and recorded. Attention should be paid to printing by hand, which should be rechecked at regular intervals.

16.30 Special care should be taken when cut labels are used and when overprinting is carried out off-line, and in hand-packaging operations. Roll-feed labels are normally preferable to cut labels in helping to avoid mix-ups. Online verification of all labels by automated electronic means can be helpful in preventing mix-ups, but checks should be made to ensure that any electronic code readers, label counters, or similar devices are operating correctly. When labels are attached manually, in-process control checks should be performed more frequently.

16.31 Printed and embossed information on packaging materials should be distinct and resistant to fading or erasing.

16.32 Regular online control of the product during packaging should include at least checks on
(a) the general appearance of the packages,
(b) whether the packages are complete,
(c) whether the correct products and packaging materials are used,
(d) whether any overprinting is correct, and
(e) the correct functioning of line monitors.
Samples taken away from the packaging line should not be returned.

16.33 Products that have been involved in an unusual event during packaging should be reintroduced into the process only after special inspection, investigation, and approval by authorized personnel. A detailed record should be kept of this operation.

16.34 Any significant or unusual discrepancy observed during reconciliation of the amount of bulk product and printed packaging materials and the number of units produced should be investigated, satisfactorily accounted for, and recorded before release.

16.35 Upon completion of a packaging operation, any unused batch-coded packaging materials should be destroyed and the destruction recorded. A documented procedure requiring checks to be performed before returning unused materials should be followed if uncoded printed materials are returned to stock.

17. GOOD PRACTICES IN QUALITY CONTROL

17.1 Quality control is the part of GMP concerned with sampling, specifications, and testing, and with the organization, documentation, and release procedures which ensure that the necessary and relevant tests are actually carried out and that materials are not released for use, nor products released for sale or supply, until their

quality has been judged to be satisfactory. Quality control is not confined to laboratory operations but must be involved in all decisions concerning the quality of the product.

17.2 The independence of quality control from production is considered fundamental.

17.3 Each manufacturer (the holder of a manufacturing authorization) should have a quality control function. The quality control function should be independent of other departments and under the authority of a person with appropriate qualification and experience, who has one or several control laboratories at his or her disposal. Adequate resources must be available to ensure that all the quality control arrangements are effectively and reliably carried out. The basic requirements for quality control are as follows:

(a) Adequate facilities, trained personnel, and approved procedures must be available for sampling, inspecting, and testing starting materials, packaging materials, and intermediate, bulk, and finished products, and where appropriate for monitoring environmental conditions for GMP purposes.

(b) Samples of starting materials, packaging materials, intermediate products, bulk products, and finished products must be taken by methods and personnel approved of by the quality control department.

(c) Qualification and validation must be performed.

(d) Records must be made (manually and/or by recording instruments) demonstrating that all the required sampling, inspecting, and testing procedures have actually been carried out and that any deviations have been fully recorded and investigated.

(e) The finished products must contain ingredients complying with the qualitative and quantitative composition of the product described in the marketing authorization; the ingredients must be of the required purity, in their proper container and correctly labeled.

(f) Records must be made of the results of inspecting and testing the materials and intermediate, bulk, and finished products against specifications; product assessment must include a review and evaluation of the relevant production documentation and an assessment of deviations from specified procedures.

(g) No batch of product is to be released for sale or supply prior to certification by the authorized person(s) that it is in accordance with the requirements of the marketing authorization. In certain countries, by law, the batch release is a task of the authorized person from production together with the authorized person from quality control.

(h) Sufficient samples of starting materials and products must be retained to permit future examination of the product if necessary; the retained product must be kept in its final pack unless the pack is exceptionally large.

17.4 Quality control as a whole will also have other duties, such as to establish, validate, and implement all quality control procedures; to evaluate, maintain, and store the reference standards for substances; to ensure the correct labeling of containers of materials and products; to ensure that the stability of the active pharmaceutical ingredients and products is monitored; to participate in the investigation of complaints related to the quality of the product; and to participate in environmental monitoring. All these operations should be carried out in accordance with written procedures and, where necessary, recorded.

17.5 Assessment of finished products should embrace all relevant factors, including the production conditions, the results of in-process testing, the manufacturing (including packaging) documentation, compliance with the specification for the finished product, and an examination of the finished pack.

17.6 Quality control personnel must have access to production areas for sampling and investigation as appropriate.

Control of Starting Materials and Intermediate, Bulk, and Finished Products

17.7 All tests should follow the instructions given in the relevant written test procedure for each material or product. The result should be checked by the supervisor before the material or product is released or rejected.

17.8 Samples should be representative of the batches of material from which they are taken in accordance with the approved written procedure.

17.9 Sampling should be carried out so as to avoid contamination or other adverse effects on quality. The containers that have been sampled should be marked accordingly and carefully resealed after sampling.

17.10 Care should be taken during sampling to guard against contamination or mix-up of, or by, the material being sampled. All sampling equipment that comes into contact with the material should be clean. Some particularly hazardous or potent materials may require special precautions.

17.11 Sampling equipment should be cleaned and, if necessary, sterilized before and after each use and stored separately from other laboratory equipment.

17.12 Each sample container should bear a label indicating

(a) the name of the sampled material,

(b) the batch or lot number,

(c) the number of the container from which the sample has been taken,

(d) the number of the sample,

(e) the signature of the person who has taken the sample, and

(f) the date of sampling.

17.13 Out-of-specification results obtained during testing of materials or products should be investigated in accordance with an approved procedure. Records should be maintained.

Test Requirements

Starting and Packaging Materials

17.14 Before releasing a starting or packaging material for use, the quality control manager should ensure that the materials have been tested for conformity with specifications for identity, strength, purity, and other quality parameters.

17.15 An identity test should be conducted on a sample from each container of starting material (see also section 14.14).

17.16 Each batch (lot) of printed packaging materials must be examined following receipt.

17.17 In lieu of testing by the manufacturer, a certificate of analysis may be accepted from the supplier, provided that the manufacturer establishes the reliability of the

supplier's analysis through appropriate periodic validation of the supplier's test results (see sections 8.8 and 8.9) and through on-site audits of the supplier's capabilities. (This does not affect section 17.15.) Certificates must be originals (not photocopies) or otherwise have their authenticity assured. Certificates must contain at least the following information:

(a) identification (name and address) of the issuing supplier,
(b) signature of the competent official, and statement of his or her qualifications,
(c) the name of the material tested,
(d) the batch number of the material tested,
(e) the specifications and methods used,
(f) the test results obtained, and
(g) the date of testing.

In-Process Control

17.18 In-process control records should be maintained and form a part of the batch records (see section 15.25).

Finished Products

17.19 For each batch of drug product, there should be an appropriate laboratory determination of satisfactory conformity to its finished product specification prior to release.

17.20 Products failing to meet the established specifications or any other relevant quality criteria should be rejected.

Batch Record Review

17.21 Production and quality control records should be reviewed as part of the approval process of batch release. Any divergence or failure of a batch to meet its specifications should be thoroughly investigated. The investigation should, if necessary, extend to other batches of the same product and other products that may have been associated with the specific failure or discrepancy. A written record of the investigation should be made and should include the conclusion and follow-up action.

17.22 Retention samples from each batch of finished product should be kept for at least one year after the expiry date. Finished products should usually be kept in their final packaging and stored under the recommended conditions. If exceptionally large packages are produced, smaller samples might be stored in appropriate containers. Samples of active starting materials should be retained for at least one year beyond the expiry date of the corresponding finished product. Other starting materials (other than solvents, gases, and water) should be retained for a minimum of two years if their stability allows. Retention samples of materials and products should be of a size sufficient to permit at least two full reexaminations.

Stability Studies

17.23 Quality control should evaluate the quality and stability of finished pharmaceutical products and, when necessary, of starting materials and intermediate products.

17.24 Quality control should establish expiry dates and shelf-life specifications on the basis of stability tests related to storage conditions.

17.25 A written program for ongoing stability determination should be developed and implemented to include elements such as

(a) a complete description of the drug involved in the study;
(b) the complete set of testing parameters and methods, describing all tests for potency, purity, and physical characteristics and documented evidence that these tests indicate stability;
(c) provision for the inclusion of a sufficient number of batches;
(d) the testing schedule for each drug;
(e) provision for special storage conditions;
(f) provision for adequate sample retention; and
(g) a summary of all the data generated, including the evaluation and the conclusions of the study.

17.26 Stability should be determined prior to marketing and following any significant changes in processes, equipment, packaging materials, etc.

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WHO INSPECTIONS SUMMARY

- Types of GMP Inspection
  - **Routine inspection**
  - **Concise inspection**
  - **Follow-up inspection**
  - **Special inspection**
  - **Quality systems review**
- Routine Inspection
  - **Full inspection of all components of GMP**
  - **Newly established manufacturer**
  - **Renewal of a license**
  - **Changes:**
    - *New product or product lines*
    - *Modifications to manufacturing methods*
    - *Key personnel, premises, or equipment*
  - **History of noncompliance with GMP**
  - **Not inspected in the last 3–5 years**
- Concise Inspection
  - **Consistent record of compliance with GMP**
  - **Focus on limited number of GMP requirements**
  - *Selected as indicators*
  - **Identify significant changes**

- **Indicate attitude toward GMP**
- **Noncompliance**
- *Should trigger comprehensive inspection*

- Follow-up Inspection
  - **Reassessment or reinspection**
  - **Monitor result of corrective actions**
  - **weeks to 6 months after initial inspection**
  - *Nature of defects*
  - *Work undertaken*
  - **Specific GMP requirements**
  - Not observed
  - **Not adequately implemented**
- Special Inspection
  - **Spot-check focusing on**
  - *One product, a group of related products*
  - *Specific operations, for example, mixing, labeling*
  - **Complaints or recalls**
  - **Adverse drug reactions**
  - **Marketing approval or export certificate**
  - **Information or investigation**
  - *Specific information*
  - *Advice on regulatory requirements*
- Quality Systems Review
  - **Assess the quality assurance (QA) system**
  - **Description of the QA system (e.g., manual)**
  - **Policy and standards to be observed**
  - **Management structure**
  - *Implementation*
  - **Procedures**
  - *Quality standards set for products*
  - *Correctly defined manufacturing processes*
  - *Records kept*
  - *QC and QA functions are performed*
- Frequency of Inspections
  - **Depends on type of inspection**
  - **Inspectorate resources (e.g. workload, number of inspectors)**
  - **New facilities—before licensed**
  - **All companies—regular schedule**
  - *Ideally annual*
  - **Large companies**
  - *Several visits over a period, for example, 5 years*
  - *Validity of manufacturing license or GMP certificate*
- Duration of Inspections
  - **Depends on type of inspection**
  - **Inspectorate resources (e.g., workload, number of inspectors)**
  - **Size of the company**
  - **Purpose of the visit**
  - **Days to weeks**
  - **Number of inspectors**
  - *Including specialist support*
- Announced and Unannounced Inspections
  - **Depends on type of inspection**
  - **Announced**
  - *Comprehensive inspection*
  - **Unannounced**
  - *Routine inspection (depending on country policy)*
  - *Concise inspection*
  - *Follow-up inspection*
  - *Special inspection*
- Regulatory Actions
  - **Based on national regulations**
  - **Correction of unsatisfactory situations**
  - **Closing down of a factory**
  - **Withholding of authorizations**
  - **Product recall**
- Group Session
  - **The inspectorate received a complaint that an injectable product [water for injection (WFI), 10 mL ampoule] is possibly contaminated with microorganisms. You have to organize an inspection of the company in question**
  - **What type of inspection would be performed?**
  - **Will the inspection be announced or unannounced?**
  - **Who will be part of the inspection team?**
  - **What will you consider in preparation for the inspection?**
- Possible Issues
  - **Purpose of the inspection**
  - **Notification (or not) of the company in advance**
  - **Makeup of the team**
  - **Program for the inspection**
  - **Sterility test, leak test, and visual inspection**
  - **Validation and qualification**
  - **Documentation review**

5

Solid Oral Dosage Forms Validation

I. INTRODUCTION

The *Validation Guidelines* issued by the FDA in 1987 define process validation as establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes. The three components of this definition include

- documented evidence,
- consistency, and
- predetermined specifications.

Documented evidence includes the experiments, data, and analytical results that support the master formula, the in-process and finished product specifications, and the filed manufacturing process.

With regard to consistency, several batches would have to be manufactured, using the full-scale batch size, to demonstrate that a process meets the consistency test. At least three batches are needed to demonstrate consistency.

The development of a product and its manufacturing process and specifications, the design of the validation protocol, and the demonstration (validation) runs of the full-scale manufacturing process requires scientific judgment based on good scientific data. The FDA expects that in-process control and product specifications will be established during the product development process, with the test batch serving as the critical batch used for the establishment of specifications.

Specifications, such as hardness and particle size, should be established prior to validation of the process; these specifications should be included in the validation protocol. Problems often arise when the product development runs of the process are used to establish both specifications and demonstrate that the system is validated. In these cases, more in-depth inspection and evaluation will be required; some of these process runs often produce failing product because the product specifications have not been fully established and tested.

II. BACKGROUND

Two common complaints regarding validation issues have frequently been raised. The first concerns the misconception that the 1987 *Validation Guideline* represents a new requirement. The second concerns the lack of specificity in the FDA's guides. In 1978, however, the current good manufacturing practice regulations (cGMPRs) were revised and provided for process validation, so this guideline does not represent a new requirement.

Both the FDA and the industry have recognized the need to establish general guidance for the validation of manufacturing processes, and the FDA published a draft guideline in 1983. However, this draft guideline was a very general document that addressed general principles and was applicable to both sterile and nonsterile drugs and devices. In 1984, the guideline was reissued as a draft guideline and was finalized in 1987. The 1987 *Validation Guidelines* merely points out the need to adequately develop and control manufacturing processes. It discusses microbiological issues and provides few specific and practical applications for the validation of manufacturing processes for a marketed solid oral dosage form.

The issue of retrospective validation and its application to marketed products is frequently encountered. This concept of using historical data (test results), along with process control and process specificity was of value until more scientific methods for demonstrating process validation evolved. It should be pointed out that retrospective validation is not merely the review of test results. It also requires that the manufacturing process be specific and the same each time a batch is manufactured. Thus, specific raw-material specifications (including particle size when necessary), in-process specifications (tablet hardness, etc.), and specific manufacturing directions are required. Obviously, any failing batches attributed to the process would necessitate the conclusion that the process is not validated and is inadequate.

Prospective process validation is required, particularly for those products introduced in the last 7 to 8 years or those for which manufacturing changes have been made; however, in some cases where older products have been on the market without sufficient premarket process validation, it may be possible to validate, in some measure, the adequacy of the process by examination of accumulated test data on the product and records of the manufacturing procedures used.

III. PRODUCT DEVELOPMENT

A. Product Development Reports

No statute or regulation specifically requires a product development report, although companies are required to produce scientific data that justify the formulation and the manufacturing and control processes. Most companies use product development reports, technology transfer reports, and others to summarize the scientific data that justify the product and process. The product development report should satisfy the needs of the company. No specific format is required for the contents of the report.

It is suggested that a company develop a product development standard operating procedure (SOP) that describes the development process, the documentation requirements, and the individuals responsible for approving the filed process. This SOP can be brief, and again no legal requirement exists stating that companies must produce such an SOP. Failure to have a formal development report is not a GMP deficiency, nor is it a filing requirement to have a formal development report; however, where such reports *are* written, the development data found in these reports should include the following.

1. Drug Substance Characterization

Characterization of the chemical and physical properties of the drug substance is one of the most critical steps in the development of a solid dosage form. Chemical properties, especially the identification of impurities, are very important. In addition, the physical properties of the API, such as solubility, polymorphism, hygroscopicity, particle size, density, etc., must be addressed. The literature and actual experience demonstrate that the physical quality (e.g., particle size of raw materials) can sometimes have a significant impact on the availability and clinical effect of a dosage form drug; therefore, it is appropriate that the physical characteristics of a drug substance be characterized, that the impact of the physical characteristics be determined, and that a specification for the bulk drug product be established, if necessary.

Development data will vary between new drugs and generics (e.g., characterization and establishment of specifications for the drug substance). In most cases, the manufacturing process for a new drug substance (new chemical entity) is developed and scaled up before the dosage form. In early development stages, very little information is available regarding polymorphic forms, solubility, etc. Consequently, changes to the manufacturing process for the drug substance may change the purity profile or physical characteristics and thus cause problems with the finished dosage form. Although these types of problems are expected, the firm must investigate and document batch failures for the API and dosage form product.

On the other hand, generic manufacturers usually purchase drug substances from API manufacturers who may not be willing to supply information regarding the synthesis or analysis of the drug substance; therefore, the manufacturer of the finished dosage form must perform the appropriate tests to characterize the drug substance chemically and physically and establish appropriate specifications. This may require developing analytical methods to identify impurities. In some cases, this information can be obtained from literature searches.

In either case, it is important that each firm compare the drug substance used to manufacture the biobatch or clinical batch(es) and the drug substances used for the commercial batches, including specifications, analytical methods, and test results for the lots of each drug substance. Remember that the safety of the drug may be based upon the type and level of impurities, and different physical characteristics may affect dissolution or content uniformity. This is particularly important for those drug substances that are poorly soluble in water.

For those products on which biostudies have been conducted, the physical characteristics of the drug substance used for the study should serve as the basis for the physical specifications.

It is widely recognized that when discussing in vivo release rates and drug absorption rates, fast and immediate release is not always best. For some "immediate"-release drug products, such as carbamazepine tablets, a slower release is desired; therefore, it is frequently desirable to have minimum and maximum particle size specifications to control the release rate. For example, micronizing or milling a drug substance to provide a greater surface area of the substance may also result in faster dissolution and possibly faster absorption and higher blood levels. Such changes to improve the dissolution may not always be desired.

In addition to release or dissolution, variation in particle size, particle shape, and/or bulk density can also have an effect on the uniformity of dosage forms, particularly those manufactured by direct compression or direct encapsulation.

Particulate solids, once mixed, have a tendency to segregate by virtue of differences in the shape, size, and density (other variables are also important) of the particles of which they are composed. This process of separation occurs during mixing, as well as during subsequent handling of the completed mix. Generally, large differences in particle size, density, or shape within the mixture result in instability in the mixture. The segregation process normally requires energy input and can be reduced following mixing by careful handling.

Some manufacturers establish wide ranges for specifications. These must be established based on a GMP and validation perspective. Even though a wide range for a physical specification, such as particle size or surface area, may be established in a filing, it is expected that such ranges will be verified during validation of the process. In a recent court decision, the judge ruled that companies cannot hide behind approval of processes listed in an application when these processes do not work. In other words, the approval of a filing has no impact on processes that do not perform consistently. For example, in a particular filed process it was determined that particle size would have no effect on drug absorption and dissolution, and a wide-range particle size specification was established; however, during the GMP review, it was found that variation in particle size did have a major effect on content uniformity. Therefore, a tighter particle size specification had to be established.

Control of the physical characteristics of the excipient is also important because variations in such characteristics may also affect the performance of the dosage form. Changes in particle size of some excipients, for example, may affect content uniformity. In other cases, a change in the supplier of an excipient or lubricant may affect dissolution or bioavailability. In fact, the release of the active ingredients in some products is timed by varying lubricant blending time and concentration. The literature contains many examples of lubricant processing causing major changes. Such changes in excipients illustrate deficiencies with the utilization of retrospective validation; for such validation to be satisfactory, control of all parameters and key steps in the process is necessary.

The control of mixing times and physical characteristics of all ingredients is critical to successful validation of all formulations and processes. A major question that must be addressed is the need for testing physical characteristics (particle size) for each batch of excipient. For many single-source excipients, particle size is a supplier specification and is usually tightly controlled. Having established a specification and not testing each lot of excipient upon receipt may be satisfactory in such cases; however, for some multisource excipients and where the dosage formulator expects to shift sources of supply, some resulting differences in physical characteristics (particle size) may have an effect on dose uniformity and dissolution. Definite justification should exist for not testing lots of excipients for physical characteristics.

2. Manufacturing Procedures

Procedures used to manufacture development batches must be specific and well documented. This is necessary for scale-up and subsequent comparison to the commercial process. This is another area where differences between new drug application (NDA)/new animal drug application (NADA) and abbreviated new drug application (ANDA)/abbreviated new animal drug application (ANADA) products arise. In the case of the NDA/NADA, there will be several clinical and/or test batches manufactured over a period of time showing

changes in the process as more is learned about the drug and the process. The level of documentation should increase as the process becomes more defined and the firm begins phase II and III studies.

The generic product focus is on the biobatch. Again, the process used to manufacture the biobatch must be well defined and well documented; test batches must be manufactured to establish that biobatch manufactured is reproducible.

3. In-Process Testing

Specific specifications required to control the manufacturing process must be established and justified. Doing so will require granulation studies, including blend uniformity, sieve analysis, and moisture.

4. Finished Product Testing

Testing for standards given in FDA monographs such as content uniformity (when a specification applies), assay, hardness, friability, dissolution, and others are essential.

5. Dissolution Profile

The dissolution profiles for the biobatch or pivotal clinical batches should be evaluated in the product development report. Good correlation should exist between the dissolution specifications and test results for the biobatch/clinical test batches and the full-scale commercial process.

6. Stability

The Center for Drug Evaluation and Research (CDER) conducts an evaluation of stability data and approves proposed expiration dates. The product development report should contain an evaluation of the stability data that have been obtained. During postapproval inspections, stability data are reviewed by the field. An FDA inspection, therefore, inevitably includes an audit of underlying raw data and analytical worksheets to ensure the accuracy and authenticity of stability data contained in summary reports.

B. Preapproval Inspections

Validation of three full-size commercial lots is not required for approval of the marketing application; however, the firm must have data that justify the full-scale commercial process filed in the NDA/ANDA or NADA/ANADA application. In other words, the firm should have sufficient research on the test batches to establish specifications for the manufacturing and control procedures listed in the application. These data and specifications form the basis for the validation protocol that may be developed following approval of the application. The final step in the process is demonstration (validation) runs to prove that the process will perform consistently. Firms should validate the process using the specifications listed in the filing. To evaluate the proposed manufacturing process, the following areas must be covered during the preapproval inspection:

1. Master Formula

This document must include specific manufacturing directions for the full-scale commercial process, including in-process and finished product specifications. Make sure that the process filed in the application complies with the process used to manufacture the bio/clinical batch. In some cases, the process may be different after scale-up. This is acceptable if the firm has data showing the product produced by this process will be equivalent. Data such as granulation studies, finished product test results, and dissolution profiles are used to document that the two processes are equivalent.

2. History Section of the Application

This section of the application is used to identify the biobatch or batches used for pivotal clinical studies. Any batches in which in vivo studies were carried out, particularly those for which in vivo studies showed a lack of equivalency, are subject to review.

3. Development Data (Product Development Report)

The firm cannot logically proceed to the validation step without some prior evaluation of the process. During the development phase, the critical process parameters must be identified and specifications established. These predetermined specifications must be established during the development of the process, with the biobatch or pivotal clinical batch serving as the reference batch.

Development of a solid dosage form will vary from firm to firm and will be dependent upon the specific product and process; however, the formula ranges, physical and chemical specifications of the drug substance and excipients, in-process variables, and interaction effects of the dosage form ingredients under normal and stress aging conditions should be confirmed by limited challenge in pilot-scale and production-size batches.

Such development data serve as the foundation for the manufacturing procedures, specifications, and validation of the commercial process. In some cases, manufacturers establish specifications such as hardness and particle size during validation; however, as the validation definition states, specifications must be determined prior to validation of the process.

When a manufacturer files a manufacturing process in an application, the FDA expects that the process will yield a product that is equivalent to the product on which the biostudy or pivotal clinical study was conducted; therefore, it is important that the development and scale-up of the process be well documented so that a link between the bio/clinical batches and the commercial process can be established. The firm should have data such as granulation studies, finished product test results, and dissolution profiles that may be used to document that the two processes are equivalent.

In most cases, in vitro data alone will not be sufficient to document equivalency. The bioequivalency evaluation must be made by qualified individuals, and the firm should have a signed statement documenting that the processes are equivalent.

4. Inspection of the Facilities

The FDA inspectors physically inspect the facility to ensure that the area and ancillary equipment such as air handling and water systems are suitable for the proposed manufacturing process. Construction of new walls, installation of new equipment, and other significant changes must be evaluated for their impact on the overall compliance with GMP requirements. These inspections include facilities used for development batches and to be used for full-scale production batches.

5. Raw Materials

The FDA inspectors review the information contained in the raw materials section of the product development report. Inventory records are a good source for identification of batches used for product development and biostudies.

6. Laboratory

The regulatory inspection of a laboratory involves observations of the laboratory in operation and of the raw laboratory data to evaluate compliance with GMPs and to specifically

carry out the commitments in an application or Drug Master File (DMF). The raw laboratory data, laboratory procedures and methods, laboratory equipment, and methods validation data must be periodically reviewed to ensure overall quality of the laboratory operation and the ability to comply with GMP regulations.

It is not uncommon for the FDA inspecting team to identify foreign peaks and impurities not filed or discussed in applications. Also, many inspections reveal laboratory test methods that are not validated. The transfer of laboratory methods and technology from the research and development department to the quality control department should be firmly established. Be aware that FDA inspectors are not bound by any rules to restrict their investigation to particular product files. They can and often do pick up data files, charts, and recordings that are lying around in the area and will raise queries. It is a good idea to keep these records properly secured to avoid unnecessary distractions in the inspection process.

7. Equipment

At the time of the preapproval inspection, the FDA expects that the equipment will be in place and qualified. New products, particularly potent drug products, can present cleaning problems for existing equipment. Manufacturers must validate their cleaning processes for the new drug/dosage form.

IV. VALIDATION PROTOCOLS

Validation protocols are developed from the information obtained during product development research. These protocols list the specific manufacturing process and specifications that will be tested during the demonstration runs. Validation protocols are not required for the preapproval inspection but are required for postapproval inspections. Key processes and control specifications should have been established during product development research and should be carefully listed in the validation protocol.

V. DEMONSTRATION RUNS (VALIDATION OF THE PROCESS)

A. Test Batch Relationships

A validated process should produce a dosage form that is directly related to the dosage form on which equivalency and/or efficacy and safety data were determined. This is usually the test batch; therefore, ensure that the process used to make the test batch has been used for routine full-scale production batches. These processes and specifications must be equivalent, and the importance and need for good control of the manufacturing process used to produce the test and clinical batches cannot be overemphasized. Typically, the control of test batches includes, among other components, drug substance characterization, granulation analyses, and dose uniformity and dissolution profiles. The validation report should compare the manufacturing processes and specifications for the test batches to those for the full-scale batches; however, such findings may be contained in other documents, such as bioequivalency reports, and should be readily available.

B. Postapproval Prospective Validation Inspections

In the postapproval, premarketing phase, the FDA reviews the validation protocol and validation report. Obviously, a validation protocol that lists all of the variables and parameters that should be controlled when the process is validated cannot be written until the variables are identified in the development phase. In many of the FDA's postapproval, premarketing inspections, validation (and consistency) are often not well established. Failures of production-size batches include dissolution, lack of content uniformity, and variable potency. Validation reports on batch scale-ups may also reflect selective reporting of data. Several parameters must be considered when ensuring validation of the manufacturing process for an oral solid dosage form. For example, at least eight major areas must be evaluated:

- Biobatch relationship
- Raw materials
- Manufacturing procedures and equipment
- Granulation/mix analysis
- In-process controls
- Test results with validated methods
- Investigations/product failures
- Site review

1. Raw Materials

Physical characteristics of raw materials can vary among manufacturers of drug substances and, on occasion, have varied from lot to lot from the same manufacturer. The examination of retained samples of the lots of raw materials can reveal physical differences between the two lots and thus should become a routine measure. A quantitative compliance must be present for the raw material inventory records to evaluate the use of the drug substance in biobatch, clinical, and/or test batches. Make sure to account for the quantities and sources of materials used and the testing performed. Physical specifications for drug substances should be well established. If no such specifications are available, or only a very vague specification is, support data should exist to demonstrate that dissolution profiles and content uniformity will be satisfactory over a wide range of particle sizes. For example, a manufacturer may establish a specification that 90% of the particles must be less than 300 microns. For validation of this process, one would expect the use of micronized as well as nonmicronized material with particles close to 300 microns in size.

2. Manufacturing Procedures and Equipment

Regardless of the nature of the specificity of the manufacturing directions contained in the application, a detailed master formula with specific manufacturing directions and specifications must have been developed before any validation protocol is prepared and before the validation process begins. The basic premise of validation of a process is that a detailed process already exists that, it is hoped, will be shown to perform consistently and produces products in compliance with predetermined specifications; therefore, detailed manufacturing directions specifying equipment and operating parameters must be specified in the master formula.

The importance of specific written directions and specifications cannot be overemphasized. For example, problem areas include

- failure to specify the amount of granulating solution, resulting in overwetting and dissolution failures of aged batches;
- failure to specify the encapsulation machine and operating parameters, such as dosing discs, resulting in weight variation failures; and
- failure to specify the compression machine(s) and operating parameters, resulting in content uniformity failures.

In addition to the concern about specific manufacturing directions, equipment presents its own set of unique problems that have to be considered in the control of the manufacturing and the validation processes. The following is a brief description of some issues associated with equipment.

a. Blenders

Many solid oral dosage forms are made by direct compression. The two types of mixers are low energy and high energy. The low-energy mixers represent the classical type of slow mixers, such as ribbon blenders, tumblers, and planetary pony pan; the high-energy mixers include some basic features of the low-energy mixers but also contain some type of high-speed blade, commonly termed an intensifier bar or chopper. The various types of mixers can be described as follows:

1. *Pony pan type.* This mixer has historically been used for the manufacture of wet granulations. Because of its open pan or pot, granulating agents such as starch paste can be added while mixing. Because the pan is open at the top to allow the mixing blades to penetrate the powder, mixing operations are usually dusty and can lead to potential cross-contamination problems. The usefulness of these mixers is limited to wet granulating. This type of mixer provides good horizontal (side-to-side) blending; however, vertical (top-to-bottom) mixing does not occur. Powder placed in the mixer first will be poorly mixed. Segregation or unmixing is also a recognized problem. To minimize this problem, some manufacturers have emptied the pan contents halfway through the mixing cycle in an attempt to turn the powder over at the bottom of the mixer. To alleviate the problem of the lack of mixing along the sides or walls of the pan, manufacturers have used a hand-held steel paddle at various times during mixing. This type of mixing is difficult to control and reproduce; thus, it would be difficult to validate.

   The potential for segregation and poor mixing along the sides and particularly the bottom of the pony blender makes this type of blender less desirable for the dry blending of granulations of drug products; consequently, whenever such dry blending is encountered, investigators will look for potential problems with blending validation and content uniformity. Whenever in-process samples of the granulation are collected as part of an investigation or inspection, the formula card and the weight of the dosage unit to be manufactured are needed for the calculations.
2. *Ribbon blender.* In the ribbon blender, powder is mixed both horizontally and vertically. Loading operations can be dusty, but during the actual blending the unit is enclosed, thereby limiting the amount of dust released to the environment. The major and potentially the most serious problem with the ribbon blender is the "dead spot" or zone at the discharge valve in some of these blenders. To compensate for this dead spot, manufacturers have to recycle the powder from this area at some point during the mixing process. Obviously, adequate and very specific directions and procedures should be available to ensure that this critical step is performed. Another concern with this mixer is the poor mixing at the ends of the center horizontal mixing bar and at the shell wall because of blade clearance. The level of powder placed in this mixer is normally at the top of the outer ribbon blade, and, as with other mixers, care must be taken not to overfill the mixer. Cleaning problems, particularly at the ends of the ribbon blender where the horizontal bar enters the blender, have been identified. Manufacturers who do not disassemble and clean the seals/packing between batches should have data to demonstrate the absence of foreign contaminants between batches of different products processed in the blender.
3. *Tumbler blender.* Common mixers of this type include the twin shell and double cone. These mixers exert a gentle mixing action; because of this mild action, lumps of powder will not be broken up and mixed. Powders may also clump due to static charges and segregation can occur. Low humidity can contribute to this problem. Blending under very dry conditions has been found to lead to charge buildup and segregation, while blending of some products under humid conditions has led to lumping. More so than with other mixers, powder charge levels should not exceed 60% to 65% of the total volume of the mixer. Fabricators of tumbler-type blenders identify the volume as the actual working capacity and not the actual volume of the blender. It is important to correlate the bulk density of the granulation with the working capacity of the blender.
4. *High-shear (high-energy) mixers*. The several fabricators of these mixers include GRAL, Diosna, and Littleford/Lodige. These mixers are highly efficient and ideally suited for wet granulations. End points of wet granulations can be determined by measurements on a gauge of the work required to agitate the blend. The mixing vessel is enclosed, and dust only enters the environment when loading. One of the problems associated with these mixers is the transfer or conversion of products blended in the older types of mixers to these blenders. Mixing times are going to be different, and the physical characteristics of the blend may also be different. These mixers are very efficient. For wet granulations, it is important to control the rate and amount of addition of the solvent. Because of their efficiency, drug substance may partially dissolve and recrystallize upon drying as a different physical form. An intensifier bar in the center of the blender rotates at very high speeds to break down the smaller, harder agglomerates. A major disadvantage of this type of blender is that the extremely high speed of the intensifier bar generates considerable heat, which can sometimes result in charring of some sugar-based granulations. It should be pointed out that these same comments are applicable to other high-energy mixers that also rely on high-speed choppers to disperse powders. Also, cleaning of the blender requires disassembly of the intensifier bar between products.
5. *Plastic bag.* Any discussion of mixers would not be complete without addressing the plastic bag. Firms have resorted to the blending or manufacture of a trituration in a plastic bag. Obviously, it is very difficult to reproduce such a process, and there is the potential for loss of powder as a result of breakage or handling. The use of a plastic bag cannot be justified in the manufacture of a pharmaceutical product. When the plastic bag has been used, directions are usually not specific, and one would not know by reading the directions that a plastic bag was employed. Some companies have been known to hide the use of plastic bags by indicating in the manufacturing records that a blender was used; these bags are easy to spot during an inspection, and the practice is highly discouraged.

b. Dryers

The two basic types of dryers are the oven dryer, in which the wet granulation is spread on trays and dried in an oven, and the fluid-bed dryer, in which the wet granulation is "fluidized" or suspended in air. Generally, the fluid-bed dryer

yields a more uniform granulation with spherical particles; however, this may result in compression problems that may require additional compression force. It is not unusual to see manufacturers change from an oven dryer to the fluid-bed dryer; however, such a change should be examined for equivalency with in vitro testing such as hardness, disintegration, and comparative dissolution and stability testing.

Other issues of concern with drying include moisture uniformity and cross-contamination. Tray dryers present more moisture uniformity problems than fluid-bed dryers. Obviously, a dryer should be qualified for heat uniformity and a program developed to ensure moisture uniformity in granulations at the end point of drying. With respect to fluid-bed dryers, moisture problems can occur if the granulation is not completely fluidized.

In regard to cross-contamination, oven dryers, particularly those in which air is recirculated, present cross-contamination problems because air recirculates through a common filter and duct. For fluid-bed dryers, the bag filters present cross-contamination problems. In order to minimize such problems, manufacturers should use product-dedicated bags.

c. Tablet and Capsule Equipment

Another important variable in the manufacturing process is the tablet press or encapsulating machine. The newer dosage form equipment requires granulations with good flow characteristics and good uniformity. The newer tablet presses control weight variation by compression force and require a uniform granulation to function correctly. Setup of the microprocessor-controlled tablet press usually includes some type of challenge to the system. For example, a short punch is sometimes placed among the other punches. If the press is operating correctly, it will alarm when a lower- or higher-weight tablet is compressed.

Different tablet compression equipment can cause dose uniformity, weight uniformity, and hardness problems. For example, vibrations during tablet compression can cause segregation of the granulation in the feed hopper. The speed of the machine can affect the fill of the die and tablet weight; therefore, as previously noted, it is important to have specific operating directions.

Many unit operations now provide for blending in totes, with direct discharge of the tote into the tablet compression equipment. Because of segregation problems at the end of the discharge, tablets from the end of the compression should be tested for content uniformity. The use of inserts in totes has been shown to minimize segregation.

With regard to the newer computer-controlled tablet compression equipment, buckets of tablets are often rejected because of potential weight variation problems. The disposition of these tablets, as well as the granulation and tablets used to set up the press, should be documented, and reworking processes must be validated.

With regard to encapsulation operations, the hygroscopic nature of gelatin capsules and some of the granulations require humidity controls for storage of the empty capsules and their subsequent filling. Scale-up of capsule products has also presented some problems because of the different types of encapsulation equipment. Older equipment that operated on gravity fill, such as Lilly and Parke-Davis machines, was commonly used for manufacturing capsules in clinical manufacturing areas. When formulations were scaled up to high-speed encapsulation equipment, flow problems and weight variation resulted. Additionally, some of the newer equipment provides for the formation of a slug which could have an impact on dissolution.

Many firms, in order to recondition (rework) batches, pass those particular batches through a sorter, such as the MOCON VERICAP®. This machine works on the principal of current (dielectric constant), and moisture variation in the filled capsules can cause inaccurate results. Manufacturers should qualify equipment and examine equipment logs for these sorting machines to identify batches with weight problems. Data supporting the accuracy of equipment in regard to rejecting low- or high-weight capsules should be available during an FDA inspection.

d. Coating Equipment

Many tablets are now coated with an aqueous film coat that is usually very soluble. Current technology provides for fixed sprays of the coating solution. The volume of coating solution, rate, and temperature can be controlled by some of the more highly automated operations; however, for many sugar-coated, enteric-coated, and delayed-release products, some components of the coating are not highly soluble and that part of the process is performed manually. Generally, the shellac undercoat used for sugar-coated tablets has presented disintegration/dissolution problems, particularly in aged samples.

With respect to poor disintegration, the example of ferrous sulfate tablets probably represents the classical example. Over the years, many different manufacturers have issued recalls for poor disintegration of coated ferrous sulfate tablets; likewise, problems with poor dissolution have been attributed to the coating process. Again, the shellac undercoat hardens and even sometimes cracks, resulting in poor dissolution.

On many occasions the coating process has not been validated. The number of applications of coats, volume of coating solution in a specific application, and temperature of the solution during application are all parameters that must be addressed. For example, the temperature of application and even heat during drying has been found to cause dissolution failures in aged tablets.

Another problem associated with the coating process concerns heat applied to products that are sensitive to heat. For example, it has been shown that estrogen tablets are heat sensitive and have exhibited stability problems; thus, it is important to control this phase of the process.

For a few products, such as some of the antihistamine tablets or multivitamin tablets containing folic acid or cyanocobalamine, the drug substance is applied during the coating process. Some products require the active drug substance to be applied as a dust on tacky tablets as part of the coating process; for these products, it is particularly important to apply the drug in the coating solution through controlled applications. Again, it is important as part of the validation of these processes to demonstrate dose uniformity and dissolution and to control the parameters of the coating process.

3. Granulation/Mix Analysis

A critical step in the manufacture of an oral solid dosage form is the blending of the final granulation. If uniformity is not achieved at this stage, then one could assume that some dosage units would not comply with uniformity requirements. The major advantage of blend analysis (from a

uniformity perspective) is that specific areas of the blender that have the greatest potential to be nonuniform can be sampled. This is particularly true of the ribbon-type blender and planetary or pony-type mixers.

In some cases, such as for large or tumbler-type blenders, it is impractical to sample from the blender directly. In such cases, granulations or blends could be sampled at the time of blender discharge or directly from drums. If sampling from drums, samples from the top, middle, and bottom of each drum should be collected.

In most cases, sampling thieves are readily available for sampling the small quantities that need to be taken from key areas of the blender or the drums. If samples larger than one dosage unit must be collected, however, adequate provisions must be made to prevent excessive handling manipulation between the time of sampling and the time of analysis.

Good science and logic would seem to dictate that sample sizes of the approximate equivalent weight of the dosage unit should be sampled in order to test for uniformity. Many industrial pharmacy and engineering texts confirm this approach. Large granulation sample sizes (e.g., 1 oz) will provide little information with respect to uniformity. Generally, further mixing after sampling and prior to analysis can yield misleading results.

The acceptance criteria for granulation dose uniformity testing must be established. Although many firms evaluate dose uniformity using the compendial dose uniformity specifications [85 to 115% with a relative standard deviation (RSD) of 6 to 7.8], such specifications should be tighter where supported by the firm's historical data on the level of blend uniformity with its equipment for a given product. In many cases, compendial assay limits for the finished product (90 to 110% of label claim) are broad enough for this purpose, and most firms should be able to demonstrate blend assay results well within these limits. If larger sample sizes are taken for assay to evaluate total composite assay, then the specific U.S. Pharmacopeia (USP) or filed criteria for assay should be used.

In addition to analysis of blends for dose uniformity and potency, blends are tested for physical characteristics. A major physical parameter used to demonstrate equivalence between batches is the particle size profile. This is particularly important for comparison of the biobatch with production batches and also when processes are modified or changed. The particle size profile will provide useful information for demonstrating comparability.

Particle size profiles are particularly important for tablets made by a wet granulation process. The size and even the type of granule can affect the pore size in a tablet and have an effect on dissolution. For example, a recent dissolution failure was attributed to a change in the milling screen size, yielding a granulation with larger granules. It was a coated tablet, and the larger pores permitted increased penetration of the coating solution into the tablet, resulting in slower dissolution.

Another test that is typically performed in regard to granulation, particularly when the wet granulation process is used, is loss on drying (LOD) and/or moisture content. If organic solvents are employed, then residual solvent residues are also tested. To validate a drying process, LOD levels are determined prior to, during, and after drying in order to demonstrate times and levels. As with processing variables, levels (specifications) are established in the development phase, with the validation phase being used to confirm the adequacy of the process.

4. In-Process Testing

In-process testing is testing performed on dosage forms during their compression/encapsulation stages to ensure consistency throughout these operations. For tablets, individual tablet weight, moisture, hardness (compression force), and disintegration tests are performed. For capsules, individual weight and moisture tests are performed. In many of the validation reports, it has been found that manufacturers have neglected to supply results of individual (not composite) dosage unit weight tests that should be performed throughout compression/encapsulation. Such testing is particularly important for capsule products, which may exhibit weight variation problems. If not part of the validation reports, the individual dosage unit weights should be recorded and be available for FDA inspectors to review.

With regard to individual capsule weights, a major question that arises concerns acceptable levels. Because most USP assay limits are 90% to 110%, it would seem reasonable that each unit manufactured complies with these specifications. It should be pointed out that 85% to 115% limits are established by the USP for variability in both blending and compression or encapsulation operations.

Because hardness and disintegration specifications are established during development and biobatch production, testing is performed to demonstrate both equivalency (comparability) and consistency.

With regard to moisture, some tablets set up upon aging as a result of poor moisture control and inadequate specifications. For example, this has been shown to be a major problem with carbamazepine tablets and often for ferrous sulfate tablets.

5. Test Results

Finished product testing, particularly assay, content uniformity, and dissolution, should be carefully recorded. With regard to dissolution, it is important to establish dissolution profiles. Validation batches with dissolution profiles not comparable to biobatches indicate nonequivalency of the manufacturing process. Depending on the discriminating nature of the dissolution test, it may also indicate lack of equivalence of the dosage forms made during validation with the biobatch. In the review of dissolution test results, it is important to eventually see results very close to 100% dissolution. In some cases, manufacturers will profile the dissolution results only to the specification; however, if lower but still acceptable results are obtained (such as 85%), it is important to continue the test by increasing the speed of the apparatus. If a product completely dissolves, yet only results in a value of 85%, it may indicate some problem with the test. Likewise, high dissolution results (115%) also indicate some problem with the test. Obviously, unusual or atypical results should be explained in the validation report.

6. Investigations and Product Failures

In any process validation exercise, a basic objective is to prove that a process is satisfactory; unfortunately, some processes are unsatisfactory and may sometimes yield unacceptable results. It is important, therefore, that when the final validation report is reviewed, all results, including failing results, are discussed and evaluated. Historically, reviews of manufacturing processes typically show that one out of every

eight batches manufactured has failed content uniformity testing. Manufacturers often recognize that the process is unsatisfactory and not validated, but fail to draw this conclusion in the written validation report. This is a dangerous precedence and is often easily identified during FDA inspections.

7. Site Review

A major aspect and possibly the most critical phase of process validation is the review of data to ensure that failing batches were not omitted without justification. Additionally, manufacturers must ensure that the raw data, including analytical raw data, are accurate.

6

Current Regulatory Status of Over-the-Counter Products

BACKGROUND

Over-the-Counter (OTC) drug products are those drugs that are available to consumers without a prescription. There are more than 80 classes (therapeutic categories) of OTC drugs, ranging from acne drug products to weight control drug products. As with prescription drugs, CDER oversees OTC drugs to ensure that they are properly labeled and that their benefits outweigh their risks.

OTC drugs play an increasingly vital role in America's health-care system by providing easy access to certain drugs that can be used safely without the help of a health-care practitioner. This enables consumers to take control of their own health care in many situations. There are more than 100,000 OTC drug products marketed, encompassing about 800 significant active ingredients. Most OTC drug products have been marketed for many years, prior to the laws that require proof of safety and effectiveness before marketing. For this reason, FDA has been evaluating the ingredients and labeling of these products as part of "The OTC Drug Review Program." The goal of this program is to establish OTC drug monographs for each class of products. OTC drug monographs are a kind of "recipe book" covering acceptable ingredients, doses, formulations, and labeling. Monographs will continually be updated adding additional ingredients and labeling as needed. Products conforming to a monograph may be marketed without further FDA clearance, while those that do not, must undergo separate review and approval through the "new drug approval system." The NDA system—and not the monograph system—is also used for new ingredients entering the OTC marketplace for the first time. For example, the newer OTC products (previously available only by prescription) are first approved through the NDA system and their "switch" to OTC status is approved via the NDA system.

FDA's review of OTC drugs is primarily handled by CDER's Division of Over-the-Counter Drug Products in the Office of Drug Evaluation V. However, scientists and regulators throughout CDER, the Office of General Counsel, and other Centers within FDA are routinely asked to assist in this massive effort. There is also an advisory committee, "The Nonprescription Drug Advisory Committee," which meets regularly to assist the agency in evaluating issues surrounding these products.

REGULATORY DEFINITIONS

An OTC drug product is a drug product marketed for use by the consumer without the intervention of a health-care professional in order to obtain the product. Two post-1938 regulatory pathways exist for the legal marketing of such products: (a) marketing in compliance with an OTC drug monograph; (b) marketing under the authority of an approved product-specific new drug application (NDA), or an abbreviated new drug application (ANDA). The OTC drug review was established to evaluate the safety and effectiveness of OTC drug products marketed in the United States before May 11, 1972. It is a three-phase public rulemaking process (each phase requiring a *Federal Register* publication) resulting in the establishment of standards (monographs or nonmonographs) for an OTC therapeutic drug category. The first phase was accomplished by advisory review panels. The panels were charged with reviewing the ingredients in nonprescription drug products to determine whether these ingredients could be generally recognized as safe and effective for use in self-treatment. They were also charged with reviewing claims and recommending appropriate labeling, including therapeutic indications, dosage instructions, and warnings about side effects and preventing misuse. According to the terms of the review, the panels classified ingredients in three categories are as follows:

Category I: generally recognized as safe and effective for the claimed therapeutic indication
Category II: not generally recognized as safe and effective or unacceptable indications
Category III: insufficient data available to permit final classification

The second phase of the OTC drug review was the agency's review of ingredients in each class of drugs, based on the panel's findings, on public comment, and on new data that may have become available. The agency, in turn, publishes its conclusions in the *Federal Register* in the form of a tentative final monograph. After publication of the tentative final monograph, a period of time is allotted for objections to the agency's proposal or for requests to be submitted for a hearing before the Commissioner of FDA.

The publication of final regulations in the form of drug monographs is the third and last phase of the review process. The monographs establish conditions under which certain OTC drug products are generally recognized as safe and effective.

The term human drug application means an application for approval of a new drug submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) or approval of a new drug submitted under section 505(b)(2) of the FD&C Act or approval of an abbreviated new drug application under section 505(j) of the FD&C Act or licensure of certain biological products under section 351 of the Public Health Service Act. A 505(b)(1) application is an application that contains full reports of investigations of safety and effectiveness. The investigations the applicant relied on for approval were conducted by, or for the applicant, or the applicant has obtained a right of reference or use for the investigations.

Appendix I to this chapter is a listing of OTC ingredients and their respective recommended uses and classification.

The U.S. FDA has recently issued guidance on unproven safety of OTC drug components (current as of April 2008) [CITE: 21CFR310.545]. A number of active ingredients have been present in OTC drug products for various uses, as described below. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses. These ingredients are listed as Appendix II to this chapter.

Appendix I OTC Ingredient List

Review Panel	Report	Drug Category	ANPR	PR	FR
2-Ethylhexyl salicylate [see octyl salicylate]					
= == =	= == =	= == =	= == =	= == =	= == =
2-Ethylhexyl-4-phenylbenzophenone-2-carboxylic acid					
Topical analgesic	Sunscreen	Sunscreen	IISE	IISE	Pending
5-(3,3-Dimethyl-2-norbornyliden)3-pentene-2-one [see bornelone]					
= == =	= == =	= == =	= == =	= == =	= == =
8-Hydroxyquinoline [see oxyquinoline]					
= == =	= == =	= == =	= == =	= == =	= == =
Acetaminophen					
Internal analgesic	Internal analgesic	Analgesic	I	I	Pending
Internal analgesic	Internal analgesic	Antipyretic	I	I	Pending
Internal analgesic	Internal analgesic	Antirheumatic	IIE	Not OTC	n/a
Miscellaneous internal	Menstrual/diuretic	Analgesic	I	I	Pending
Miscellaneous internal	Overindulgence in alcohol/food	Overindulgence remedies (hangover)	I	I	Pending
Sedative	Nighttime sleep aid	Sleep aid	IIE	IIE	[54 FR 6826]
Sedative	Daytime sedative	Sedative	IISE	IISE	310.519(a)
= == =	= == =	= == =	= == =	= == =	= == =
Acetanilide					
Internal analgesic	Internal analgesic	Analgesic	IIS	IIS	Pending
Internal analgesic	Internal analgesic	Antipyretic	IIS	IIS	Pending
Internal analgesic	Internal analgesic	Antirheumatic	IISE	not OTC	n/a
Acetic acid					
= == =	Otic	Swimmer's ear prevention	n/a	IIIE	310.545(15)(i)
Contraceptive/vaginal	Vaginal	Alters vaginal pH	IIIE	Withdraw	n/a
Miscellaneous external	Wart remover	Wart remover	IIISE	IIISE	[55 FR 33254]
Acetic acid, glacial					
Miscellaneous external	Wart remover	Wart remover	IIIE	IIISE	[55 FR 33254]
Miscellaneous external	Corn/callus remover	Corn/callus remover	IIIE	IIISE	[55 FR 33261]
Acetone					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(18)(ii)
Acidulated phosphate fluoride (sod fluoride/sod phos/phos acid)					
Dental	Anticaries	Anticavity dental rinse	I	I	355.10(a)(2)(ii)
Acidulated phosphate fluoride (sodium fluoride/hydrogen fluoride)					
Dental	Anticaries	Anticavity dental rinse	IIS	IIS	355.10(a)(2)(ii)
Acidulated phosphate fluoride (sodium fluoride/sodium phos dibasic/phos acid)					
Dental	Anticaries	Anticavity dental rinse	I	I	355.10(a)(3)(ii)
Agar					
Laxative	Laxative	Bulk laxative	IIIE	IIIE	310.545(12)(i)
Alanine					
Miscellaneous internal	Benign prostatic hypertrophy	Benign prostatic hypertrophy	IIE	IIISE	310.532(a)
Alcloxa					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(1)
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(22)(ii)
Hemorrhoidal	Anorectal	Keratolytic (external)	I	I	346.20(a)
Hemorrhoidal	Anorectal	Keratolytic (intrarectal)	I	I	346.20(a)

Review Panel	Report	Drug Category	ANPR	PR	FR
Alcohol					
Miscellaneous external	Alcohols (topical)	Antiseptic	I	Defer	n/a
Miscellaneous external	Mercury	First aid antiseptic	n/a	I	Pending
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	Defer	n/a
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(18)(vi)
Miscellaneous external	Skin protectant	Fever blister (topical)	IISE	IISE	Pending
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Menstrual/diuretic	Analgesic adjuvant	n/a	IISE	310.545(a)(24)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Oral cavity	Oral health care	Antimicrobial	IIIE	IIISE	Pending
Alcohol, 14% [see Alcohol]					
====	====	====	====	====	====
Alcohol, ethoxylated alkyl					
====	Insect bite/sting	Insect bite/sting	n/a	n/a	310.545(a)(18)(v)(A)
Aldioxa					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(ii)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	Pending
Alfalfa					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Alfalfa leaves					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Alginic acid					
Antacid	Antacid	Antacid	IIIE	IIIE	[39 FR 19873]
Miscellaneous internal	Weight control	Anorectic	IIIE	IISE	310.545(a)(20)
Alkaloids of sabadilla [see sabadilla alkaloids]					
====	====	====	====	====	====
Alkyl arylsulfonate					
Contraceptive/vaginal	Vaginal	Lowers surface tension mucolytic effects	IIIE	Withdraw	n/a
Alkyl dimethyl amine oxide and alkyl dimethyl glycine					
====	Gingivitis/plaque	Antiplaque/gingivitis	n/a	IIISE	Pending
Alkyl isoquinolinium bromide					
Antimicrobial II	Acne	Acne	IISE	IISE	310.545(a)(1)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	IISE	IIIE	310.545(a)(7)
Alkyldimethyl benzylammonium chloride [see benzalkonium chloride]					
====	====	====	====	====	====
Allantoin					
Contraceptive/vaginal	Vaginal	Minor irritations	IIIE	Withdraw	n/a
Dental	Oral mucosal injury	Wound healing agent	IIIE	IIIE	310.534(a)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/ psoriasis	IIIE	IIIE	310.545(a)(7)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	Pending
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	IISE	Pending
Miscellaneous external	Hair growth/loss	Hair grower	IISE	n/a	310.527(a)
Miscellaneous external	Skin protectant	Diaper rash	Defer	I	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	I	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	Pending

Review Panel	Report	Drug Category	ANPR	PR	FR
Miscellaneous external	Corn/callus remover	Corn/callus remover	IISE	IISE	[55 FR 33261]
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(a)
Topical analgesic	Skin protectant	Wound healing agent	IIIE	IIIE	310.545(a)(18)(i)(A)
Allantoin (with aminobenzoic acid)					
Topical analgesic	Sunscreen	Sunscreen	IIIE	IIIE	[64 FR 27682]
Allyl isothiocyanate					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	IISE	IISE	310.545(a)(6)(ii)(A)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IISE	310.545(a)(10)(v)
Topical analgesic	External analgesic	Counterirritant	I	I	Pending
Almadrate sulfate					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIIE	n/a	310.545(a)(8)(ii)
Aloe					
====	Skin protectant	Diaper rash	n/a	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Minor irritations	IIIE	Withdraw	n/a
Laxative	Laxative	Stimulant laxative	I	I/IIIS	310.545(a)(12)(iv)(C)
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Aloe extract					
====	Laxative	Stimulant laxative	n/a	n/a	310.545(a)(12)(iv)(C)
Aloe flower extract					
====	Laxative	Stimulant laxative	n/a	n/a	310.545(a)(12)(iv)(C)
Aloe vera [see aloe]					
====	Gingivitis/plaque	Antiplaque/gingivitis	n/a	IIIE	Pending
Aloe vera stabilized [see aloe]					
====	====	====	====	====	====
Aloes [see aloe]					
====	====	====	====	====	====
Aloin					
Laxative	Laxative	Stimulant laxative	IIISE	IIISE	310.545(a)(12)(iv)(A)
Alum (powdered alum) [see alum, ammonium/alum, potassium]					
====	====	====	====	====	====
Alum [see alum, ammonium/alum, potassium]					
====	====	====	====	====	====
Alum ammonium [see alum, ammonium]					
====	====	====	====	====	====
Alum, ammonium					
Contraceptive/vaginal	Vaginal	Astringent	IIIE	Withdraw	n/a
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Oral cavity	Astringent	Astringent	I	Defer	n/a
Oral cavity	Oral health care	Astringent	I	I	Pending
Alum, potassium					
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(ii)
Antiperspirant	Antiperspirant	Antiperspirant	IIISE	IIISE	310.545(a)(4)
Contraceptive/vaginal	Vaginal	Astringent	IIIE	Withdraw	n/a
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(18)(ii)
Oral cavity	Oral health care	Astringent	I	I	Pending
Aluminum acetate					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Astringent	I	I	347.12(a)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Astringent	I	I	347.10(a)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	Pending
Aluminum aspirin [see aspirin, aluminum]					
====	====	====	====	====	====
Aluminum bromohydrate					
Antiperspirant	Antiperspirant	Antiperspirant	IISE	IISE	310.545(a)(4)
Aluminum carbonate (gel) [see aluminum hydroxide]					
====	====	====	====	====	====
Aluminum carbonate gel (basic)					
Antacid	Antacid	Antacid	I	I	331.11(a)(1)
Aluminum carbonate gel [see basic aluminum carbonate gel]					
====	====	====	====	====	====

Review Panel	Report	Drug Category	ANPR	PR	FR
Aluminum chlorhydroxy complex					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Aluminum chloride (aerosol) (15% or less aqueous solution)					
Antiperspirant	Antiperspirant	Antiperspirant	IIIS	IIIS	310.545(a)(4)
Aluminum chloride (alcoholic solutions)					
Antiperspirant	Antiperspirant	Antiperspirant	IIS	IIS	310.545(a) (4)
Aluminum chloride (nonaerosol) (15% or less aqueous solution)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(a)
Aluminum chloride hexahydrate					
Miscellaneous external	External analgesic	Astringent	n/a	IIIE	Pending
Aluminum chlorohydrate (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIIS	I	350.10(b)
Aluminum chlorohydrate (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(b)
Aluminum chlorohydrex					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Aluminum chlorohydrex polyethylene glycol (aerosol)					
Antiperspirant t	Antiperspiran	Antiperspirant	IIIS	I	350.10(c)
Aluminum chlorohydrex polyethylene glycol (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(c)
Aluminum chlorohydrex polyethylene glycol complex [see name with "complex"]					
====	====	====	====	====	====
Aluminum chlorohydrex polyplene glycol (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIIS	I	350.10(d)
Aluminum chlorohydrex polyplene glycol (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(d)
Aluminum dichlorohydrate					
Antiperspirant	Antiperspirant	Antiperspirant	IIIS	I	350.10(e)
Aluminum dichlorohydrate (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(e)
Aluminum dichlorohydrex polyethylene glycol (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIIS	I	350.10(f)
Aluminum dichlorohydrex polyethylene glycol (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(f)
Aluminum dichlorohydrex polyethylene glycol complex [see name with "complex"]					
====	====	====	====	====	====
Aluminum dichlorohydrex propylene glycol (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIIS	I	350.10(g)
Aluminum dichlorohydrex propylene glycol (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(g)
Aluminum dichlorohydrex propylene glycol complex [see name with "complex"]					
====	====	====	====	====	====
Aluminum dihydroxy allantoinate [see aldioxa]					
====	====	====	====	====	====
Aluminum hydroxide					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Antimicrobial II	Antifungal	Acne	IIE	IIE	310.545(a)(1)
Antacid	Antacid	Antacid	I	I	331.11(a)(2)
Laxative	Antidiarrheal	Antidiarrheal	IIIE	IIIE	310.545(a)(3)(i)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	310.545(a)(18)(iii)

Review Panel	Report	Drug Category	ANPR	PR	FR
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIIE	n/a	310.545(a)(8)(ii)
Miscellaneous internal	Overindulgence in alcohol/food	Overindulgence remedies (hangover)	I	I	Pending
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(b)
Aluminum hydroxide (gel) [see aluminum hydroxide gel]					
====	====	====	====	====	====
Aluminum hydroxide gel					
====	Skin protectant	Poison ivy/oak/sumac	n/a	I	347.10(b)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(1)
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(1)
Internal analgesic	Internal analgesic	Corrective	I	n/a	n/a
Miscellaneous internal	Overindulgence in alcohol/food	Overindulgence remedies (hangover)	I	I	Pending
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(b)
Aluminum hydroxide sucrose powder hydrated					
Antacid	Antacid	Antacid	I	I	331.11(a)(2)
Aluminum hydroxide-hexitol, stabilized polymer					
Antacid	Antacid	Antacid	I	I	331.11(a)(2)
Aluminum hydroxide-magnesium carbonate, co-dried gel					
Antacid	Antacid	Antacid	I	I	331.11(a)(2)
Aluminum hydroxide-magnesium trisilicate, co-dried gel					
Antacid	Antacid	Antacid	I	I	331.11(a)(2)
Aluminum phosphate (gel) [see aluminum phosphate gel]					
====	====	====	====	====	====
Aluminum phosphate gel					
Antacid	Antacid	Antacid	I	I	331.11(i)(1)
Miscellaneous internal	Hypophosphatemia/hyperphosphatemia	Hypophosphatemia	IIS	IIS	310.541(a)
Aluminum phosphate gel (when used as part of antacid combination)					
Antacid	Antacid	Antacid	I	I	331.11(a)(4)
Aluminum sesquichlorohydrate (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIIS	I	350.10(h)
Aluminum sesquichlorohydrate (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(h)
Aluminum sesquichlorohydrate propylene glycol (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(j)
Aluminum sesquichlorohydrate propylene glycol complex [see name without "complex"]					
====	====	====	====	====	====
Aluminum sesquichlorohydrate poylethylene glycol (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIIS	I	350.10(i)
Aluminum sesquichlorohydrate poylethylene glycol (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(i)
Aluminum sulfate					
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(ii)
Antiperspirant	Antiperspirant	Antiperspirant	IIISE	IIISE	310.545(a)(4)
Miscellaneous external	External analgesic	Astringent	IIIE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IIIE	I	347.12(b)
Aluminum sulfate, buffered (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIIS	IIIS	310.545(a)(4)(ii)
Aluminum sulfate, buffered (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	310.545(a)(4)(ii)
Aluminum zirconium octachlorohydrate (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIS	IIS	310.502(a)(2)

Review Panel	Report	Drug Category	ANPR	PR	FR
Aluminum zirconium octachlorohydrate (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(k)
Aluminum zirconium octachlorohydrex glycine (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIS	IIS	310.502(a)(2)
Aluminum zirconium octachlorohydrex glycine (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(l)
Aluminum zirconium octachlorohydrex glycine complex [see name without "complex"]					
====	====	====	====	====	====
Aluminum zirconium pentachlorohydrate (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIS	IIS	350.10(m)
Aluminum zirconium pentachlorohydrate (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(m)
Aluminum zirconium pentachlorohydrex glycine (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIS	IIS	310.502(a)(2)
Aluminum zirconium pentachlorohydrex glycine (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(m)
Aluminum zirconium pentachlorohydrex glycine complex [see name without "complex"]					
====	====	====	====	====	====
Aluminum zirconium tetrachlorohydrate (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIS	IIS	310.502(a)(2)
Aluminum zirconium tetrachlorohydrate (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(o)
Aluminum zirconium tetrachlorohydrex glycine (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIS	IIS	310.502(a)(2)
Aluminum zirconium tetrachlorohydrex glycine (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(p)
Aluminum zirconium tetrachlorohydrex glycine complex [see name without "complex"]					
====	====	====	====	====	====
Aluminum zirconium trichlorohydrate (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIS	IIS	310.502(a)(2)
Aluminum zirconium trichlorohydrate (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(q)
Aluminum zirconium trichlorohydrex glycine (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIS	IIS	310.502(a)(2)
Aluminum zirconium trichlorohydrex glycine (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	I	I	350.10(r)
Aluminum zirconium trichlorohydrex glycine complex [see name without "complex"]					
====	====	====	====	====	====
Aluminum sesquichlorohydrate propylene glycol (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIIS	I	350.10(r)
Aminacrine hydrochloride					
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Amiloxate					
n/a	TEA	Sunscreen	n/a		
Amino acids					
Miscellaneous external	Hair growth/loss	Hair grower	IISE	IIE	310.527(a)
Aminoacetic acid [see glycine]					
====	====	====	====	====	====

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Aminoacridine hydrochloride [see aminacrine hydrochloride]					
====	====	====	====	====	====
Aminobenzoic acid					
Internal analgesic	Internal analgesic	Analgesic adjuvant	IISE	IISE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antipyretic adjuvant	IISE	IISE	310.545(a) (23)(i)
Internal analgesic	Internal analgesic	Antirheumatic adjuvant	IISE	n/a	310.545(a) (23)(i)
Miscellaneous external	Hair growth/loss	Hair grower	n/a	IIE	310.527(a)
Aminobenzoic acid (PABA)					
Topical analgesic	Sunscreen	Sunscreen	I	I	352.10(b)
Aminophylline					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	I	IIS	310.545(a)(6)(iv)(A)
Ammonia					
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	Pending
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	Pending
Ammonia solution, strong					
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)(A)
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)
Topical analgesic	External analgesic	Counterirritant	I	I	Pending
Topical analgesic	External analgesic	Fever blister (topical)	n/a	IISE	310.545(a)(10)(v)
Ammonium alum [see alum, ammonium]					
====	====	====	====	====	====
Ammonium bromide					
Sedative	Daytime sedative	Sedative	IISE	IISE	310.519(a)
Sedative	Nighttime sleep aid	Sleep aid	IISE	IISE	[54 FR 6826]
Ammonium carbonate					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	Pending
Ammonium chloride					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Miscellaneous internal	Menstrual/diuretic	Diuretic	I	I	Pending
Oral cavity	Oral health care	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Sedative	Stimulant	Stimulant	IIE	IIE	[39 FR 6104]
Ammonium hydroxide					
Miscellaneous external	External analgesic	Insect bite/sting	IIIE	IIIE	310.545(a)(18)(v)(A)
Miscellaneous external	Skin protectant	Insect bite/sting	IIIE	IIISE	310.545(a)(18)(v)(A)
Amyl para-dimethylaminobenzoate [see padimate A]					
====	====	====	====	====	====
Amylase					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(8)(ii)
Amyltricresols, secondary					
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(ii)
Oral cavity	Oral health care	Antimicrobial	IIISE	IIISE	Pending
Amylum [see starch]					
====	====	====	====	====	====
Amyltricresol, secondary [see amyltricresols, secondary]					
====	====	====	====	====	====
Anion and cation exchange resins buffered					
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	IIIE	IIIE	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	IIIE	IIIE	310.545(a)(10)(vii)(A)
Anise					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	n/a	n/a	310.528(a)
Anise oil					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Anise seed					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Antimony potassium tartrate					
Cough/cold	Cough/cold (expectorant)	Expectorant	IISE	IISE	310.545(a)(6)(iii)

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Antipyrine					
Internal analgesic	Internal analgesic	Analgesic	IIISE	IIISE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antipyretic	IIISE	IIISE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antirheumatic	IIISE	not OTC	310.545(a)(23)(i)
Oral cavity	Oral health care	Analgesic/anesthetic	IISE	IISE	310.545(a)(14)
Ophthalmic	Ophthalmic	Analgesic/anesthetic	IIS	IIS	310.545(a)(21)(i)
Topical analgesic	Otic	Analgesic/anesthetic	IISE	IISE	[51 FR 28660]
Aqua ammonia [see ammonium solution, strong]					
====	====	====	====	====	====
Aqueous coconut oil soap [see coconut oil soap, aqueous]					
====	====	====	====	====	====
Arginine					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Aromatic oils					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	Pending
Aromatic powder					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Aromatics					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Asafetida					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Asclepias tuberosa					
Miscellaneous internal	Menstrual/diuretic	Dysmenorrhea	IISE	IISE	310.545(a)(24)(i)
Ascorbic acid					
Miscellaneous external	Hair growth/loss	Hair grower	IIIE	IIIE	310.527(a)
Miscellaneous external	Wart remover	Wart remover	IIIE	IIIE	[55 FR 33254]
Miscellaneous external	Corn/callus remover	Corn/callus remover	IISE	IISE	[55 FR 33261]
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Asparagus					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Aspergillus oryzae enzymes (except lactase enzyme from aspergillus oryzae)					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Aspirin					
====	External analgesic	Fever blister (topical)	n/a	IIIE	310.545(a)(10)(v)
====	External analgesic	Poison ivy/oak/sumac	n/a	IIIE	310.545(a)(10)(vii)
Internal analgesic	Internal analgesic	Analgesic	I	I	Pending
Internal analgesic	Internal analgesic	Antipyretic	I	I	Pending
Internal analgesic	Internal analgesic	Antirheumatic	I	not OTC	n/a
Miscellaneous internal	Menstrual/diuretic	Analgesic	I	I	Pending
Miscellaneous internal	Overindulgence in alcohol/food	Overindulgence remedies (hangover)	I	I	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	I	IIIE	Pending
Sedative	Daytime sedative	Sedative	IIE	IISE	310.519(a)
Sedative	Nighttime sleep aid	Sleep aid	IIE	IIE	[54 FR 6826]
Topical analgesic	External analgesic	Analgesic/anesthetic	IIIE	IIIE	310.545(a)(10)(i)
Aspirin, aluminum					
Internal analgesic	Internal analgesic	Analgesic	n/a	IISE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antipyretic	IIIE	IIIE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antirheumatic	IIIE	Not OTC	310.545(a)(23)(i)
Aspirin, calcium					
Internal analgesic	Internal analgesic	Analgesic	I	I	Pending
Internal analgesic	Internal analgesic	Antipyretic	I	I	Pending
Internal analgesic	Internal analgesic	Antirheumatic	I	Not OTC	n/a
Miscellaneous internal	Menstrual/diuretic	Analgesic	I	I	Pending

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Atropine					
====	Menstrual/diuretic	Menstrual	n/a	n/a	310.545(a)(24)(ii)
====	Internal analgesic	Analgesic	n/a	n/a	310.545(a)(23)(ii)
Hemorrhoidal	Anorectal	Anticholinergic (external)	IISE	IISE	310.545(a)(26)(i)
Hemorrhoidal	Anorectal	Anticholinergic (intrarectal)	IISE	IISE	310.545(a)(26)(i)
Atropine sulfate					
Cough/cold	Cough/cold (anticholinergic)	Anticholinergic	IIIE	IIIE	310.533(a)
Laxative	Antidiarrheal	Antidiarrheal	IIISE	IIISE	310.545(a)(3)(i)
Attapulgite, activated					
Laxative	Antidiarrheal	Antidiarrheal	IIIE	I	310.545(a)(3)(ii)
Avobenzone					
====	n/a	Sunscreen	n/a	1	352.10(a)
Bacillus acidophilus					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Bacitracin					
Antimicrobial II	Antibiotic	First aid antibiotic	n/a	I	333.110(a)
Antimicrobial II	Antibiotic	Skin wound antibiotic	IIIE	Defer	n/a
Bacitracin zinc					
Antimicrobial II	Antibiotic	First aid antibiotic	n/a	I	333.110(b)
Balsam Peru [see Peruvian balsam]					
====	====	====	====	====	====
Balsam Peru oil [see Peruvian balsam oil]					
====	====	====	====	====	====
Barosma					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Basic aluminum carbonate gel					
Miscellaneous internal	Hypophosphatemia/ hyperphosphatemia	Hyperphosphatemia	IIS	IIS	310.541(a)
Basic fuchsin					
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(ii)
Bean					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Bearberry					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Bearberry (extract of uva ursi)					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Bearberry fluidextract (extract of bearberry)					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Beeswax					
====	Insect bite/sting	Insect bite/sting	n/a	n/a	310.545(a)(18)(v)(B)
====	Poison ivy/oak/sumac	Poison ivy/oak/ sumac	n/a	n/a	310.545(a)(18)(vi)(B)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	310.545(a)(18)(i)(B)
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	Pending
Belladonna alkaloids					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator (inhalation)	IISE	IISE	310.545(a)(6)(iv)(A)
Cough/cold	Cough/cold (anticholinergic)	Anticholinergic	IIIE	IIIE	310.533(a)
Miscellaneous external	Corn/callus remover	Corn/callus remover	IISE	IISE	[55 FR 33261]
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Belladonna alkaloids (inhalation) atropa belladonna/datura stramonium					
Cough/cold	Cough/cold (anticholinergic)	Anticholinergic	IISE	IISE	310.533(a)
Belladonna extract					
Hemorrhoidal	Anorectal	Anticholinergic (intrarectal)	IISE	IISE	310.545(a)(26)(i)
Hemorrhoidal	Anorectal	Anticholinergic (external)	IISE	IISE	310.545(a)(26)(i)

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Belladonna leaves, powdered extract					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Bemotrizinol					
n/a	TEA	Sunscreen	n/a		
Benzalkonium chloride					
Antimicrobial I	Antimicrobial	Antimicrobial soap	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	First aid antiseptic	n/a	I	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	I	I	Pending
Antimicrobial I	Antimicrobial	Skin wound protectant	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIISE	IIISE	Pending
Contraceptive/vaginal	Vaginal	Minor irritations	IIISE	Withdraw	n/a
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	IIISE	Pending
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	IIIE	IIIE	310.545(a)(7)
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	Pending
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)(A)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Benzethonium chloride					
Antimicrobial I	Antimicrobial	First aid antiseptic	n/a	I	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	I	I	Pending
Antimicrobial I	Antimicrobial	Skin wound protectant	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IISE	IISE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IIIE	IIIE	Pending
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(ii)
Miscellaneous external	Antifungal	Diaper rash	Defer	IISE	310.545(a)(22)(i)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/cradle cap	IIIE	IIIE	310.545(a)(7)
Miscellaneous external	External analgesic	Astringent	IISE	n/a	310.545(a)(18)(ii)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)(A)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Oral cavity	Oral health care	Antimicrobial	IIISE	IIISE	Pending
Benzocaine					
Antimicrobial II	Acne	Acne	IISE	IISE	310.545(a)(1)
Contraceptive/vaginal	Vaginal	Minor irritations	IIIE	Withdraw	n/a
Dental	Relief of oral discomfort	Oral mucosal analgesic	I	I	Pending
Dental	Relief of oral discomfort	Toothache relief	IIIE	IIIE	Pending
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIIE	IIIE	[55 FR 1779]
Hemorrhoidal	Anorectal	Anesthetic (external)	I	I	346.10(a)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Boil treatment	Boil treatment	IISE	IIISE	310.531(a)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Psoriasis	IIE	IIE	[56 FR 63567]
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	IISE	310.545(a)(10)(iv)

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Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Miscellaneous external	External analgesic	Insect bite/sting	n/a	IIIE	Pending
Miscellaneous external	Male genital desensitizer	Male genital desensitizer	I	I	348.10(a)(1)
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	I	Pending
Miscellaneous external	External analgesic	Poison/ivy/oak/sumac	Defer	IIIE	IISE (0.5–1.25%)
Miscellaneous external	Pediculicide	Pediculicide	IISE	IISE	310.545(a)(25)(i)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	DEF	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	n/a	310.545(a)(10)(vii)
Miscellaneous external	Wart remover	Wart remover	IISE	IISE	[55 FR 33254]
Miscellaneous internal	Weight control	Anorectic	I	IISE	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	I	I	Pending
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Topical analgesic	Otic	Analgesic/anesthetic	IISE	IISE	[51 FR 28660]
Topical analgesic	External analgesic	Poison ivy/oak/ sumac	IIIE	n/a	310.545(a)(10)(vii)
Benzoic acid					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(ii)
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	Hair growth/loss	Hair grower	IIE	IIE	310.527(a)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	Pending
Benzoin tincture, compound					
Cough/cold	Cough/cold (expectorant)	Expectorant (topical/inhalant)	IIIE	IIIE	310.545(a)(6)(iii)
Dental	Relief of oral discomfort	Oral mucosal protectant	I	I	Pending
Benzoin, tincture					
Cough/cold	Cough/cold (expectorant)	Expectorant	n/a	n/a	310.545(a)(6)(iii)
Benzonatate					
Cough/cold	Cough/cold (antitussive)	Antitussive	n/a	I	310.533(a)
Benzoxiquine					
Antimicrobial II	Antifungal	Antifungal	IISE	IISE	310.545(a)(22)(ii)
Benzoyl peroxide					
Antimicrobial II	Acne	Acne	I	I	Pending
Benzyl alcohol					
Dental	Relief of oral discomfort	Toothache relief	IIISE	IIISE	Pending
Dental	Relief of oral discomfort	Oral mucosal analgesic	IIISE	I	Pending
Hemorrhoidal	Anorectal	Anesthetic (external)	IIIE	I	346.10(b)
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIIE	IIIE	[55 FR 1779]
Miscellaneous external	Alcohols (topical)	Antiseptic	IIE	Defer	n/a
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Miscellaneous external	Male genital desensitizer	Male genital desensitizer	IISE	IISE	310.545(a)(10)(iii)
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	I	Pending
Miscellaneous external	Pediculicide	Pediculicide	IISE	IISE	310.545(a)(25)(i)
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)(A)
Oral cavity	Oral health care	Analgesic/anesthetic	I	I	Pending
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Benzyl benzoate					
Miscellaneous external	Pediculicide	Pediculicide	IISE	IISE	310.545(a)(25)(i)
Betaine hydrochloride					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Stomach acidifier	Stomach acidifier	IIE	IIE	310.540(a)
Bicarbonate					
Antacid	Antacid	Antacid	n/a	n/a	331.11(b)

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Bicarbonate of soda [see sodium bicarbonate]					
====	====	====	====	====	====
Bile salts/acids					
Laxative	Laxative	Stimulant laxative	IIISE	IIISE	310.545(a)(12)(iv)(A)
Biotin					
Miscellaneous external	Hair growth/loss	Hair grower	n/a	IISE	310.527(a)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Bisacodyl					
Laxative	Laxative	Stimulant laxative	I	I/IIIS	Pending
Bismuth aluminate					
Antacid	Antacid	Antacid	I	I	331.11(c)(1)
Bismuth carbonate					
Antacid	Antacid	Antacid	I	I	331.11(c)(2)
Bismuth oxide					
Hemorrhoidal	Anorectal	Protectant (external)	IIIE	IIIE	310.545(a)(26)(viii)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	IIIE	IIIE	310.545(a)(26)(viii)
Bismuth sodium tartrate					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIISE	310.545(a)(10)(v)
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	Defer	Pending
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IISE	IISE	310.545(a)(8)(i)
Bismuth subcarbonate					
Antacid	Antacid	Antacid	I	I	331.11(c)(3)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	IIIE	IIIE	310.545(a)(26)(viii)
Hemorrhoidal	Anorectal	Protectant (external)	IIIE	IIIE	310.545(a)(26)(viii)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Bismuth subgallate					
Antacid	Antacid	Antacid	I	I	331.11(c)(4)
Hemorrhoidal	Anorectal	Protectant (external)	IIIE	IIIE	310.545(a)(26)(viii)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	IIIE	IIIE	310.545(a)(26)(viii)
Miscellaneous internal	Deodorants for internal use	Internal deodorant	IIIE	I	357.810(a)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Bismuth subnitrate					
====	Insect bite/sting	Insect bite/sting	n/a	n/a	310.545(a)(18)(v)(B)
====	Poison ivy/oak/sumac	Poison ivy/oak/sumac	n/a	n/a	310.545(a)(18)(vi)(B)
====	Skin protectant	Fever blister (topical)	n/a	IISE	310.545(a)(10)(iv)
====	Skin protectant	Poison ivy/oak/sumac	n/a	IISE	310.545(a)(10)(vii)(A)
Antacid	Antacid	Antacid	I	I	331.11(c)(5)
Hemorrhoidal	Anorectal	Protectant (external)	IIS	IIS	310.545(a)(26)(viii)
Laxative	Antidiarrheal	Antidiarrheal	IIISE	IIISE	Pending
Miscellaneous external	Anorectal	Protectant (intrarectal)	IIS	IIS	310.545(a)(26)(viii)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IISE	Pending
Topical analgesic	Skin protectant	Skin protectant	IISE	IISE	Pending
Bismuth subsalicylate					
Laxative	Antidiarrheal	Antidiarrheal	IIIE	IIIE	335.10(a)
Laxative	Antiemetic	Antiemetic	IIIE	IIIE	Defer (overindulgence)
Miscellaneous internal	Overindulgence in alcohol/food	Upset stomach	I	I	Pending
Bisoctrizole					
n/a	TEA	Sunscreen	n/a		
Bithionol					
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Black radish powder					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Blessed thistle (cnicus benedictus)					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Menstrual/diuretic	Menstrual	n/a	IISE	310.545(a)(24)(i)

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Bone marrow, red					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Borax [see sodium borate]					
====	====	====	====	====	====
Boric acid					
====	Insect bite/sting	Insect bite/sting	n/a	n/a	310.545(a)(18)(v)(B)
====	Poison ivy/oak/sumac	Poison ivy/oak/sumac	n/a	n/a	310.545(a)(18)(vi)(B)
====	Skin protectant	Fever blister (topical)	n/a	IISE	310.545(a)(18)(iv)
====	Skin protectant	Poison ivy/oak/sumac	n/a	IISE	310.545(a)(10)(vii)(A)
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(ii)
Contraceptive/vaginal	Vaginal	Astringent	IIISE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Alters vaginal pH	IIISE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Lowers surface tension mucolytic effects	IIISE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Minor irritations	IIISE	Withdraw	n/a
Hemorrhoidal	Anorectal	Antiseptic (external)	IISE	IISE	310.545(a)(26)(ii)
Hemorrhoidal	Anorectal	Antiseptic (intrarectal)	IISE	IISE	310.545(a)(26)(ii)
Miscellaneous external	Antifungal	Diaper rash	Defer	IISE	310.545(a)(22)(ii)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	IISE	Pending
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis	IISE	IISE	310.545(a)(7)
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIS	Pending
Oral cavity	Oral health care	Antimicrobial	IISE	IISE	Pending
Ophthalmic	Ophthalmic	Anti-infective	IIIE	IIE	310.545(a)(21)(ii)
Topical analgesic	Skin protectant	Skin protectant	IISE	IISE	310.545(a)(18)(i)(B)
Bornelone					
Topical analgesic	Sunscreen	Sunscreen	IIIE	IIIE	[64 FR 27682]
Bornyl acetate					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical)	IIIE	IIIE	310.545(a)(6)(ii)(B)
Boroglycerin					
Contraceptive/vaginal	Vaginal	Minor irritations	IIISE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Alters vaginal pH	IIISE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Astringent	IIISE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Lowers surface tension mucolytic effects	IIISE	Withdraw	n/a
Hemorrhoidal	Anorectal	Antiseptic (external)	IISE	IISE	310.545(a)(26)(ii)
Hemorrhoidal	Anorectal	Antiseptic (intrarectal)	IISE	IISE	310.545(a)(26)(ii)
Oral cavity	Oral health care	Antimicrobial	IISE	IISE	Pending
Boroglycerin glycerite [see boroglycerin]					
====	====	====	====	====	====
Bran					
Laxative	Laxative	Bulk laxative	I	I	Pending
Bran, dietary [see bran]					
====	====	====	====	====	====
Bran, tablets [see bran]					
====	====	====	====	====	====
Bromopheniramine maleate					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	I	I	341.12(a)
Buchu					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Buchu powdered extract (extract of buchu)					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Buchu, extract					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Buckthorn					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Buffered mixture anion/cation exchange resin [see anion/cation exchange resins]					
====	====	====	====	====	====

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Butacaine sulfate					
Dental	Relief of oral discomfort	Oral mucosal analgesic	I	I	Pending
Dental	Relief of oral discomfort	Toothache relief	IIISE	IIISE	Pending
Butamben picrate					
====	External analgesic	Fever blister (topical)	n/a	I	Pending
====	External analgesic	Poison ivy/oak/sumac	n/a	I	Pending
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Butylated hydroxyanisole					
====	External analgesic	Fever blister (topical)	n/a	n/a	Pending
====	Skin protectant	Fever blister (topical)	n/a	n/a	Pending
Caffeine					
Cough/cold	Cough/cold (miscellaneous)	Corrective	IIIE	IIIE	Pending
Internal analgesic	Internal analgesic	Analgesic adjuvant	IIIE	IIIE	Pending
Internal analgesic	Internal analgesic	Antipyretic adjuvant	IIIE	IIIE	Pending
Internal analgesic	Internal analgesic	Antirheumatic adjuvant	IIIE	n/a	Pending
Miscellaneous internal	Menstrual/diuretic	Analgesic adjuvant	IIIE	IIIE	Pending
Miscellaneous internal	Menstrual/diuretic	Diuretic	I	I	Pending
Miscellaneous internal	Overindulgence in alcohol/food	Overindulgence remedies (hangover)	I	I	Pending
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Sedative	Stimulant	Stimulant	I	I	340.10
Calamine					
Hemorrhoidal	Anorectal	Astringent (external)	I	I	346.18(a)
Hemorrhoidal	Anorectal	Astringent (intrarectal)	I	I	346.18(a)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(b)(1)
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(b)(1)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(ii)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Skin protectant	I	I	347.10(c)
Miscellaneous external	Skin protectant	Diaper rash	Defer	I	Pending
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	I	347.10(c)
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(c)
Calamine (in combination only)					
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(b)(1)
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(b)(1)
Calcium					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Calcium acetate					
====	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Calcium carbaspirin [see carbaspirin calcium]					
====	====	====	====	====	====
Calcium carbonate					
Antacid	Antacid	Antacid	I	I	331.11(d)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIIE	IIIE	310.545(a)(8)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Calcium carbonate, precipitated					
Laxative	Antidiarrheal	Antidiarrheal	IIIE	IIIE	310.545(a)(3)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Calcium casinate					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)

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Calcium gluconate					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Calcium hydroxide					
Laxative	Antidiarrheal	Antidiarrheal	IIIE	IIIE	310.545(a)(3)(ii)
Calcium iodide, anhydrous					
Cough/cold	Cough/cold (expectorant)	Expectorant	IISE	IISE	310.545(a)(6)(iii)
Calcium lactate					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Calcium pantothenate					
Laxative	Laxative	Stimulant laxative	IIIE	IIIE	310.545(a)(12)(iv)(A)
Miscellaneous external	Wart remover	Wart remover	IIIE	IIIE	[55 FR 33254]
Miscellaneous internal	Menstrual/diuretic	Premenstrual/menstrual period	n/a	IISE	310.545(a)(24)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Calcium phosphate					
Antacid	Antacid	Antacid	I	I	331.11(d)
Calcium phosphate, dibasic					
Dental	Anticaries	Anticavity agent	IIE	n/a	[60 FR 52504]
Internal analgesic	Internal analgesic	Corrective	I	n/a	n/a
Calcium phosphate, tribasic					
Antacid	Antacid	Antacid	I	I	331.11(d)
Calcium polysulfide					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Calcium propionate					
Contraceptive/vaginal	Vaginal	Minor irritations	I	Withdraw	n/a
Calcium salicylate					
Internal analgesic	Internal analgesic	Analgesic	n/a	IISE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antirheumatic	n/a	Not OTC	310.545(a)(23)(i)
Calcium salt (mono or dibasic)					
Antacid	Antacid	Antacid	n/a	n/a	331.11(i)(2)
Calcium silicate					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	Pending
Calcium sucrose phosphate					
Dental	Anticaries	Anticavity agent	IIE	n/a	310.545(a)(2)(ii)
Calcium thiosulfate					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Calcium undecylenate					
Antimicrobial II	Antifungal	Antifungal	I	I	333.210(f)
Miscellaneous external	Antifungal	Diaper rash	Defer	IISE	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	IIISE	Pending
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/psoriasis	IIISE	IIISE	310.545(a)(7)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Calomel					
Laxative	Laxative	Stimulant laxative	IIS	IIS	310.545(a)(12)(iv)(A)
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Calomel (mercurous chloride)					
Miscellaneous external	Antimicrobial	First aid antiseptic	n/a	IIIE	310.545(a)(27)(i)
Calomel [see mercuric chloride]					
====	====	====	====	====	====
Camphor					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Antimicrobial II	Antifungal	Antifungal	IIE	IIE	310.545(a)(22)(ii)
Cough/cold	Cold/cough (antitussive)	Antitussive (topical/inhalant)	IIIE	I	341.14(b)(1)
Cough/cold	Cough/cold (expectorant)	Expectorant (lozenge)	IIIE	IIIE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (expectorant)	Expectorant (topical/inhalant)	IIIE	IIIE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	IIIE	IIIE	[59 FR 43408]
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (lozenge)	IIIE	IIIE	310.545(a)(6)(ii)(A)

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Dental	Relief of oral discomfort	Oral mucosal analgesic	IISE	IISE	Pending
Hemorrhoidal	Anorectal	Analgesic (external)	n/a	I	346.16(a)
Miscellaneous external	Antifungal	Diaper rash	Defer	IISE	310.545(a)(22)(ii)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Boil treatment	Boil treatment	IISE	IIISE	310.531(a)
Miscellaneous external	External analgesic	Diaper rash	Defer	IISE	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Insect bite/sting	IISE	I	Pending
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	I	Pending
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	Defer	Pending
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)(A)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)(A)
Miscellaneous external	Wart remover	Wart remover	IISE	IISE	[55 FR 33254]
Miscellaneous external	External analgesic	External analgesic (less than 2.5%)	I	I	Pending
Miscellaneous external	External analgesic	External analgesic (greater than 2.5%)	IISE	IISE	Pending
Oral cavity	Oral health care	Antimicrobial	IISE	IISE	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	IISE	IISE	310.545(a)(14)
Topical analgesic	External analgesic	Counterirritant	I	I	Pending
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Topical analgesic	External analgesic	External analgesic	I	I	Pending
Topical analgesic	Sunscreen	Sunscreen	IISE	IISE	[64 FR 27682]
Topical analgesic	External analgesic	Antipyretic	n/a	I	Pending
Camphor (>3–11%)					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IISE	310.545(a)(10)(v)
Camphor (0.1–3%)					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Camphor (greater than 3–11%)					
Hemorrhoidal	Anorectal	Counterirritant (intrarectal)	IISE	IISE	310.545(a)(26)(iv)
Hemorrhoidal	Anorectal	Counterirritant (external)	IISE	IISE	310.545(a)(26)(iv)
Camphor gum					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Camphorated metacresol					
====	External analgesic	Fever blister (topical)	n/a	I	Pending
====	External analgesic	Poison ivy/oak/sumac	n/a	I	Pending
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(iv)
Miscellaneous external	Male genital desensitizer	Male genital desensitizer	n/a	IISE	310.545(a)(10)(iii)
Topical analgesic	External analgesic	Analgesic/anesthetic	IIISE	I	Pending
Camphorated oil					
Miscellaneous external	Camphorated oil	Counterirritant	IIS	n/a	310.502(a)(4)
Candelillia wax [see wax, candelilla]					
====	====	====	====	====	====
Candicidin					
Antimicrobial II	Antifungal	Anticandidial	IISE	IISE	310.545(a)(22)(ii)
Cantharides					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Capsaicin					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IISE	310.545(a)(10)(v)
Topical analgesic	External analgesic	Counterirritant	I	I	Pending
Capsicum					
Dental	Relief of oral discomfort	Counterirritant (external)	IIIE	IIIE	Pending
Dental	Relief of oral discomfort	Toothache relief	IISE	IISE	Pending
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IISE	310.545(a)(10)(v)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(8)(ii)
Topical analgesic	External analgesic	Counterirritant	I	I	Pending

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Capsicum oleoresin					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IISE	310.545(a)(10)(v)
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Topical analgesic	External analgesic	Counterirritant	I	I	Pending
Capsicum, fluid extract of					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Captan					
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	IIIE	IIIE	310.545(a)(7)
Caramiphen edisylate					
Cough/cold	Cold/cough (antitussive)	Antitussive	IIIE	IIIE	[52 FR 30054]
Carbamide peroxide					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	Defer	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	Defer	Pending
Oral cavity	Oral health care	Debriding agent	III	III	Pending
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	Pending
Carbamide peroxide (in anhydrous glycerin)					
Dental	Oral mucosal injury	Wound cleanser	I	I	Pending
Dental	Oral mucosal injury	Wound healing agent	IIIE	IIIE	310.534(a)
Carbamide peroxide 6.5% (in anhydrous glycerin)					
Topical analgesic	Otic	Ear wax softening agent	I	I	344.10
Carbaspirin calcium					
Internal analgesic	Internal analgesic	Antipyretic	I	I	Pending
Internal analgesic	Internal analgesic	Analgesic	I	I	Pending
Internal analgesic	Internal analgesic	Antirheumatic	I	Not OTC	n/a
Miscellaneous internal	Menstrual/diuretic	Analgesic	I	I	Pending
Carbetapentane citrate					
Cough/cold	Cold/cough (antitussive)	Antitussive	IIIE	IIIE	[52 FR 30054]
Carbon					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Carbon dioxide, released					
Laxative	Laxative	Laxative	I	I	Pending
Carboxymethylcellulose					
Antacid	Antacid	Antacid	IIIE	IIIE	[39 FR 19874]
Carboxymethylcellulose sodium					
Laxative	Antidiarrheal	Antidiarrheal	IIIE	IIIE	310.545(a)(3)(i)
Laxative	Laxative	Bulk laxative	I	I	Pending
Miscellaneous internal	Weight control	Anorectic	IIIE	IISE	310.545(a)(20)
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(a)(1)
Carnauba wax [see wax, carnauba]					
====	====	====	====	====	====
Carrageenan					
Miscellaneous internal	Weight control	Anorectic	IIIE	IISE	310.545(a)(20)
Carrageenan (degraded) [see carrageenan, degraded]					
====	====	====	====	====	====
Carrageenan (native) [see carrageenan, native]					
====	====	====	====	====	====
Carrageenan, degraded					
Laxative	Laxative	Bulk laxative	IIS	IIS	310.545(a)(12)(i)
Carrageenan, native					
Laxative	Laxative	Bulk laxative	IIIE	IIIE	310.545(a)(12)(i)
Casanthranol					
Laxative	Laxative	Stimulant laxative	I	I/IIIS	Pending
Cascara fluidextract aromatic [see cascara fluidextract, aromatic]					
====	====	====	====	====	====
Cascara fluidextract, aromatic					
Laxative	Laxative	Stimulant laxative	I	I/IIIS	310.545(a)(12)(iv)(C)
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Cascara sagrada					
Laxative	Laxative	Stimulant laxative	I	I/IIIS	310.545(a)(12)(iv)(C)

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Cascara sagrada bark [see cascara sagrada]					
====	====	====	====	====	====
Cascara sagrada extract					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Cascarasagrada extract					
Laxative	Laxative	Stimulant laxative	I	I/IIIS	310.545(a)(12)(iv)(C)
Cascarasagrada fluid extract					
Laxative	Laxative	Stimulant laxative	I	I/IIIS	310.545(a)(12)(iv)(C)
Casein					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	n/a
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	Withdraw	n/a
Castor oil					
Laxative	Laxative	Stimulant laxative	I	I	Pending
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Wart remover	Wart remover	IISE	IISE	[55 FR 33254]
Catechu, tincture					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Catnip					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Cedar leaf oil					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical)	IIIE	IIIE	310.545(a)(6)(ii)(B)
Cellulase					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIIE	IIIE	310.545(a)(8)(i)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIE	IIE	310.545(a)(8)(i)
Cellulose					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	n/a
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	n/a
Cellulose, microporous					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	Pending
Cetalkonium chloride					
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vii)(A)
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	Pending
Cetyl alcohol					
====	Insect bite/sting	Insect bite/sting	n/a	n/a	310.545(a)(18)(v)(B)
====	Poison ivy/oak/sumac	Poison ivy/oak/sumac	n/a	n/a	310.545(a)(18)(vi)(B)
====	Skin protectant	Skin protectant	n/a	n/a	310.545(a)(18)(i)(B)
Miscellaneous external	External analgesic	Fever blister (topical)	n/a	n/a	n/a
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	Pending
Cetylpyridinium chloride					
====	Antigingivitis/antiplaque	Antigingivitis/antiplaque	I	====	Pending
Oral cavity	Oral health care	Antimicrobial	IIISE	IIISE	Pending
Chamomile flowers					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Charcoal, activated					
Antacid	Antacid	Antacid	IIE	IIE	[39 FR 19873]
Laxative	Antidiarrheal	Antidiarrheal	IIIE	IIIE	310.545(a)(3)(ii)
Miscellaneous internal	Deodorants for internal use	Internal deodorant	IIIE	IIIE	[55 FR 19864]
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIIE	IIIE	310.545(a)(8)(iii)
Miscellaneous internal	Overindulgence in alcohol/food	Minimize hangover symptoms	IIIE	IIIE	[48 FR 32873]
Miscellaneous internal	Poison treatment	Poison absorbent	n/a	I	Pending
Miscellaneous internal	Acute toxic ingestion	Poison treatment	I	I	Pending
Charcoal, wood					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIIE	IIIE	310.545(a)(18)(ii)
Chlophedianol hydrochloride					
Cough/cold	Cold/cough (antitussive)	Antitussive	n/a	I	341.14(a)(1)

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Chloral hydrate					
====	External analgesic	Fever blister (topical)	n/a	IIE	310.545(a)(10)(v)
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	IIE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)(A)
Topical analgesic	External analgesic	Analgesic/anesthetic	IIE	IIE	310.545(a)(10)(i)
Topical analgesic	External analgesic	Counterirritant	n/a	n/a	310.545(a)(10)(ii)
Chlorcyclizine hydrochloride					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	n/a	I	341.12(b)
Chlorhydroxyquinoline [see cloxyquin]					
====	====	====	====	====	====
Chlorobutanol					
====	External analgesic	Fever blister (topical)	n/a	IIIE	310.545(a)(10)(v)
====	External analgesic	Poison ivy/oak/ sumac	n/a	IIIE	310.545(a)(10)(vii)
Miscellaneous external	Alcohols (topical)	Antiseptic	IIE	Defer	n/a
Miscellaneous external	Corn/callus remover	Corn/callus remover	IISE	IISE	[55 FR 33261]
Topical analgesic	External analgesic	Analgesic/anesthetic	IIIE	IIIE	310.545(a)(10)(i)
Chloroform					
Cough/cold	Cough/cold (expectorant)	Expectorant	IISE	IISE	310.545(a)(6)(iii)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Chlorophenothane					
Miscellaneous external	Pediculicide	Pediculicide	IISE	IISE	310.545(a)(25)(i)
Chlorophyll [see chlorophyllin copper complex]					
====	====	====	====	====	====
Chlorophyllin					
Dental	Relief of oral discomfort	Oral mucosal analgesic	n/a	IIISE	Pending
Chlorophyllin copper complex					
Dental	Oral mucosal injury	Wound healing agent	IIIE	IIIE	310.534(a)
Miscellaneous internal	Deodorants for internal use	Internal deodorant	IIIE	I	357.810(b)
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	Pending
Chlorophyllins, water-soluble [see chlorophyllin copper complex]					
====	====	====	====	====	====
Chlorothymol					
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(ii)
Chloroxlyneol					
Antimicrobial I	Antimicrobial	First aid antiseptic	n/a	IIIE	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin wound protectant	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IIIE	IIIE	Pending
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(iv)
Miscellaneous external	Antifungal	Diaper rash	Defer	IISE	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	IIISE	Pending
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis	IIISE	IIISE	310.545(a)(7)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Ingrown toenail	Ingrown toenail	IISE	IISE	310.538(a)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Chlorpheniramine maleate					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	I	I	341.12(c)
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)(A)

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Chlorprophenpyridamine maleate					
Miscellaneous internal	Menstrual/diuretic	Menstrual	n/a	IISE	310.545(a)(24)(i)
Chlortetracycline hydrochloride					
Antimicrobial II	Antibiotic	First aid antibiotic	n/a	I	333.110(c)
Antimicrobial II	Antibiotic	Skin wound antibiotic	IIE	Defer	n/a
Antimicrobial II	Antibiotic	Skin wound protectant	I	Defer	n/a
Chloxyquin					
Antimicrobial II	Acne	Acne	IISE	IISE	310.545(a)(1)
Cholecalciferol					
Hemorrhoidal	Anorectal	Wound healing agent (external)	IIIE	IIIE	310.545(a)(26)(x)
Hemorrhoidal	Anorectal	Wound healing agent (intrarectal)	IIIE	IIIE	310.545(a)(26)(x)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	Pending
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Cholesterol					
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Choline					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Choline salicylate					
Internal analgesic	Internal analgesic	Analgesic	I	I	Pending
Internal analgesic	Internal analgesic	Antipyretic	I	I	Pending
Internal analgesic	Internal analgesic	Antirheumatic	I	Not OTC	n/a
Miscellaneous internal	Menstrual/diuretic	Analgesic	I	I	Pending
Chondrus					
Miscellaneous internal	Weight control	Anorectic	IIIE	IISE	310.545(a)(20)
Cimicifuga racemosa					
Miscellaneous internal	Menstrual/diuretic	Dysmenorrhea	IISE	IISE	310.545(a)(24)(i)
Cinnamedrine hydrochloride					
Miscellaneous internal	Menstrual/diuretic	Smooth muscle relaxant	IIIE	IIIE	Pending
Cinnamon oil					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Cinnamon tincture					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Cinoxate					
Topical analgesic	Sunscreen	Sunscreen	I	I	352.10(c)
Citric acid					
Contraceptive/vaginal	Vaginal	Alters vaginal pH	IIIE	Withdraw	n/a
Dental	Relief of oral discomfort	Tooth desensitizer (in combination only)	IIIE	IIIE	Pending
Internal analgesic	Internal analgesic	Corrective	I	n/a	n/a
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIIE	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIIE	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Citric acid/salt					
Antacid	Antacid	Antacid	I	I	331.11(e)
Citrus pectin					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Climbazole					
n/a	TEA	Dandruff	n/a		
Clioquinol					
Antimicrobial II	Antifungal	Antifungal	I	I	333.210(a)
Cloflucarban					
Antimicrobial I	Antimicrobial	Skin antiseptic	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Skin wound protectant	IISE	IISE	Pending
Antimicrobial I	Antimicrobial	First aid antiseptic	IISE	IISE	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	IIIS	IIIS	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	IISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IISE	IISE	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IISE	IISE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IIISE	IIISE	Pending
Clotrimazole					
n/a	n/a	Antifungal	n/a	I	[67 FR 5942]

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Clove					
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IIE	IIE	310.544(d)
Clove oil					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Cloves, ground [see clove]					
====	====	====	====	====	====
Cnicus benedictus					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Coal tar					
Antimicrobial II	Acne	Acne	IISE	IISE	310.545(a)(1)
Antimicrobial II	Antifungal	Antifungal	IISE	IISE	310.545(a)(22)(ii)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Psoriasis	I	I	358.710(c)(1)
Coal tar (shampoo)					
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	I	I	358.710(a)(1)
Coal tar (nonshampoo)					
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Seborrheic dermatitis	IIIE	I	358.710(b)(1)
Cocoa butter					
====	Skin protectant	Diaper rash	Defer	IIISE	310.545(a)(18)(iii)
====	Skin protectant	Fever blister (topical)	n/a	I	Pending
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(2)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(2)
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(d)
Cocoa butter substitutes [see hard fat]					
====	====	====	====	====	====
Coconut oil soap, aqueous					
Miscellaneous external	Pediculicide	Pediculicide	IISE	IISE	310.545(a)(25)(i)
Cod liver oil					
====	Skin protectant	Skin protectant	n/a	n/a	347.10(e)
Cough/cold	Cold/cough (antitussive)	Antitussive	IIIE	IIIE	[52 FR 30054]
Hemorrhoidal	Anorectal	Wound healing agent (intrarectal)	IIISE	IIISE	310.545(a)(26)(x)
Hemorrhoidal	Anorectal	Wound healing agent (external)	IIISE	IIISE	310.545(a)(26)(x)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	I	Pending
Cod liver oil (in combination only)					
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(b)(2)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(b)(2)
Codeine					
====	Menstrual/diuretic	Menstrual	n/a	n/a	310.545(a)(24)(i)
Cough/cold	Cold/cough (antitussive)	Antitussive	I	I	341.14(a)(2)(i)
Internal analgesic	Internal analgesic	Analgesic	IISE	IISE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antipyretic	IISE	IISE	310.545(a)(23)(i)
Miscellaneous internal	Menstrual/diuretic	Analgesic	IIS	IISE	310.545(a)(24)(i)
Codeine phosphate					
Cough/cold	Cold/cough (antitussive)	Antitussive	I	I	341.14(a)(2)(ii)
Internal analgesic	Internal analgesic	Analgesic	IISE	n/a	310.545(a)(23)(i)
Codeine sulfate					
Cough/cold	Cold/cough (antitussive)	Antitussive	I	I	341.14(a)(2)(iii)
Internal analgesic	Internal analgesic	Analgesic	IISE	n/a	310.545(a)(23)(i)
Codeine, alkaloid [see codeine]					
====	====	====	====	====	====
Collinsonia extract					
Hemorrhoidal	Anorectal	Anorectal (external)	IISE	IISE	310.545(a)(26)(vii)
Hemorrhoidal	Anorectal	Anorectal (intrarectal)	IISE	IISE	310.545(a)(26)(vii)
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)

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Colloidal oatmeal					
====	Skin protectant	Skin protectant	n/a	n/a	347.10(f)
====	Skin protectant	Poison ivy/oak/sumac	n/a	I	347.10(f)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	IIE	IIE	310.545(a)(7)
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IIE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IISE	Pending
Colocynth					
Laxative	Laxative	Stimulant laxative	IIS	IIS	310.545(a)(12)(iv)(A)
Compound white pine syrup [see white pine syrup, compound]					
====	====	====	====	====	====
Copper					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Copper gluconate					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Copper oleate					
Miscellaneous external	Pediculicide	Pediculicide	IISE	IISE	310.545(a)(25)(i)
Copper undecylenate					
Antimicrobial II	Antifungal	Antifungal	I	I	333.210(f)
Coriander					
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IIE	IIE	310.544(d)
Coriander, ground [see coriander]					
====	====	====	====	====	====
Corn oil					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Corn oil, aqueous emulsion					
Miscellaneous internal	Cholecystokinetic	Cholecystokinetic	I	I	357.210(a)
Corn silk					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Corn silk, potassium extract					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Corn starch [see starch, corn]					
====	====	====	====	====	====
Corn syrup					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Couch grass					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Creosote					
Dental	Relief of oral discomfort	Toothache relief	IIIE	IIIE	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)(A)
Creosote, beechwood					
====	Skin protectant	Poison ivy/oak/sumac	n/a	IISE	310.545(a)(18)(vi)
Cough/cold	Cold/cough (antitussive)	Antitussive	IIIE	IIIE	[52 FR 30054]
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (oral)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical)	IIIE	IIIE	310.545(a)(6)(ii)(B)
Dental	Relief of oral discomfort	Toothache relief	IIISE	IIISE	Pending
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Cresol					
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(iv)
Dental	Relief of oral discomfort	Toothache relief	IIISE	IIISE	Pending
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Astringent	Antiseptic	IIE	Defer	n/a
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Oral cavity	Oral health care	Antimicrobial	IIS	IISE	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	IISE	IISE	310.545(a)(14)
Oral cavity	Relief of oral discomfort	Oral mucosal analgesic	IIISE	IIISE	Pending
Cresol saponated					
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Psoriasis	IIE	IIE	310.545(a)(7)

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Cupric sulfate					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Cyanocobalamin (vitamin B12)					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Cyclizine hydrochloride					
Laxative	Antiemetic	Antiemetic	I	I	336.10(a)
Cyclomethycaine sulfate					
====	External analgesic	Fever blister (topical)	n/a	IIIE	310.545(a)(10)(v)
====	External analgesic	Poison ivy/oak/ sumac	n/a	IIIE	310.545(a)(10)(vii)
Internal analgesic	External analgesic	Analgesic/anesthetic	IIIE	IIIE	310.545(a)(10)(i)
Cysteine hydrochloride					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	310.545(a)(18)(iii)
Cystine					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Danthron					
Laxative	Laxative	Stimulant laxative	I	IIS	310.545(a)(12)(iv)(B)
D-**Calcium pantothenate** [see calcium pantothenate]					
====	====	====	====	====	====
Dehydrocholic acid					
Laxative	Laxative	Stimulant laxative	I	I	Pending
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIE	IIE	310.545(a)(8)(i)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIE	IIE	310.545(a)(8)(i)
Denatonium benzoate					
Miscellaneous external	Nailbiting/thumbsucking	Nailbiting/thumbsucking deterrent	IIIE	IIIE	310.536(a)
Dequalinium chloride					
Oral cavity	Oral health care	Antimicrobial	IIISE	IIISE	Pending
Desoxyephedrine, L-[see levomethamphetamine]					
====	====	====	====	====	====
Dexbromopheniramine maleate					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	IIISE	I	341.12(d)
Cough/cold	Cough/cold (antihistamine)	Antihistamine	n/a	I	341.12(f)
Dexchlorpheniramine maleate					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	n/a	I	341.12(e)
Dexpanthenol					
====	External analgesic	Poison ivy/oak/ sumac	n/a	IIIE	310.545(a)(10)(vii)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Insect bite/sting	n/a	IIIE	Pending
Miscellaneous external	Hair growth/loss	Hair grower	n/a	IIE	310.527(a)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	Pending
Dextran 70					
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(b)
Dextromethorphan					
Cough/cold	Cold/cough (antitussive)	Antitussive	I	I	341.14(a)(3)
Dextromethorphan hydrobromide					
Cough/cold	Cough/cold (antitussive)	Antitussive	n/a	n/a	341.14(a)(4)
Dextrose					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Diastase					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Diastase malt					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Dibenzothiophene					
Antimicrobial II	Acne	Acne	IIS	IIS	310.545(a)(1)

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Dibucaine					
====	External analgesic	Poison ivy/oak/ sumac	n/a	I	Pending
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIISE	IIISE	[55 FR 1779]
Hemorrhoidal	Anorectal	Anesthetic (external)	IIIS	I	346.10(d)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	IISE	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	IIS	IIS	310.545(a)(14)
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Dibucaine hydrochloride					
====	External analgesic	Fever blister (topical)	n/a	I	Pending
====	External analgesic	Poison ivy/oak/ sumac	n/a	I	Pending
Hemorrhoidal	Anorectal	Anesthetic (external)	IIIS	I	346.10(c)
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIISE	IIISE	[55 FR 1779]
Oral cavity	Oral health care	Analgesic/anesthetic	IIS	IIS	310.545(a)(14)
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Dicalcium phosphate dihydrate [see calcium phosphate, dibasic]					
====	Gingivitis/plaque	Gingivitis/antiplaque	n/a	IIIE	Pending
Dichlorodiphenyl trichloroethane [see chorophenothane]					
====	====	====	====	====	====
Dichlorophen					
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(ii)
Miscellaneous external	Hair growth/loss	Hair grower	IISE	n/a	310.527(a)
Diethanolamine methoxycinnamate					
Topical analgesic	Sunscreen	Sunscreen	I	I	310.545(a)(29)
Diethanolamine *p*-methoxy-cinnamate [see diethanolamine methoxycinnamate]					
====	====	====	====	====	====
Diethylhexyl butamido triazone (Uvasorb HEB)					
n/a TEA	Sunscreen	n/a			
Digalloyltrioleate					
Topical analgesic	Sunscreen	Sunscreen	I	I	310.545(a)(29)
Dihydroxyaluminum aminoacetate					
Antacid	Antacid	Antacid	I	I	331.11(a)(3)
Dihydroxyaluminum aminoacetic acid					
Antacid	Antacid	Antacid	n/a	n/a	331.11(a)(3)
Internal analgesic	Internal analgesic	Corrective	I	n/a	n/a
Dihydroxyaluminum sodium carbonate					
Antacid	Antacid	Antacid	I	I	331.11(a)(5)
Internal analgesic	Internal analgesic	Corrective	I	n/a	n/a
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIIE	IIIE	310.545(a)(8)(i)
Dimenhydrinate					
Laxative	Antiemetic	Antiemetic	I	I	336.10(b)
Dimethicone					
====	Skin protectant	Diaper rash	n/a	I	Pending
====	Skin protectant	Fever blister (topical)	n/a	I	Pending
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(g)
Dimethisoquin hydrochloride					
====	External analgesic	Poison ivy/oak/ sumac	n/a	I	Pending
====	External analgesic	Fever blister (topical)	n/a	I	Pending
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Dioxybenzone					
Topical analgesic	Sunscreen	Sunscreen	I	I	352.10(e)
Diperodon					
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIISE	IIISE	310.545(a)(26)(vi)
Hemorrhoidal	Anorectal	Anesthetic (external)	IIE	IIIE	310.545(a)(26)(vi)

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Diperodon hydrochloride					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)(A)
Miscellaneous external	Corn/callus remover	Corn/callus remover	IISE	IISE	[55 FR 33261]
Diphenhydramine citrate					
Cough/cold	Cough/cold (antitussive)	Antitussive	n/a	n/a	341.14(a)(5)
Cough/cold	Cough/cold (antihistamine)	Antihistamine	n/a	n/a	341.12(f)
Sedative	Nighttime sleep aid	Sleep aid	n/a	n/a	338.10(b)
Diphenhydramine hydrochloride					
====	External analgesic	Fever blister (topical)	n/a	I	Pending
Cough/cold	Cough/cold (antitussive)	Antitussive	I	IIIE	341.14(a)(6)
Cough/cold	Cough/cold (antihistamine)	Antihistamine	I	I	341.12(g)
Laxative	Antiemetic	Antiemetic	IIIE	IIIE	336.10(c)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	I	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Sedative	Daytime sedative	Sedative	IISE	IISE	310.519(a)
Sedative	Nighttime sleep aid	Sleep aid	IIISE	IIISE	336.10(a)
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Diphenhydramine monocitrate [see diphenhydramine citrate]					
====	====	====	====	====	====
Dipropylene glycol salicylate					
Topical analgesic	Sunscreen	Sunscreen	IIISE	IIISE	[64 FR 27682]
DL-Methionine [see racemethionine]					
====	====	====	====	====	====
Docusate calcium					
Laxative	Laxative	Stool softener	I	I	Pending
Docusate potassium					
Laxative	Laxative	Stool softener	I	I	Pending
Docusate sodium					
Contraceptive/vaginal	Vaginal	Lowers surface tension mucolytic effects	I	Withdraw	n/a
Laxative	Laxative	Stool softener	I	I	Pending
Miscellaneous external	Pediculicide	Pediculicide	IISE	IISE	310.545(a)(25)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Dodecaethylene glycol monolaurate					
Contraceptive/vaginal	Contraceptive (vaginal)	Contraceptive	IIIE	Withdraw	310.545(a)(28)
Dodecaethyleneglycol monolaurate [see dodecaethylene glycol monolaurate]					
====	====	====	====	====	====
Dog grass					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Dog grass extract					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Domiphen bromide					
Oral cavity	Oral health care	Antimicrobial	IIISE	IIISE	Pending
Don qual					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Doxylamine succinate					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	I	I	341.12(h)
Sedative	Daytime sedative	Sedative	IISE	IISE	310.519(a)
Sedative	Nighttime sleep aid	Sleep aid	IIISE	IIISE	[54 FR 6826]
Duodenal substance					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IISE	IISE	310.545(a)(8)(i)
Dyclonine hydrochloride					
====	External analgesic	Fever blister (topical)	n/a	I	Pending
====	External analgesic	Poison ivy/oak/sumac	n/a	I	Pending
Hemorrhoidal	Anorectal	Anesthetic (external)	IIIE	I	346.10(e)
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIIE	IIIE	[55 FR 1779]
Oral cavity	Oral health care	Analgesic/anesthetic	I	I	Pending
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending

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E. coli vaccines					
Hemorrhoidal	Anorectal	Anorectal (External)	IISE	IISE	310.545(a)(26)(vii)
Hemorrhoidal	Anorectal	Anorectal (intrarectal)	IISE	IISE	310.545(a)(26)(vii)
Edetate disodium					
Contraceptive/vaginal	Vaginal	Minor irritations	IIISE	Withdraw	n/a
Dental	Relief of oral discomfort	Tooth desensitizer (in combination only)	IISE	IISE	Pending
Edetate sodium					
Contraceptive/vaginal	Vaginal	Minor irritations	IIISE	Withdraw	n/a
Elaterin resin					
Laxative	Laxative	Stimulant laxative	IIS	IIS	310.545(a)(12)(iv)(A)
Elecampane					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Elm bark					
Cough/cold	Cough/cold (antitussive)	Antitussive	IIIE	IIIE	[52 FR 30054]
Oral cavity	Oral health care	Demulcent	I	I	Pending
Endothermic hectorite [see hectorite]					
====	====	====	====	====	====
Ensulizole					
Topical analgesic	Sunscreen	Sunscreen	I	I	352.10(n)
Enzacamene					
n/a	TEA	Sunscreen	n/a		
Ephedrine					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	I	I	341.16(a)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	I	I	341.20(b)(1)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (oral)	IIIE	IIIE	310.545(a)(6)(ii)(B)
Ephedrine (any ingredient)					
====	Menstrual/diuretic	Menstrual	n/a	n/a	310.545(a)(24)(ii)
====	Internal analgesic	Analgesic	n/a	n/a	310.545(a)(23)(ii)
Ephedrine hydrochloride					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	I	I	341.16(b)
Miscellaneous external	Male genital desensitizer	Male genital desensitizer	IISE	IISE	310.545(a)(10)(iii)
Ophthalmic	Ophthalmic	Vasoconstrictor	I	I	349.18(a)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (oral)	IIIE	IIIE	310.545(a)(6)(ii)(B)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	I	I	341.20(b)(3)
Ephedrine sulfate					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	I	I	341.16(c)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	I	I	341.20(b)(4)
Hemorrhoidal	Anorectal	Vasoconstrictor (intrarectal)	I	I	346.12(a)
Hemorrhoidal	Anorectal	Vasoconstrictor (external)	I	I	346.10(a)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (oral)	IIIE	IIIE	310.545(a)(6)(ii)(B)
Epinephrine					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator (inhalation)	I	I	341.16(d)
Hemorrhoidal	Anorectal	Vasoconstrictor (external)	IIISE	I	346.10(b)
Hemorrhoidal	Anorectal	Vasoconstrictor (intrarectal)	IIISE	IIISE	346.10(b)
Epinephrine bitartrate					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator (inhalation)	I	I	341.16(e)
Epinephrine hydrochloride					
Hemorrhoidal	Anorectal	Vasoconstrictor (external)	I	I	346.10(c)
Hemorrhoidal	Anorectal	Vasoconstrictor (intrarectal)	IIE	IIE	346.10(c)
Epinephrine hydrochloride (racemic) [see epinephine hydrochloride]					
====	====	====	====	====	====
Epinephrine undecylenate					
Hemorrhoidal	Anorectal	Vasoconstrictor (external)	IIISE	IIISE	310.545(a)(26)(ix)
Hemorrhoidal	Anorectal	Vasoconstrictor (intrarectal)	IIE	IIE	310.545(a)(26)(ix)
Ergocalciferol					
Contraceptive/vaginal	Vaginal	Minor irritations	IIIE	Withdraw n/a	

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Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Ergot fluidextract					
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)(A)
Escalol 506 [see padimate A]					
Essential oils					
Miscellaneous external	Hair growth/loss	Hair grower	IISE	n/a	310.527(a)
Estradiol					
Miscellaneous external	Hair growth/loss	Hair grower	IIE	IIE	310.527(a)
Estrogens					
Miscellaneous external	Hormone	Hormone	IIE	IIE	310.530(a)
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IIS	IIS	310.528(a)
Estrone					
Antimicrobial II	Acne	Acne	IISE	IISE	310.545(a)(1)
Ether					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Ethohexadiol					
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	IIIE	IIIE	310.545(a)(7)
Ethoxylated alkyl alcohol					
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)
Ethyl 4-[bis(hydroxypropyl)] aminobenzoate					
Topical analgesic	Sunscreen	Sunscreen	I	I	310.545(a)(29)
Ethyl alcohol [see alcohol]					
====	====	====	====	====	====
Ethyl nitrate					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Ethylhexyl *p*-methoxycinnamate [see white pine extract, compound]					
====	====	====	====	====	====
Ethylmorphine hydrochloride					
Cough/	cold Cough/cold (antitussive)	Antitussive	IIIE	IIIE	[52 FR 30054]
Eucalyptol					
Cough/cold	Cough/cold (antitussive)	Antitussive (topical/inhalant)	IIIE	IIIE	[52 FR 30055]
Cough/cold	Cough/cold (antitussive)	Antitussive (mouthwash)	IIIE	IIIE	[52 FR 30055]
Cough/cold	Cough/cold (antitussive)	Antitussive (lozenge)	IIIE	IIIE	[52 FR 30054]
Cough/cold	Cough/cold (expectorant)	Expectorant (lozenge)	IIIE	IIIE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (expectorant)	Expectorant (topical/inhalant)	IIIE	IIIE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (mouthwash)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (lozenge)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (lozenge)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	pending
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	IIIE	IIIE	310.545(a)(7)
Miscellaneous external	External analgesic	Diaper rash	Defer	IISE	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	pending
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	pending
Oral cavity	Oral health care	Analgesic/anesthetic	IIIE	IIIE	310.545(a)(14)
Eucalyptol, menthol, methyl salicylate, and thymol					
====	Gingivitis/plaque	Antiplaque/gingivitis	I	====	pending

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Eucalyptus oil					
====	External analgesic	Fever blister (topical)	n/a	IIIE	310.545(a)(10)(v)
Cough/cold	Cough/cold (antitussive)	Antitussive (mouthwash)	IIIE	IIIE	[52 FR 30055]
Cough/cold	Cough/cold (antitussive)	Antitussive (lozenge)	IIIE	IIIE	[52 FR 30054]
Cough/cold	Cough/cold (antitussive)	Antitussive (topical/inhalant)	IIIE	IIIE	[52 FR 30055]
Cough/cold	Cough/cold (expectorant)	Expectorant (lozenge)	IIIE	IIIE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (expectorant)	Expectorant (topical/inhalant)	IIIE	IIIE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (mouthwash)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (inhalant room spray)	IIIE	IIIE	[59 FR 43408]
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (lozenge)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Hair growth/loss	Hair grower	IISE	n/a	310.527(a)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IIE	IIE	310.544(d)
Topical analgesic	External analgesic	Counterirritant	IIIE	IIIE	310.545(a)(10)(ii)
Eugenol					
====	External analgesic	Poison ivy/oak/sumac	n/a	IIIE	310.545(a)(10)(vii)
Dental	Relief of oral discomfort	Toothache relief	I	IIISE	Pending
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIIE	310.545(a)(10)(v)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Topical analgesic	External analgesic	Analgesic/anesthetic	IIIE	IIIE	310.545(a)(10)(i)
Euphorbia pilulifera					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	IIIE	IIIE	310.545(a)(6)(iv)(A)
Extract white pine compound [see white pine extract, compound]					
====	====	====	====	====	====
Fatty acids					
Miscellaneous external	Hair growth/loss	Hair grower	IISE	n/a	310.527(a)
Fennel acid					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Ferric ammonium citrate					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Ferric chloride					
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)(A)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	IISE	IISE	310.545(a)(18)(vi)(A)
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Oral cavity	Oral health care	Antimicrobial	IISE	IISE	Pending
Ferric pyrophosphate					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Ferric subsulfate					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Ferrous furnarate					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Ferrous gluconate					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Ferrous sulfate					
Miscellaneous internal	Menstrual/diuretic	Premenstrual/menstrual period	n/a	IISE	310.545(a)(24)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Flax seed					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Fluid extract ergot [see ergot, fluidextract]					
====	====	====	====	====	====
Fluorosalan					
Antimicrobial I	Antimicrobial	Antimicrobial	IIS	IIS	Pending

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Folic acid					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Formaldehyde solution					
Dental	Relief of oral discomfort	Tooth desensitizer	IIIE	IIIE	Pending
Formic acid					
Miscellaneous external	Pediculicide	Pediculicide	n/a	n/a	310.545(a)(25)(i)
Frangula					
Laxative	Laxative	Stimulant laxative	IIISE	IIISE	310.545(a)(12)(iv)(A)
Fructose					
Miscellaneous internal	Overindulgence in alcohol/food	Minimize inebriation	IIIE	IIIE	[48 FR 32873]
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Galega					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Gamboge					
Laxative	Laxative	Stimulant laxative	IIS	IIS	310.545(a)(12)(iv)(A)
Garlic, dehydrated					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIE	IIE	310.545(a)(8)(i)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIE	IIE	310.545(a)(8)(i)
Gastric mucin					
Antacid	Antacid	Antacid	IIIE	IIIE	[39 FR 19873]
Gelatin					
Oral cavity	Oral health care	Demulcent	I	I	Pending
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(c)
Gentian violet					
Miscellaneous internal	Anthelmintic	Anthelmintic	I	IIS	[51 FR 27758]
Oral cavity	Oral health care	Antimicrobial	IIIE	IIE	Pending
Gentiana lutea (gentian)					
Miscellaneous internal	Menstrual/diuretic	Premenstrual/menstrual period	n/a	IISE	310.545(a)(24)(i)
Ginger					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Ginger, ground [see ginger, Jamaica]					
====	====	====	====	====	====
Ginger, Jamaica					
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IIE	IIE	310.544(d)
Ginseng					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Sedative	Stimulant	Stimulant	IIE	IIE	[39 FR 6104]
Ginseng, korean					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Glutamic acid					
Miscellaneous internal	Benign prostatic hypertrophy	Benign prostatic hypertrophy	IIE	IIISE	310.532((a)
Glutamic acid hydrochloride					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIE	IIE	310.545(a)(8)(i)
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIE	IIE	310.545(a)(8)(i)
Miscellaneous internal	Stomach acidifier	Stomach acidifier	IIE	IIE	310.540(a)
Glycerin					
Hemorrhoidal	Anorectal	Antiseptic (intrarectal)	IISE	IISE	310.545(a)(26)(ii)
Hemorrhoidal	Anorectal	Antiseptic (external)	IISE	IISE	310.545(a)(26)(ii)
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(3)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(3)
Laxative	Laxative	Hyperosmotic laxative	I	I	Pending
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	DEF	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	310.545(a)(18)(iii)
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	I	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Oral cavity	Oral health care	Demulcent	I	I	Pending
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(d)(1)
Topical analgesic	Otic	Ear wax softening agent	I	IIIE	[51 FR 28660]
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(h)
Glycerin, anhydrous					
====	Otic	Drying water/water clogged ears	n/a	IIIE	310.545(a)(15)(ii)
====	Otic	Swimmer's ear prevention	n/a	IIIE	310.545(a)(15)(ii)

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Glycerin, anhydrous [see glycerin]					
====	====	====	====	====	====
Glyceryl aminobenzoate					
Topical analgesic	Sunscreen	Sunscreen	I	I	310.545(a)(29)
Glycine					
Antacid	Antacid	Antacid	I	I	331.11(f)
Internal analgesic	Internal analgesic	Corrective	I	n/a	Pending
Laxative	Antidiarrheal	Antidiarrheal	IIE	IIE	310.545(a)(3)(i)
Laxative	Antiemetic	Antiemetic	IIE	IIE	[52 FR 15891]
Miscellaneous internal	Benign prostatic hypertrophy	Benign prostatic hypertrophy	IIE	IIISE	310.532(a)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Glycol salicylate					
====	External analgesic	Poison ivy/oak/sumac	n/a	IIIE	310.545(a)(10)(vii)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIIE	310.545(a)(10)(v)
Topical analgesic	External analgesic	Analgesic/anesthetic	IIIE	IIIE	Pending
Glycyrrhiza					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IIE	IISE	310.528(a)
Miscellaneous internal	Menstrual/diuretic	Premenstrual/menstrual period	n/a	IISE	310.545(a)(24)(i)
Golden seal					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Golden seal [see hydratis]					
====	====	====	====	====	====
Gotu kola					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Gramicidin					
Antimicrobial II	Antibiotic	First aid antibiotic	n/a	IIISE	[52 FR 47322]
Antimicrobial II	Antibiotic	Skin wound protectant	IIS	Defer	[52 FR 47322]
Antimicrobial II	Antibiotic	Skin wound antibiotic	IIISE	Defer	[52 FR 47322]
Guaifenesin					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	341.18
Guar gum					
Laxative	Laxative	Bulk laxative	IIIE	IIIE	310.545(a)(12)(i)
Miscellaneous internal	Weight control	Anorectic	IIIE	IISE	310.545(a)(20)
Haloprogin					
Antimicrobial II	Antifungal	Anticandidal	I	n/a	n/a
Antimicrobial II	Antifungal	Antifungal	I	I	333.210(b)
Hamamelis water of xi [see witch hazel]					
====	====	====	====	====	====
Hard fat					
====	Skin protectant	Skin protectant	n/a	n/a	347.10(i)
Hemorrhoidal	Anorectal	Protectant (external)	n/a	n/a	346.14(4)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	n/a	n/a	346.14(4)
Hectorite					
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Hemicellulase					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIIE	IIIE	310.545(a)(8)(i)
Miscellaneous internal	Exocrine pancreatic insufficiency	Exocrine pancreatic insufficiency	IIE	IIE	310.543(a)
Hexachlorophene					
Antimicrobial I	Antimicrobial	Antimicrobial	IIS	n/a	[37 FR 20163]
Contraceptive/vaginal	Vaginal	Minor irritations	IISE	Withdraw	n/a
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	IISE	Pending
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Hexylresorcinol					
====	External analgesic	Poison ivy/oak/sumac	n/a	IIIE	310.545(a)(10)(vii)
Antimicrobial I	Antimicrobial	Antimicrobial soap	n/a	IIE	Pending
Antimicrobial I	Antimicrobial	First aid antiseptic	n/a	I	Pending

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Antimicrobial I	Antimicrobial	Health care personnel handwash	IIIE	IIIE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IIIE	IIIE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIIE	IIIE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	I	I	Pending
Antimicrobial I	Antimicrobial	Skin wound protectant	IIIE	IIIE	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIIE	IIIE	Pending
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIIE	310.545(a)(10)(v)
Oral cavity	Oral health care	Analgesic/anesthetic	I	I	Pending
Topical analgesic	External analgesic	Analgesic/anesthetic	IIIE	IIIE	310.545(a)(10)(i)
Histamine dihydrochloride					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IISE	310.545(a)(10)(v)
Topical analgesic	External analgesic	Counterirritant	I	I	Pending
Histidine					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Homatropine methylbromide					
Laxative	Antidiarrheal	Antidiarrheal	IIISE	IIISE	310.545(a)(3)
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIIE	IIIE	310.545(a)(8)(i)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIE	IIE	310.545(a)(8)(i)
Miscellaneous internal	Menstrual/diuretic	Smooth muscle relaxant	IIE	IIIE	310.545(a)(24)(i)
Homosalate					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	Defer	Pending
Topical analgesic	n/a	Sunscreen	n/a	I	352.10(f)
Honey					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Horehound					
Cough/cold	Cough/cold (antitussive)	Antitussive	IIIE	IIIE	[52 FR 30054]
Oral cavity	Oral health care	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Hormone constituents					
Miscellaneous external	Hair growth/loss	Hair grower	IISE	IIE	310.527(a)
Horsetail					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Huckleberry					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Hyascyamine sulfate					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Hydrangea, powdered extract (extract of hydrangea)					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Hydrastis					
Hemorrhoidal	Anorectal	Counterirritant (intrarectal)	IISE	IISE	310.545(a)(26)(iv)
Hemorrhoidal	Anorectal	Antiseptic (external)	IISE	IISE	310.545(a)(26)(iv)
Hemorrhoidal	Anorectal	Counterirritant (external)	IISE	IISE	310.545(a)(26)(iv)
Hemorrhoidal	Anorectal	Antiseptic (intrarectal)	IISE	IISE	310.545(a)(26)(ii)
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Hydrastis canadensis (golden seal)					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Menstrual/diuretic	Menstrual	n/a	IISE	310.545(a)(24)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Hydrastis fluid extract					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Hydrate magnesium aluminate activated sulfate					
Antacid	Antacid	Antacid	n/a	n/a	331.11(g)(1)
Hydriodic acid syrup					
Cough/cold	Cough/cold (expectorant)	Expectorant	IISE	IISE	310.545(a)(6)(iii)
Hydrochloric acid					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)

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Hydrochloric acid diluted [see hydrochloric acid, diluted]					
====	====	====	====	====	====
Hydrochloric acid, diluted					
Miscellaneous internal	Stomach acidifier	Stomach acidifier	IIE	IIE	310.540(a)
Hydrocodone bitartrate					
Cough/cold	Cough/cold (antitussive)	Antitussive	IIS	IIS	[52 FR 30054]
Hydrocortisone					
Antimicrobial II	Antifungal	Anti-inflammatory	I combo	n/a	n/a
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/psoriasis	IIISE	Defer	n/a
Topical analgesic	External analgesic	Antipruritic	I	I	Pending
Hydrocortisone (0.25–5%)					
Miscellaneous external	External analgesic	Dandruff/seborrheic dermatitis/psoriasis	n/a	I	Pending
Hydrocortisone (0.5–1%)					
Miscellaneous external	External analgesic	Dandruff	n/a	IIISE	Pending
Hydrocortisone acetate					
====	External analgesic	Poison ivy/oak/sumac	n/a	I	Pending
Antimicrobial II	Antifungal	Anti-inflammatory (dissent)	I combo	n/a	n/a
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/psoriasis	IIISE	Defer	n/a
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Topical analgesic	External analgesic	Antipruritic	I	I	Pending
Hydrocortisone acetate (0.25–5.0%)					
Miscellaneous external	External analgesic	Dandruff/seborrheic Dermatitis/psoriasis	n/a	I	Pending
Hydrocortisone acetate (0.25–0.5%)					
Miscellaneous external	External analgesic	Dandruff/seborrheic dermatitis /psoriasis	n/a	I	Pending
Hydrocortisone alcohol [see hydrocortisone]					
====	====	====	====	====	====
Hydrogen fluoride					
Dental	Anticaries	Anticavity dental rinse	n/a	IIISE	310.545(a)(2)(i)
Hydrogen peroxide					
Antimicrobial I	Antimicrobial	First aid antiseptic	n/a	I	Pending
Dental	Oral mucosal injury	Wound cleanser	I	I	Pending
Dental	Oral mucosal injury	Wound healing agent	IIIE	IIIE	310.534(a)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	Pending
Oral cavity	Oral health care	Debriding agent	III	III	Pending
Hydrogen peroxide and povidone iodine					
====	Gingivitis/plaque	Antiplaque/gingivitis	n/a	IIISE	Pending
Hydrogen peroxide and sodium bicarbonate					
====	Gingivitis/plaque	Antiplaque/gingivitis	n/a	IIISE	Pending
Hydrogen peroxide, sodium citrate, sodium lauryl sulfate, and zinc chloride					
====	Gingivitis/plaque	Antiplaque/gingivitis	n/a	IIISE	Pending
Hydroquinone					
Miscellaneous external	Skin bleach	Skin bleaching	I	I	Pending
Hydroxyethyl cellulose					
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(a)(2)
Hydroxyethylcellulose [see hydroxyethyl cellulose]					
====	====	====	====	====	====
Hydroxypropyl methylcellulose [see hypromellose]					
====	====	====	====	====	====
Hyoscyamine sulfate					
Laxative	Antidiarrheal	Antidiarrheal	IIISE	IIISE	310.545(a)(3)
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Hypromellose					
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(a)(3)

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Ibuprofen	Internal analgesic	Analgesic	n/a	I	[67 FR 54139]
====	Internal analgesic	Antipyretic	n/a	I	[67 FR 54139]
====					
Ichthammol					
Miscellaneous external	Boil treatment	Boil treatment	IISE	IIISE	310.531(a)
Miscellaneous external	Corn/callus remover	Corn/callus remover	IISE	IISE	[55 FR 33261]
Impatiens biflora tincture					
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Infusion of rose petal [see rose petal, infusion of]					
====	====	====	====	====	====
Inositol					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Iodine					
Miscellaneous external	Wart remover	Wart remover	IISE	IISE	[55 FR 33254]
Miscellaneous external	Corn/callus remover	Corn/callus remover	IISE	IISE	[55 FR 33261]
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Oral cavity	Oral health care	Antimicrobial	IIISE	IIISE	Pending
Iodine complex/phosphate ester of alkylaryloxy polyethylene					
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin wound protectant	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin preparation	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIISE	IIISE	Pending
Iodine tincture					
Antimicrobial I	Antimicrobial	First aid antiseptic	n/a	I	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	I	I	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIS	IIS	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Skin wound protectant	IISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	IIS	IIIS	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIS	IIIS	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IISE	IISE	Pending
Iodine topical solution					
Antimicrobial I	Antimicrobial	First aid antiseptic	n/a	I	Pending
Iodized lime					
Cough/cold	Cough/cold (expectorant)	Expectorant	IISE	IISE	310.545(a)(6)(iii)
Iodoantipyrine					
Internal analgesic	Internal analgesic	Analgesic	IISE	IISE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antipyretic	IISE	IISE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antirheumatic	IISE	Not OTC	310.545(a)(23)(i)
Iodochlorhydroxyquin [see clioquinol]					
====	====	====	====	====	====
Ipecac					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIE	IIE	310.545(a)(6)(iii)
Ipecac fluidextract					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIE	IIE	310.545(a)(6)(iii)
Miscellaneous internal	Poison treatment	Emetic	n/a	IIS	310.545(a)(16)
Ipecac syrup					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Miscellaneous internal	Emetic	Emetic	I	I	Pending
Miscellaneous internal	Poison treatment	Emetic	n/a	I	Pending
Ipecac tincture					
Miscellaneous internal	Poison treatment	Emetic	n/a	IIS	310.545(a)(16)
Ipomea					
Laxative	Laxative	Stimulant laxative	IIS	IIS	310.545(a)(12)(iv)(A)

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Iron ox bile					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Iron oxide					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Isobornyl thiocyanoacetate					
Miscellaneous external	Pediculicide	Pediculicide	IISE	IISE	310.545(a)(25)(i)
Isobutamben					
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Isobutyl *p*-aminobenzoate [see isobutaben]					
====	====	====	====	====	====
Isoleucine					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Isopropyl alcohol					
Miscellaneous external	Alcohols (topical)	Antiseptic	I	I	Pending
Miscellaneous external	Mercury	First aid antiseptic	n/a	I	Pending
Miscellaneous external	Analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Isopropyl palmitate					
====	Insect bite/sting	Insect bite/sting	n/a	n/a	310.545(a)(18)(v)(B)
====	Poison ivy/oak/sumac	Poison ivy/oak/sumac	n/a	n/a	310.545(a)(18)(vi)(B)
====	Skin protectant	Skin protectant	n/a	n/a	310.545(a)(18)(i)(B)
Jalap					
Laxative	Laxative	Stimulant laxative	IIS	IIS	310.545(a)(12)(iv)(A)
John's wort					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Jojoba oil					
Miscellaneous external	Hair growth/loss	Hair grower	n/a	IIE	310.527(a)
Juniper					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Juniper oil (oil of juniper)					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Juniper tar					
====	Antifungal	Diaper rash	n/a	n/a	310.545(a)(22)(i)
====	Antimicrobial	Diaper rash	n/a	n/a	Pending
====	External analgesic	Diaper rash	n/a	IISE	310.545(a)(10)(iv)
====	External analgesic	Fever blister (topical)	n/a	I	Pending
====	External analgesic	Poison ivy/oak/sumac	n/a	I	Pending
====	Skin protectant	Diaper rash	n/a	n/a	Pending
Hemorrhoidal	Anorectal	Counterirritant (external)	IIISE	n/a	n/a
Hemorrhoidal	Anorectal	Analgesic (external)	n/a	I	346.16(b)
Hemorrhoidal	Anorectal	Counterirritant (intrarectal)	IIISE	n/a	n/a
Miscellaneous external	Boil treatment	Boil treatment	IISE	IIISE	310.531(a)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/psoriasis	IIIE	IIIE	310.545(a)(7)
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Juniper, extract					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Kaolin					
====	Skin protectant	Poison ivy/oak/sumac	n/a	I	347.10(j)
Antacid	Antacid	Antacid	IIIE	IIIE	[39 FR 19873]
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(5)
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(5)
Laxative	Antidiarrheal	Antidiarrheal	IIIE	IIIE	347.10(b)
Miscellaneous external	Skin protectant	Diaper rash	n/a	I	Pending
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(j)
Kaolin, colloidal					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Karaya [see karaya gum]					
====	====	====	====	====	====

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Karaya gum					
Laxative	Laxative	Bulk laxative	I	I	Pending
Miscellaneous internal	Weight control	Anorectic	IIIE	IISE	310.545(a)(20)
Kelp					
Miscellaneous internal	Weight control	Anorectic	IIIE	IISE	310.545(a)(20)
Knotgrass					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Lactic acid					
Contraceptive/vaginal	Vaginal	Lowers surface tension mucolytic effects	IIIE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Alters vaginal pH	IIIE	Withdraw	n/a
Miscellaneous external	Wart remover	Wart remover	IIIE	IIIE	[55 FR 33254]
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Lactobacillus acidophilus					
Laxative	Antidiarrheal	Antidiarrheal	IIIE	IIIE	310.545(a)(3)(i)
Miscellaneous internal	Fever blister (oral)	Fever blister/oral	IIIE	IIIE	310.537(a)
Lactobacillus bulgaricus					
Laxative	Antidiarrheal	Antidiarrheal	IIIE	IIIE	310.545(a)(3)(i)
Miscellaneous internal	Fever blister (oral)	Fever blister/oral	IIIE	IIIE	310.537(a)
Lactose					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Lanolin					
====	Skin protectant	Skin protectant	n/a	n/a	347.10(k)
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(6)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(6)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Hair growth/loss	Hair grower	IIE	IIE	310.527(a)
Miscellaneous external	Skin protectant	Diaper rash	Defer	I	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)
Lanolin (in combination)					
Ophthalmic	Ophthalmic	Emollient	I	I	349.14(a)(2)
Lanolin alcohol [see lanolin alcohols]					
====	====	====	====	====	====
Lanolin alcohols					
Hemorrhoidal	Anorectal	Protectant (external)	I	IIISE	310.545(a)(26)(viii)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	IIISE	310.545(a)(26)(viii)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	Pending
Lanolin anhydrous [see lanolin, anhydrous]					
====	====	====	====	====	====
Lanolin nonionic derivatives					
Ophthalmic	Ophthalmic	Emollient	I	I	349.14
Lanolin, anhydrous (in combination)					
Ophthalmic	Ophthalmic	Emollient	I	I	349.14(a)(1)
lappa extract					
Hemorrhoidal	Anorectal	Anorectal (external)	IISE	IISE	310.545(a)(26)(vii)
Hemorrhoidal	Anorectal	Anorectal (intrarectal)	IISE	IISE	310.545(a)(26)(vii)
Laureth 10s					
Contraceptive/vaginal	Contraceptive (vaginal)	Contraceptive	IIIE	Withdraw)	310.545(a)(28
Lauric diethanolamide					
Miscellaneous external	Hair growth/loss	Hair grower	IISE	n/a	310.527(a)
Lauryl isoquinolinium bromide					
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	IIIE	IIIE	310.545(a)(7)

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Lavender compound, tincture of					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Lavender oil					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Lawsone with dihydroxyacetone					
Topical analgesic	Sunscreen	Sunscreen	I	I	310.545(a)(29)
L-Desoxyephedrine [see desoxyephedrine, L-]					
====	====	====	====	====	====
Lead acetate					
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Lecithin					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Lemon oil (terpeneless)					
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IIE	IIE	310.544(d)
Leptandra extract					
Hemorrhoidal	Anorectal	Anorectal (external)	IISE	IISE	310.545(a)(26)(vii)
Hemorrhoidal	Anorectal	Anorectal (intrarectal)	IISE	IISE	310.545(a)(26)(vii)
Leucine					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Levmetamfetamine					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant))	IIIE	I	341.20(b)(1)
Levomethamphetamine [see desoxyephedrine, L-]					
====	====	====	====	====	====
Licorice					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Licorice root extract					
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IIE	IIE	310.544(d)
Lidocaine					
Hemorrhoidal	Anorectal	Anesthetic (external)	IIIE	I	346.10(f)
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIIE	IIIE	[55 FR 1779]
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Miscellaneous external	Male genital desensitizer	Male genital desensitizer	I	I	348.10(a)(2)
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	I	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Oral cavity	Oral health care	Analgesic/anesthetic	IIS	IIS	310.545(a)(14)
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Lidocaine hydrochloride					
====	External analgesic	Poison ivy/oak/ sumac	n/a	I	Pending
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	IIS	IIS	310.545(a)(14)
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Linden					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Lipase					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Live yeast cell derivative					
====	Insect bite/sting	Insect bite/sting	n/a	n/a	310.545(a)(18)(v)(B)
====	Poison ivy/oak/sumac	Poison ivy/oak/ sumac	n/a	n/a	310.545(a)(18)(vi)(B)
Topical analgesic	Skin protectant	Skin protectant	IIIE	IIIE	310.545(a)(18)(i)(B)
Liver concentrate					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Lobeline					
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IIIE	IIIE	310.544(d)

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Lysine					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Lysine aspirin					
Internal analgesic	Internal analgesic	Analgesic	n/a	IISE	310.545(a)(23)(i)
Lysine hydrochloride					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Fever blister (oral)	Fever blister/oral	IIIE	IIIE	310.537(a)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Magaldrate					
Antacid	Antacid	Antacid	I	I	331.11(g)(2)
Magnesium					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Magnesium aluminum silicate					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Antacid	Antacid	Antacid	I	I	331.11(g)(3) 331.11(k)(2)(1)
Magnesium aluminumsilicate [see magnesium aluminum silicate]					
====	====	====	====	====	====
Magnesium carbonate					
Antacid	Antacid	Antacid	I	I	331.11(g)(4)
Internal analgesic	Internal analgesic	Corrective	I	n/a	n/a
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous internal	Overindulgence in alcohol/food	Overindulgence remedies (hangover)	I	I	Pending
Magnesium citrate					
Laxative	Laxative	Saline laxative (oral solution)	I	I	Pending
Magnesium glycinate					
Antacid	Antacid	Antacid	I	I	331.11(g)(5)
Magnesium hydroxide					
Antacid	Antacid	Antacid	I	I	331.11(g)(6)
Internal analgesic	Internal analgesic	Corrective	I	n/a	Pending
Laxative	Laxative	Saline laxative	I	I	Pending
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIIE	IIIE	310.545(a)(8)(i)
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIIE	IIIE	310.545(a)(8)(i)
Magnesium oxide					
Antacid	Antacid	Antacid	I	I	331.11(g)(7)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Magnesium salicylate					
Internal analgesic	Internal analgesic	Analgesic	I	I	Pending
Internal analgesic	Internal analgesic	Antipyretic	I	I	Pending
Internal analgesic	Internal analgesic	Antirheumatic	I	Not	OTC n/a
Miscellaneous internal	Menstrual/diuretic	Analgesic	I	I	Pending
Magnesium sulfate					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Laxative	Laxative	Saline laxative	I	I	Pending
Miscellaneous external	Boil treatment	Boil treatment	IISE	IIISE	310.531(a)
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Magnesium trisilicate					
Antacid	Antacid	Antacid	I	I	331.11(g)(8) 331 11(k)(3)(1)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIIE	IIIE	310.545(a)(8)(i)
Miscellaneous internal	Overindulgence in alcohol/food	Overindulgence remedies (hangover)	I	I	Pending
Malt					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Malt soup extract					
Laxative	Laxative	Bulk laxative	I	I	Pending
Maltodextrin					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)

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Mandrake					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	n/a	n/a	310.528(a)
Manganese citrate					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Mannitol					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Meclizine hydrochloride					
Laxative	Antiemetic	Antiemetic	I	I	336.10(d)
Menfegol					
Contraceptive/vaginal	Contraceptive (vaginal)	Contraceptive (dissent)	I	Withdraw	n/a
Menthol					
Antimicrobial II	Antifungal	Antifungal	IIE	IIE	310.545(a)(22)(ii)
Cough/cold	Cough/cold (antitussive)	Antitussive (mouthwash)	IIIE	IIIE	[52 FR 30055]
Cough/cold	Cough/cold (antitussive)	Antitussive (topical/inhalant)	IIIE	I	341.14(b)(2)
Cough/cold	Cough/cold (antitussive)	Antitussive (lozenge)	IIIE	I	341.14(b)(2)
Cough/cold	Cough/cold (expectorant)	Expectorant (topical/inhalant)	IIIE	IIIE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (expectorant)	Expectorant (lozenge)	IIIE	IIIE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (lozenge)	IIIE	IIIE	[59 FR 43408]
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (mouthwash)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Dental	Relief of oral discomfort	Toothache relief	IIS	IIS	Pending
Hemorrhoidal	Anorectal	Analgesic (external)	n/a	I	346.16(c)
Miscellaneous external	Antifungal	Diaper rash	Defer	IISE	310.545(a)(22)(ii)
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/ psoriasis	IIIE	IIIE	310.545(a)(7)
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	IISE	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Insect bite/sting	IISE	I	Pending
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	I	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	Defer	Pending
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)(A)
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Miscellaneous external	Wart remover	Wart remover	IISE	IISE	[55 FR 33254]
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IIE	IIE	310.544(d)
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	I	I	Pending
Topical analgesic	External analgesic	Counterirritant	I	I	Pending
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Menthol (0.1–1.0%)					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Menthol (1.25–16%)					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIIE	310.545(a)(10)(v)
Hemorrhoidal	Anorectal	Counterirritant (intrarectal)	IIE	IIE	310.545(a)(26)(iv)
Hemorrhoidal	Anorectal	Counterirritant (external)	I	IIE	310.545(a)(26)(iv)
Menthyl anthranilate [see meradimate]					
====	====	====	====	====	====
Meradimate					
Topical analgesic	Sunscreen	Sunscreen	I	I	352.10(h)
Meralein sodium					
Oral cavity	Oral health care	Antimicrobial	IISE	IISE	Pending

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Merbromin					
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(18)(vi)
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Merbromin (mercurochrome)					
Miscellaneous external	Mercury	First aid antiseptic	n/a	IIIE	310.545(a)(27)(i)
Mercufenol chloride					
Miscellaneous external	Mercury	First aid antiseptic	n/a	IIIE	310.545(a)(27)(i)
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Miscellaneous external	Antimicrobial	First aid antiseptic	n/a	IIS	310.545(a)(27)(i)
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Mercuric chloride [see calomel]					
====	====	====	====	====	====
Mercuric oxide, yellow					
Miscellaneous external	Mercury	First aid antiseptic	n/a	IISE	310.545(a)(27)(i)
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Ophthalmic	Ophthalmic	Anti-infective	IIISE	IISE	310.545(a)(21)(ii)
Mercuric salicylate					
Miscellaneous external	Mercury	First aid antiseptic	n/a	IISE	310.545(a)(27)(i)
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Mercuric sulfide, red					
Miscellaneous external	Mercury	First aid antiseptic	n/a	IISE	310.545(a)(27)(i)
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Mercurous chloride [see calomel]					
====	====	====	====	====	====
Mercury					
Miscellaneous external	Mercury	First aid antiseptic	n/a	IISE	310.545(a)(27)(i)
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Mercury (any ingredient)					
====	Antimicrobial	Diaper rash	Defer	n/a	310.545(a)(27)(ii)
====	Contraceptive (vaginal)	Contraceptive	n/a	n/a	310.545(a)(28)
Mercury chloride [see mercuric chloride]					
====	====	====	====	====	====
Mercury oleate					
Miscellaneous external	Mercury	First aid antiseptic	n/a	IISE	310.545(a)(27)(i)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Psoriasis	IIE	IIE	310.545(a)(7)
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Mercury, ammoniated					
Miscellaneous external	Antimicrobial	First aid antiseptic	n/a	IISE	310.545(a)(27)(i)
Miscellaneous external	Skin bleach	Skin bleaching	IISE	IISE	310.545(a)(17)
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Metaproterenol sulfate					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	n/a	III	310.545(a)(6)(iv)(A)
Methapyrilene					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Methapyrilene fumarate					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	I	IIS	310.545(a)(6)(i)(A)&(B)
Internal analgesic	Internal analgesic	Analgesic adjuvant	IIIE	IIS	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antihistamine	IIE	n/a	310.545(a)(6)(A)
Internal analgesic	Internal analgesic	Antipyretic adjuvant	IIIE	IIS	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antirheumatic adjuvant	IIIE	IIS	310.545(a)(23)(i)
Sedative	Daytime sedative	Sedative	IIISE	IISE	310.519(a)
Sedative	Nighttime sleep aid	Sleep aid	IIISE	IIS	[54 FR 6826]

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Methapyrilene hydrochloride					
====	External analgesic	Poison ivy/oak/ sumac	n/a	IISE	310.545(a)(10)(vii)
Cough/cold	Cough/cold (antihistamine)	Antihistamine	I	IIS	310.545(a)(6)(i)(A)&(B)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIE	310.545(a)(10)(v)
Miscellaneous internal	Menstrual/diuretic	Menstrual	n/a	IISE	310.545(a)(24)(i)
Sedative	Nighttime sleep aid	Sleep aid	IIISE	IIS	[54 FR 6826]
Sedative	Daytime sedative	Sedative	IIISE	IIS	310.519(a)
Topical analgesic	External analgesic	Analgesic/anesthetic	I	IIS	310.545(a)(10)(i)
Methenamine					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Methionine					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Methoxyphenamine hydrochloride					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	I	IIE	310.545(a)(6)(iv)(A)
Methoxypolyoxyethylene glycol 550 laurate					
Contraceptive/vaginal	Contraceptive (vaginal)	Contraceptive	IIIE	IIIE	310.545(a)(28)
Methyl nicotinate					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIIE	310.545(a)(10)(v)
Topical analgesic	External analgesic	Counterirritant	I	I	Pending
Methyl salicylate					
Dental	Relief of oral discomfort	Toothache relief	IISE	IISE	Pending
Dental	Relief of oral discomfort	Oral mucosal analgesic	IISE	IISE	Pending
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	IIIE	IIIE	310.545(a)(7)
Miscellaneous external	External analgesic	Astringent	n/a	n/a	Pending
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIIE	310.545(a)(10)(v)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Corn/callus remover	Corn/callus remover	IISE	IISE	[55 FR 33261]
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IIE	IIE	310.544(d)
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	IIIE	IIIE	310.545(a)(14)
Topical analgesic	External analgesic	Counterirritant	I	I	Pending
Methylbenzethonium chloride					
Antimicrobial I	Antimicrobial	First aid antiseptic	n/a	I	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin protectant	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	I	I	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IIIE	IIIE	Pending
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	IIISE	Pending
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Cradle cap	IIIE	IIIE	310.545(a)(7)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Corn/callus remover	Corn/callus remover	IISE	IISE	[55 FR 33261]
Methylcellulose					
Antacid	Antacid	Antacid	IIIE	IIIE	[39 FR 19873]
Laxative	Laxative	Bulk laxative	I	I	Pending
Miscellaneous internal	Weight control	Anorectic	IIIE	IISE	310.545(a)(20)
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(a)(4)
Methylene blue					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)

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Methylparaben					
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(ii)
Methyltestosterone					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IIS	IIS	310.528(a)
Miconazole nitrate					
Antimicrobial II	Antifungal	Anticandidal	I	n/a	n/a
Antimicrobial II	Antifungal	Antifungal	I	I	333.210(c)
Microporous cellulose [see cellulose, microporous]					
====	====	====	====	====	====
Milk solids, dried					
Antacid	Antacid	Antacid	I	I	331.11(h)
Mineral oil					
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(7)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(7)
Laxative	Laxative	Lubricant laxative	I	I	Pending
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Diaper rash	Defer	I	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	Pending
Ophthalmic	Ophthalmic	Emollient	I	I	349.14(b)(2)
Mineral oil, emulsified [see mineral oil]					
====	====	====	====	====	====
Mineral oil, light					
Ophthalmic	Ophthalmic	Emollient	I	I	349.14(b)(1)
Minerals					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	n/a	IISE	310.528(a)
Mono- and di-glycerides					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Mullein					
Hemorrhoidal	Anorectal	Anorectal (external)	IISE	IISE	310.545(a)(26)(vii)
Hemorrhoidal	Anorectal	Anorectal (intrarectal)	IISE	IISE	310.545(a)(26)(vii)
Mustard oil [see allyl isothiocyanate]					
====	====	====	====	====	====
Mycozyme					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Myrrh					
Dental	Relief of oral discomfort	Oral mucosal protectant	IIISE	IIISE	Pending
Myrrh tincture					
Oral cavity	Oral health care	Antimicrobial	IISE	IISE	310.545(a)(14)
Oral cavity	Oral health care	Astringent	IISE	IISE	Pending
Myrrh tincture of [see myrrh tincture]					
====	====	====	====	====	====
Myrrh, fluid extract of					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Naphazoline hydrochloride					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant))	I	I	341.20(b)(6)
Ophthalmic	Ophthalmic	Vasoconstrictor	I	I	349.18(b)
Natural estrogenic hormone					
Miscellaneous internal	Menstrual/diuretic	Menstrual	n/a	IISE	310.545(a)(24)(i)
Neomycin sulfate					
Antimicrobial II	Antibiotic	Skin wound protectant	IIIS	Defer	n/a
Neomycin sulfate (cream)					
Antimicrobial II	Antibiotic	First aid antibiotic	n/a	I	333.110(e)
Neomycin sulfate (ointment)					
Antimicrobial II	Antibiotic	First aid antibiotic	n/a	I	333.110(d)
Nettle					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)

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Niacinamide					
Miscellaneous internal	Menstrual/diuretic	Menstrual	n/a	IISE	310.545(a)(24)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Sedative	Daytime sedative	Sedative	IIE	IISE	310.519(a)
Nickel-pectin					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Nitromersol					
Miscellaneous external	Mercury	First aid antiseptic	n/a	IISE	310.545(a)(27)(i)
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Oral cavity	Oral health care	Antimicrobial	IISE	IISE	Pending
Nonoxynol 9					
Contraceptive/vaginal	Vaginal	Lowers surface tension mucolytic effects	I	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Minor irritations	IIIE	Withdraw	n/a
Contraceptive/vaginal	Contraceptive (vaginal)	Contraceptive	I	Withdraw	n/a
Nonylphenoxypoly (ethyleneoxy) ethanol iodine					
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIISE	IIISE	Pending
Noscapine					
Cough/cold	Cough/cold (antitussive)	Antitussive	IIIE	IIIE	[52 FR 30054]
Noscapine hydrochloride					
Cough/cold	Cough/cold (antitussive)	Antitussive	IIIE	IIIE	[52 FR 30054]
Nucleic acids					
Miscellaneous external	Hair growth/loss	Hair grower	n/a	n/a	310.527(a)
Nutmeg oil (oil of nutmeg)					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Nux vomica					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Nux vomica extract					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Nystatin					
Antimicrobial II	Antifungal	Anticandidia	I	IIISE	310.545(a)(22)(iv)
Obtundia surgical dressing					
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	Pending
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	Pending
Octinoxate					
Topical analgesic	Sunscreen	Sunscreen	I	I	352.10(j)
Octisalate					
Topical analgesic	Sunscreen	Sunscreen	I	I	352.10(k)
Octocrylene					
Topical analgesic	Sunscreen	Sunscreen	I	I	352.10(i)
Octoxynol 9					
Contraceptive/vaginal	Vaginal	Minor irritations	IIIE	Withdraw	310.545(a)(28)(ii)
Contraceptive/vaginal	Vaginal	Lowers surface tension mucolytic effects	I	Withdraw	310.545(a)(28)(ii)
Contraceptive/vaginal	Contraceptive (vaginal)	Contraceptive	I	Withdraw	310.545(a)(28)(ii)
Octyl salicylate [see octisalate]					
====	====	====	====	====	====
Octyldodecanol					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	Pending
Octylmethoxycinnamate [see octinoxate]					
====	====	====	====	====	====
Octyl Triazone					
n/a	TEA	Sunscreen	n/a		

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Oil of erigeron					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Olive oil					
Miscellaneous external	Hair growth/loss	Hair grower	IISE	n/a	310.527(a)
Opium powder [see opium, powdered]					
====	====	====	====	====	====
Opium tincture					
Laxative	Antidiarrheal	Antidiarrheal	I	IIISE	310.545(a)(3)(i)
Opium, tincture of [see opium tincture]					
====	====	====	====	====	====
Opium, powdered					
Laxative	Antidiarrheal	Antidiarrheal	I	IIISE	310.545(a)(3)(i)
Organic vegetables					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Orthophosphoric acid					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Orthophosphoric acid [see phosphoric acid]					
====	====	====	====	====	====
Ox bile					
Laxative	Laxative	Stimulant laxative	IIISE	IIISE	310.545(a)(12)(iv)(A)
Ox bile extract					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIE	IIE	310.545(a)(8)(i))
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIE	IIE	310.545(a)(8)(i)
Oxybenzone					
Topical analgecis	Sunscreen	Sunscreen	I	I	352.10(1)
Oxymetazoline hydrochloride					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	I	I	341.20(b)(7)
Oxyquinoline					
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(ii)
Miscellaneous external	Antifungal	Diaper rash	Defer	IISE	310.545(a)(22)(ii)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	IIISE	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Oral cavity	Oral health care	Antimicrobial	IIISE	IIISE	Pending
Oxyquinoline citrate					
Contraceptive/vaginal	Vaginal	Minor irritations	IIISE	Withdraw	n/a
Oxyquinoline sulfate					
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(ii)
Contraceptive/vaginal	Vaginal	Minor irritations	IIISE	Withdraw	n/a
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Oxyquinoline sulfate [see oxyquinoline]					
====	====	====	====	====	====
Oxytetracycline hydrochloride					
Antimicrobial II	Antibiotic	First aid antibiotic	n/a	I	333.120 [combos]
Antimicrobial II	Antibiotic	Skin wound antibiotic	IIIE	Defer	n/a
Antimicrobial II	Antibiotic	Skin wound protectant	I	Defer	n/a
Ozokerite					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Paba [see aminobenzoic acid]					
====	====	====	====	====	====
Padimate A					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	Defer	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	Defer	Pending
Topical analgesic	Sunscreen	Sunscreen ($\geq$5%)	I	IISE	Pending
Topical analgesic	Sunscreen	Sunscreen ($<$5%)	I	IIISE	Pending
Padimate O					
Topical analgesic	Sunscreen	Sunscreen	I	I	352.10(m)
Pamabrom					
Miscellaneous internal	Menstrual/diuretic	Diuretic	I	I	Pending

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Pancreatin					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIE	IIE	310.545(a)(8)(i)
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIIE	IIIE	310.545(a)(8)(i)
Miscellaneous internal	Exocrine pancreatic insufficiency	Exocrine pancreatic insufficiency	I	I	310.543(a)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Pancrelipase					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIIE	IIIE	310.545(a)(8)(i)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIE	IIE	310.545(a)(8)(i)
Miscellaneous internal	Exocrine pancreatic insufficiency	Exocrine pancreatic insufficiency	I	I	310.543(a)
Panthenol					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Insect bite/sting	n/a	IIIE	310.545(a)(10)(vi)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IIIE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)
Miscellaneous external	Corn/callus remover	Corn/callus remover	IISE	IISE	[55 FR 33261]
Pantothenic acid					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Papain					
Contraceptive/vaginal	Vaginal	Lowers surface tension mucolytic effects	IIIE	n/a	Withdraw
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIE	IIE	310.545(a)(8)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Papaya enzymes					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Papaya, natural					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Para-chloromercuriphenol					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	IISE	310.545(a)(27)(ii)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Mercury	First aid antiseptic	IISE	n/a	310.545(a)(27)(i)
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	310.545(a)(27)(ii)
Para-*t*-butyl-*m*-cresol					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Para-tertiary-butyl-meta-cresol [see para-*t*-butyl-*m*-cresol]					
====	====	====	====	====	====
Paraffin					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Ophthalmic	Ophthalmic	Emollient	I	I	349.14(b)(3)
Para-*t*-butyl-*m*-cresol					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Para-tertiary-butyl-meta-cresol [see *p*-*t*-butyl-*m*-cresol]					
====	====	====	====	====	====
Paregoric					
Laxative	Antidiarrheal	Antidiarrheal	I	IIISE	310.545(a)(3)(i)
Parethoxycaine hydrochloride					
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Parsley					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)

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Passion flower extract					
Sedative	Nighttime sleep aid	Sleep aid	IIE	IIE	[54 FR 6826]
Pectin					
Laxative	Antidiarrheal	Antidiarrheal	IIIE	IIIE	310.545(a)(3)(ii)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIISE	310.545(a)(10)(v)
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	Defer	Pending
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Oral cavity	Oral health care	Demulcent	I	I	Pending
Pega palo					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Peppermint					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Peppermint oil					
Cough/cold	Cough/cold (antitussive)	Antitussive (topical/inhalant)	IIIE	IIIE	[52 FR 30054]
Cough/cold	Cough/cold (expectorant)	Expectorant (lozenge)	IIIE	IIIE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (expectorant)	Expectorant (topical/inhalant)	IIIE	IIIE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (inhalant room spray)	IIIE	IIIE	[59 FR 43408]
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (lozenge)	IIIE	IIIE	[59 FR 43408]
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (mouthwash)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	IIIE	IIIE	[59 FR 43408]
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIIE	IIIE	310.545(a)(8)(i)
Peppermint oil and sage oil					
====	Gingivitis/plaque	Antiplaque/gingivitis	n/a	IIIE	Pending
Peppermint spirit					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Menstrual/diuretic	Premenstrual/menstrual period	n/a	IISE	310.545(a)(24)(i)
Pepsin					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIE	IIE	310.545(a)(8)(i)
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIE	IIE	310.545(a)(8)(i)
Miscellaneous internal	Stomach acidifier	Stomach acidifier	IIE	IIE	310.540(a)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Pepsin, essence					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Peruvian balsam					
Hemorrhoidal	Anorectal	Wound healing agent (intrarectal)	IIIE	IIIE	310.545(a)(26)(x)
Hemorrhoidal	Anorectal	Wound healing (external)	IIIE	IIIE	310.545(a)(26)(x)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIIE	Pending
Peruvian balsam oil					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIIE	Pending

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Petrolatum					
Hemorrhoidal	Anorectal	Protectant (external)	n/a	I	346.14(8)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	n/a	I	346.14(8)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Diaper rash	Defer	I	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	I	Pending
Ophthalmic	Ophthalmic	Emollient	n/a	I	349.14(b)(4)
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(m)
Petrolatum, red					
Topical analgesic	Sunscreen	Sunscreen	I	I	310.545(a)(29)
Petrolatum, white					
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(10)
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(10)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Diaper rash	Defer	I	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	I	Pending
Ophthalmic	Ophthalmic	Emollient	I	I	349.14(b)(6)
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(r)
Phenacaine hydrochloride					
Hemorrhoidal	Anorectal	Anesthetic (external)	IIS	IIS	310.545(a)(26)(vi)
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIS	IIS	310.545(a)(26)(vi)
Phenacetin					
Internal analgesic	Internal analgesic	Analgesic	IIS	IIS	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antipyretic	IIS	IIS	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antirheumatic	IISE	Not OTC	310.545(a)(23)(i)
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Menstrual/diuretic	Analgesic	IIS	IISE	310.545(a)(24)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Phenindamine tartrate					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	I	I	341.12(i)
Miscellaneous internal	Menstrual/diuretic	Menstrual	n/a	IISE	310.545(a)(24)(i)
Pheniramine maleate					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	I	I	341.12(j)
Internal analgesic	Internal analgesic	Analgesic adjuvant	IIIE	IIIE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antipyretic adjuvant	IIIE	IIIE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antirheumatic adjuvant	IIIE	n/a	310.545(a)(23)(i)
Phenobarbital					
Cough/cold	Cough/cold (miscellaneous)	Corrective	IIIE	IIS	Pending
Phenol					
Antimicrobial I	Antimicrobial	First aid antiseptic	n/a	n/a	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIIE	IIIE	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIS	IIS	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	IIIE	IIIE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIS	IIS	Pending
Antimicrobial I	Antimicrobial	Skin wound protectant	IIIE	IIIE	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	IIS	IIS	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	IIIE	IIIE	Pending
Antimicrobial I	Antimicrobial	Skin wound protectant	n/a	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin wound protectant	IIS	IIS	Pending

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Antimicrobial I	Antimicrobial	Preoperative skin prep	IIS	IIS	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IIIE	IIIE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	IIS	IIS	Pending
Antimicrobial I	Antimicrobial	First aid antiseptic	n/a	I	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIIE	IIIE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IIIE	IIIE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IIS	IIS	Pending
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Antimicrobial II	Antifungal	Antifungal	IISE	IIISE	310.545(a)(22)(ii)
Contraceptive/vaginal	Vaginal	Minor irritations	IIISE	Withdraw	n/a
Dental	Relief of oral discomfort	Toothache relief	IIISE	IIISE	Pending
Dental	Relief of oral discomfort	Oral mucosal analgesic	I	I	Pending
Hemorrhoidal	Anorectal	Antiseptic (intrarectal)	IISE	IISE	310.545(a)(26)(ii)
Hemorrhoidal	Anorectal	Antiseptic (external)	IISE	IISE	310.545(a)(26)(ii)
Miscellaneous external	Antifungal	Diaper rash	Defer	IISE	310.545(a)(22)(ii)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	IISE	310.545(a)(27)(ii)
Miscellaneous external	Boil treatment	Boil treatment	IISE	IIISE	310.531(a)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/ psoriasis	IIIE	IIIE	310.545(a)(7)
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	External analgesic	Diaper rash	Defer	IISE	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Miscellaneous external	External analgesic	Insect bite/sting	IISE	I	Pending
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	I	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	310.545(a)(27)(ii)
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)(A)
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	I	I	Pending
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Phenol sulfonate					
Laxative	Antiemetic	Antiemetic	IIIE	IIE	[52 FR 15891]
Topical analgesic	Sunscreen	Sunscreen	n/a	n/a	[64 FR 27682]
Phenolate sodium					
====	External analgesic	Poison ivy/oak/ sumac	n/a	I	Pending
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Antimicrobial II	Antifungal	Antifungal	IISE	IIISE	310.545(a)(22)(ii)
Contraceptive/vaginal	Vaginal	Minor irritations	IISE	Withdraw	n/a
Dental	Relief of oral discomfort	Toothache relief	IIISE	IIISE	Pending
Dental	Relief of oral discomfort	Oral mucosal analgesic	I	I	Pending
Hemorrhoidal	Anorectal	Antiseptic (external)	IISE	IISE	310.545(a)(26)(ii)
Hemorrhoidal	Anorectal	Antiseptic (intrarectal)	IISE	IISE	310.545(a)(26)(ii)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/ psoriasis	IIIE	IIIE	310.545(a)(7)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	Pending
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Phenolathalain, yellow					
Laxative	Laxative	Stimulant laxative	I	I/IIS	310.545(a)(12)(iv)(B)
Phenolphthalein, white					
Laxative	Laxative	Stimulant laxative	I	I/IIS	310.545(a)(12)(iv)(B)
Phenolphthalein, white [see phenolphthalein]					
====	====	====	====	====	====
Phenoxyacetic acid					
Miscellaneous external	Corn/callus remover	Corn/callus remover	IIIE	IIIE	[55 FR 33261]

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Phenyl salicylate					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(ii)
Laxative	Antidiarrheal	Antidiarrheal	IIIE	IIIE	310.545(a)(3)(i)
Laxative	Antiemetic	Antiemetic	IIIE	IIE	[52 FR 15891]
Miscellaneous external	Corn/callus remover	Corn/callus remover	IISE	IISE	[55 FR 33261]
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Phenylalanine					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Phenylbenzimidazole sulfonic acid [see ensulizole]					
====	====	====	====	====	====
Phenylephrine bitartrate (in an effervescent dosage form)					
n/a	====	Nasal decongestant (oral)	n/a	n/a	341.20(a)(4)
Phenylephrine hydrochloride					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (oral)	I	I	341.20(a)(1)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant))	I	I	341.20(b)(8)
Hemorrhoidal	Anorectal	Vasoconstrictor (intrarectal)	I	I	346.10(d)
Hemorrhoidal	Anorectal	Vasoconstrictor (external)	I	I	346.10(d)
Oral cavity	Oral health care	Oral mucosal decongestant	IIIE	IIIE	Pending
Phenylephrine hydrochloride (0.08–0.2%)					
Ophthalmic	Ophthalmic	Vasoconstrictor	I	I	349.18(c)
Phenylephrine hydrochloride (less than 0.08%)					
Ophthalmic	Ophthalmic	Vasoconstrictor	IIIE	IIIE	310.545(a)(21)(v)
Phenylmercuric acetate					
Contraceptive/vaginal	Contraceptive (vaginal)	Contraceptive	IIS	Withdraw	310.545(a)(28)
Phenylmercuric nitrate					
Contraceptive/vaginal	Contraceptive (vaginal)	Contraceptive	IIS	Withdraw	310.545(a)(28)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Mercury	First aid antiseptic	n/a	IIIE	310.545(a)(27)(i)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Phenylpropanolamine bitartrate					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (oral)	I	II	Pending
Phenylpropanolamine hydrochloride					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (oral)	I	II	Pending
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	IIIE	II	Pending
Miscellaneous internal	Weight control	Anorectic	I	I/IIS	Pending
Oral cavity	Oral health care	Oral mucosal decongestant	IIIE	IIIE	Pending
Phenylpropanolamine maleate					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (oral)	I	II	Pending
Phenyltoloxamine citrate					
Internal analgesic	Internal analgesic	Antipyretic adjuvant	IIIE	IIIE	Pending
Internal analgesic	Internal analgesic	Antirheumatic adjuvant	IIIE	n/a	n/a
Phenyltoloxamine citrate [see phenyltoloxamine dihydrogen citrate]					
====	====	====	====	====	====
Phenyltoloxamine dihydrogen citrate					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	IIIE	IIIE	310.545(a)(6)(i)(B)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)

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Sedative	Nighttime sleep aid	Sleep aid	IIISE	IIISE	[54 FR 6826]
Sedative	Nighttime sleep aid	Sleep aid	IIISE	IIISE	[54 FR 6826]
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)
Phosphate, disodium [see sodium phosphate, dibasic]					
====	====	====	====	====	====
Phosphate, monosodium [see sodium phosphate, monobasic]					
====	====	====	====	====	====
Phosphorated carbohydrate					
Laxative	Antiemetic	Antiemetic	IIIE	IIIE	[52 FR 15891]
Phosphoric acid					
Dental	Anticaries	Anticavity agent	IIE	n/a	310.545(a)(2)(ii)
Phosphorus					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Phytolacca					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Picrotoxin					
Miscellaneous external	Pediculicide	Pediculicide	IISE	IISE	310.545(a)(25)(i)
Pine tar					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/ psoriasis	IIIE	IIIE	310.545(a)(7)
Pine tar syrup					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Pineapple enzymes					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Piperazine citrate					
Miscellaneous internal	Antihelmintic	Anthelmintic	IIS	IIS	[51 FR 27758]
Piperocaine hydrochloride					
Ophthalmic	Ophthalmic	Analgesic/anesthetic	IIS	IIS	310.545(a)(21)(i)
Pipsissewa					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Piroctone olamine					
n/a	TEA	Dandruff	n/a		
Piscidia erythrina					
Miscellaneous internal	Menstrual/diuretic	Dysmenorrhea	IIE	IIE	310.545(a)(24)(i)
Plantago ovata husks [see psyllium husk]					
====	====	====	====	====	====
Plantago seed					
Laxative	Laxative	Bulk laxative	I	IISE	Pending
Miscellaneous internal	Weight control	Anorectic	IIIE	IISE	310.545(a)(20)
Plantago seed husks [see psyllium seed husks]					
====	====	====	====	IISE	Pending
Plantago seed, blond [see plantago seed]					
====	====	====	====	IISE	Pending
Podophyllum resin					
Laxative	Laxative	Stimulant laxative	IIS	IIS	310.545(a)(12)(iv)(A)
Poloxalkol [see polxamer 188]					
====	====	====	====	====	====
Poloxamer 188					
Antimicrobial I	Antimicrobial	Skin wound cleanser	n/a	I	Pending
Laxative	Laxative	Stool softener	IIIE	IIIE	310.545(a)(12)(iii)
Poloxamer 407					
Dental	Relief of oral discomfort	Tooth desensitizer (in combination only)	IIIE	IIIE	Pending
Poloxamer-iodine complex					
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	IIISE	IIISE	Pending

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Antimicrobial I	Antimicrobial	Skin antiseptic	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin protectant	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IIISE	IIISE	Pending
Polycarbophil					
Laxative	Antidiarrheal	Antidiarrheal	I	I	310.545(a)(3)(ii)
Laxative	Laxative	Bulk laxative	I	I	Pending
Polycarbophil, calcium					
Laxative	Antidiarrheal	Antidiarrheal	n/a	I	310.545(a)(3)(ii)
Laxative	Laxative	Bulk laxative	n/a	n/a	n/a
Polydimethylsiloxane and poloxamer					
====	Gingivitis/plaque	Antiplaque/gingivitis	n/a	IIIE	Pending
Polyethylene glycol 300					
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(d)(2)
Polyethylene glycol 400					
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(d)(3)
Polyethylene glycol 6000					
Ophthalmic	Ophthalmic	Demulcent	n/a	IIIE	310.545(a)(21)(iv)
Polymyxin B sulfate					
Antimicrobial II	Antibiotic	Skin wound protectant	I	Defer	n/a
Antimicrobial II	Antibiotic	First aid antibiotic	IIIE	I	333.120 [combos]
Antimicrobial II	Antibiotic	Skin wound antibiotic	I	Defer	n/a
Polyoxyethylene laurate					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Polyoxyethylene monolaurate [see polyoxyethylene laurate]					
====	====	====	====	====	====
Polysorbate 20					
Miscellaneous external	Hair growth/loss	Hair grower	n/a	IIE	310.527(a)
Polysorbate 60					
Miscellaneous external	Hair growth/loss	Hair grower	n/a	IIE	310.527(a)
Polysorbate 80					
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(d)(4)
Polyvinyl alcohol					
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(e)
Polyvinylpyrrolidone [see povidone]					
====	====	====	====	====	====
Potassium acetate					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Potassium alum [see alum, potassium]					
====	====	====	====	====	====
Potassium aluminum sulfate [see alum, potassium]					
====	====	====	====	====	====
Potassium bicarbonate					
Antacid	Antacid	Antacid	n/a	n/a	331.11(j)(1)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Potassium bromide					
Sedative	Nighttime sleep aid	Sleep aid	IISE	IISE	[54 FR 6826]
Sedative	Daytime sedative	Sedative	IIS	IISE	310.519(a)
Potassium carbonate					
Antacid	Antacid	Antacid	n/a	n/a	331.11(j)(1)
Laxative	Antidiarrheal	Antidiarrheal	IIE	IIE	310.545(a)(3)(ii)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Potassium chlorate					
Oral cavity	Oral health care	Antimicrobial	IISE	IISE	Pending
Potassium citrate					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Potassium extract					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Potassium ferrocyanide					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)

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Potassium guaiacolsulfonate					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Potassium iodide					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIS	IISE	310.545(a)(6)(iii)
Oral cavity	Oral health care	Expectorant	IIS	IIS	310.545(a)(6)(iii)
Potassium nitrate					
Dental	Relief of oral discomfort	Tooth desensitizer	IIIE	I	Pending
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Potassium sorbate					
Contraceptive/vaginal	Vaginal	Minor irritations	I	Withdraw	n/a
Povidone					
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IIE	310.545(a)(18)(vi)(A)
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(f)
Povidone silver nitrate					
Miscellaneous internal	Smoking deterrent	Smoking deterrent	n/a	n/a	310.544(d)
Povidone vinylacetate copolymers					
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	n/a	n/a	310.545(a)(18)(vi)(A)
Povidone-iodine					
Antimicrobial I	Antimicrobial	Antiseptic	n/a	I	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	n/a	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin protectant	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IIISE	IIISE	Pending
Antimicrobial II	Acne	Acne	IIIE	IIIE	310.545(a)(1)
Antimicrobial II	Antifungal	Antifungal	IIIE	I	333.210(d)
Contraceptive/vaginal	Vaginal	Minor irritations	I	Withdraw	n/a
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/psoriasis	IIIE	IIIE	310.545(a)(7)
Oral cavity	Oral health care	Antimicrobial	IIISE	IIISE	Pending
Povidone-iodine complex [see povidone-iodine]					
====	====	====	====	====	====
Pramoxine hydrochloride					
====	External analgesic	Poison ivy/oak/sumac	n/a	I	Pending
Hemorrhoidal	Anorectal	Anesthetic (external)	I	I	346.10(g)
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIIE	IIIE	[55 FR 1779]
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	IISE	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Pregnenolone					
Miscellaneous external	Hormone	Hormone	IISE	IIE	310.530(a)
Pregnenolone acetate					
Miscellaneous external	Hormone	Hormone	IISE	IIE	310.530(a)
Progesterone					
Miscellaneous external	Hormone	Hormone	IIE	IIE	310.530(a)
Prolase					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Promethazine hydrochloride					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	I	IIIS	[57 FR 58373]
Propionic acid					
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(ii)

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Propyl benzoate					
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Propyl *p*-benzoate					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Propylene glycol					
Miscellaneous external	Pediculicide	Pediculicide	IISE	IISE	310.545(a)(25)(i)
Ophthalmic	Ophthalmic	Demulcent	I	I	349.12(d)(5)
Miscellaneous external	Hair growth/loss	Hair grower	IISE	n/a	310.527(a)
Propylhexidrine					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant))	I	I	341.20(b)(9)
Propylparaben					
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(ii)
Protease					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Protein					
Miscellaneous external	Hair growth/loss	Hair grower	IISE	n/a	310.527(a)
Protein hydrolysate					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	310.545(a)(18)(iii)
Proteins [see protein]					
====	====	====	====	====	====
Prune concentrate dehydrate					
Laxative	Laxative	Stimulant laxative	IIIE	IIIE	310.545(a)(12)(iv)(A)
Prune powder					
Laxative	Laxative	Stimulant laxative	IIIE	IIIE	310.545(a)(12)(iv)(A)
Pseudoephedine sulfate					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (oral)	I	I	341.20(a)(3)
Pseudoephedrine hydrochloride					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator nasal	IIE	IIE	310.545(a)(6)(iv)(A)
Cough/cold	Cough/cold (nasal decongestant)	Decongestant (oral)	I	I	341.20(a)(2)
Pseudoephedrine sulfate					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	IIE	IIE	310.545(a)(6)(iv)(A)
Psyllium (hemicellulose) [see plantago seed]					
====	====	====	====	IISE	Pending
Psyllium hydrophilic mucilloid					
Laxative	Laxative	Bulk laxative	I	IISE	Pending
Psyllium seed					
Laxative	Laxative	Bulk laxative	I	IISE	Pending
Psyllium seed (blond)					
Laxative	Laxative	Bulk laxative	I	IISE	Pending
Psyllium seed husks					
Laxative	Laxative	Bulk laxative	I	IISE	Pending
Pyrantel pamoate					
Miscellaneous internal	Antihelmintic	Anthelmintic	I	I	357.110
Pyrethins [see pyrethrum extract]					
====	====	====	====	====	====
Pyrethrum extract (aerosol) with piperonyl butoxide					
====	Pediculicide	Pediculicide	n/a	n/a	310.545(a)(25)(ii)
Pyrethrum extract (nonaerosol) with piperonyl butoxide					
Miscellaneous external	Pediculicide	Pediculicide	I	I	358.610
Pyridoxine hydrochloride					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	DEF	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	IISE	310.545(a)(18)(iv)
Miscellaneous internal	Menstrual/diuretic	Premenstrual/menstrual period	IIIE	IIIE	Pending
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)

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Pyrilamine maleate					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Cough/cold	Cough/cold (antihistamine)	Antihistamine	I	I	341.12(k)
Internal analgesic	Internal analgesic	Analgesic adjuvant	IIIE	IIIE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antipyretic adjuvant	IIIE	IIIE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antirheumatic adjuvant	IIIE	n/a	310.545(a)(23)(i)
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)(A)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	n/a	IISE	Pending
Miscellaneous internal	Menstrual/diuretic	Antihistamine	I	IIISE	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	IIE	IIE	310.545(a)(14)
Sedative	Nighttime sleep aid	Sleep aid	IIISE	IIISE	[54 FR 6826]
Sedative	Daytime sedative	Sedative	IIISE	IISE	310.519(a)
Pyrithione zinc					
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	I	I	358.710(a)(2)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	I	I	358.710(a)(3)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Seborrheic dermatitis	I	I	358.710(b)(3)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Seborrheic dermatitis	I	I	358.710(b)(2)
Quinine					
Internal analgesic	Internal analgesic	Analgesic	IIS	IIS	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antipyretic	IIS	IIS	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antirheumatic	IISE	Not OTC	310.545(a)(23)(i)
Quinine ascorbate					
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IIE	IIE	310.544(d)
Quinine sulfate					
Miscellaneous internal	Leg muscle cramp	Nocturnal leg muscle cramps	IIISE	IIISE	310.546
Racemethionine					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	310.545(a)(18)(iii)
Racephedrine hydrochloride					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	I	I	341.16(f)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	I	I	310.545(a)(6)(ii)(B)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (oral)	IIIE	IIIE	310.545(a)(6)(ii)(B)
Racepinephrine hydrochloride					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	n/a	n/a	341.16(g)
Red petrolatum [see petrolatum, red]					
====	====	====	====	====	====
Released carbon dioxide [see carbon dioxide, released]					
====	====	====	====	====	====
Reosote					
====	Skin protectant	Poison ivy/oak/sumac	n/a	IISE	310.545(a)(18)(vi)(A)
Dental	Relief of oral discomfort	Toothache relief	IIISE	IIISE	Pending
Resorcinol					
====	External analgesic	Poison ivy/oak/sumac	n/a	I	Pending
====	n/a	Dandruff/seborrheic dermatitis/psoriasis	n/a	n/a	310.545(a)(7)
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Antimicrobial II	Antifungal	Antifungal	IISE	IISE	310.545(a)(22)(ii)

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Hemorrhoidal	Anorectal	Antiseptic (intrarectal)	IISE	IISE	310.545(a)(26)(ii)
Hemorrhoidal	Anorectal	Keratolytic (external)	I	I	346.20(a)
Hemorrhoidal	Anorectal	Keratolytic (intrarectal)	IISE	IISE	346.20(a)
Hemorrhoidal	Anorectal	Antiseptic (external)	IISE	IISE	310.545(a)(26)(ii)
Miscellaneous external	Antifungal	Diaper rash	Defer	IISE	310.545(a)(22)(ii)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	IISE	Pending
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Psoriasis	IIE	IIE	[56 FR 63567]
Miscellaneous external	External analgesic	Diaper rash	Defer	IISE	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Resorcinol monoacetate					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Rhubarb fluidextract					
Laxative	Antidiarrheal	Antidiarrheal	IISE	IISE	310.545(a)(3)(ii)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Rhubarb, chinese					
Laxative	Laxative	Stimulant laxative	IIISE	IIISE	310.545(a)(12)(iv)(A)
Riboflavin					
Miscellaneous internal	Menstrual/diuretic	Premenstrual/menstrual period	n/a	IISE	310.545(a)(24)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Rice polishings					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Rose petals, infusion of					
Ophthalmic	Ophthalmic	Astringent	IIIE	IIIE	310.545(a)(21)(iii)
Rosin					
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Rosin cerate					
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Sabadilla alkaloids					
Miscellaneous external	Pediculicide	Pediculicide	IISE	IISE	310.545(a)(25)(i)
Sabel, liposterolic extract of					
Miscellaneous internal	Benign prostatic hypertrophy	Benign prostatic hypertrophy	n/a	n/a	310.532(a)
Saccharin					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Sage oil					
Miscellaneous external	Skin protectant	Astringent	n/a	IISE	310.545(a)(18)(ii)
Salicyl alcohol					
Oral cavity	Oral health care	Analgesic/anesthetic	I	I	Pending
Salicylamide					
====	External analgesic	Poison ivy/oak/sumac	n/a	IIIE	310.545(a)(10)(vii)
Internal analgesic	Internal analgesic	Analgesic adjuvant	IIISE	IIISE	Pending
Internal analgesic	Internal analgesic	Analgesic	IIISE	IIISE	Pending
Internal analgesic	Internal analgesic	Antipyretic adjuvant	IIISE	IIISE	Pending
Internal analgesic	Internal analgesic	Antipyretic	IIISE	IIISE	Pending
Internal analgesic	Internal analgesic	Antirheumatic adjuvant	IIISE	n/a	n/a
Internal analgesic	Internal analgesic	Antirheumatic	IISE	Not OTC	n/a
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIIE	310.545(a)(10)(v)
Miscellaneous internal	Menstrual/diuretic	Analgesic	IIISE	IIISE	Pending
Sedative	Nighttime sleep aid	Sleep aid	IIE	IIE	[54 FR 6826]
Sedative	Daytime sedative	Sedative	IIE	IISE	310.519(a)
Topical analgesic	External analgesic	Analgesic/anesthetic	IIIE	IIIE	310.545(a)(10)(i)
Salicylic acid					
Antimicrobial II	Acne	Acne	IIIE	I	333.310(c)
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(ii)
Antimicrobial II	Acne	Acne	IISE	IISE	310.545(a)(1)
Miscellaneous external	Antifungal	Diaper rash	Defer	IISE	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	I	I	358.710(a)(4)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)

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Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Miscellaneous external	Corn/callus remover	Corn/callus remover	I	I	358.510(a)
Miscellaneous external	Wart remover	Wart remover	I	IISE	358.110(a)
Miscellaneous external	Wart remover	Wart remover	I	I	358.110(b)
Miscellaneous external	Wart remover	Wart remover	I	I	358.110(c)
Miscellaneous external	Corn/callus remover	Corn/callus remover	I	I	358.510 (b)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Seborrheic dermatitis	I	I	358.710(b)(4)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Psoriasis	I	I	358.710(c)(2)
Salsalate					
Internal analgesic	Internal analgesic	Analgesic	IIISE	IIISE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antipyretic	IIISE	IIISE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antirheumatic	IIISE	Not OTC	310.545(a)(23)(i)
Sanguinaria extract					
====	Gingivitis/plaque	Gingivitis/antiplaque	n/a	IIIE	Pending
Sarsaparrilla					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Sassafras oil					
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Saw palmetto					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Scopolamine aminoxide hydrobromide					
Sedative	Nighttime sleep aid	Sleep aid	IISE	IIS	[54 FR 6826]
Sedative	Daytime sedative	Sedative	IISE	IISE	310.519(a)
Scopolamine hydrobromide					
Laxative	Antidiarrheal	Antidiarrheal	IIE	IIE	310.545(a)(3)(i)
Laxative	Antiemetic	Antiemetic	n/a	IIIE	[52 FR 15891]
Sedative	Nighttime sleep aid	Sleep aid	IISE	IIS	[54 FR 6826]
Sedative	Daytime sedative	Sedative	IISE	IISE	310.519(a)
Sea kelp [see kelp]					
====	====	====	====	====	====
Sea minerals					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Selenium sulfide					
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	I	I	358.710(a)(5)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Seborrheic dermatitis	I	I	358.710(b)(5)
Selenium sulfide, micronized					
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	n/a	I	358.710(a)(6)
Senecio aureus					
Miscellaneous internal	Menstrual/diuretic	Dysmenorrhea	IISE	IISE	310.545(a)(24)(i)
Senna					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(8)(ii)
Senna fluidextract					
Laxative	Laxative	Stimulant laxative	I	I/IIIS	Pending
Senna pod concentrate					
Laxative	Laxative	Stimulant laxative	I	I/IIIS	Pending
Senna syrup					
Laxative	Laxative	Stimulant laxative	I	I/IIIS	Pending
Sennosides A and B [see sennosides]					
====	====	====	====	====	====
Sennosides A and B					
Laxative	Laxative	Stimulant laxative	I	I/IIIS	Pending
Sesame oil					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	Pending
Sesame seed					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)

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Shark liver oil					
====	Insect bite/sting	Insect bite/sting	n/a	n/a	310.545(a)(18)(v)(B)
====	Poison ivy/oak/sumac	Poison ivy/oak/ sumac	n/a	n/a	310.545(a)(18)(vi)(B)
====	Skin protectant	Fever blister (topical)	n/a	I	Pending
Hemorrhoidal	Anorectal	Wound healing agent (intrarectal)	IIIE	IIIE	310.545(a)(26)(x)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(b)(3)
Hemorrhoidal	Anorectal	Wound healing agent (external)	IIIE	IIIE	310.545(a)(26)(x)
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(b)(3)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Protectant	I	I	Pending
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	Pending
Topical analgesic	Skin protectant	Skin protectant	I	I	310.545(a)(18)(i)(B)
Silicone					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Silver acetate					
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IIIE	IIIE	310.544(d)
Silver nitrate					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IISE	IISE	310.544(d)
Silver protein, mild					
Ophthalmic	Ophthalmic	Anti-infective	IIIE	IIIE	310.545(a)(21)(ii)
Simethicone					
Antacid	Antacid	Antacid	IIIE	IIE	[39 FR 19873]
Antacid	Antiflatulent	Antiflatulent	IIIE	I	332.10
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIIE	IIIE	[58 FR 54454]
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIIE	IIIE	[58 FR 54454]
Sodium					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Sodium 3, 4-dimethylphenyl-glyoxylate					
Topical analgesic	Sunscreen	Sunscreen	IISE	IISE	[64 FR 27682]
Sodium acetylsalicylate					
Miscellaneous internal	Overindulgence in alcohol/food	Overindulgence remedies (hangover)	I	I	Pending
Sodium aluminum chlorohydroxy lactate (aerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIISE	IIISE	310.545(a)(4)
Sodium aluminum chlorohydroxy lactate (nonaerosol)					
Antiperspirant	Antiperspirant	Antiperspirant	IIIE	IIIE	310.545(a)(4)
Sodium aminobenzoate					
Internal analgesic	Internal analgesic	Analgesic adjuvant	IISE	IISE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antipyretic adjuvant	IISE	IISE	310.545(a)(23)(i)
Internal analgesic	Internal analgesic	Antirheumatic adjuvant	IISE	n/a	310.545(a)(23)(i)
Sodium benzoate					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Sodium bicarbonate					
====	Gingivitis/plaque	Gingivitis/antiplaque	n/a	IIIE	Pending
Antacid	Antacid	Antacid	I	I	331.11(k)(1)
Contraceptive/vaginal	Vaginal	Alters vaginal pH	IIIE	Withdraw	n/a
Dental	Anticaries	Anticavity agent	IIE	IIE	[60 FR 52504]
Internal analgesic	Internal analgesic	Corrective	I	n/a	n/a

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Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Insect bite/sting	IISE	n/a	n/a
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	Pending
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	Pending
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	I	Pending
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIIE	IIIE	310.545(a)(8)(i)
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIIE	IIIE	310.545(a)(8)(i)
Miscellaneous internal	Weight control	Anorectic	IIIE	IISE	310.545(a)(20)
Oral cavity	Oral health care	Debriding agent	I	I	Pending
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(O)
Sodium borate					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(ii)
Contraceptive/vaginal	Vaginal	Lowers surface tension mucolytic effects	IIISE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Minor irritations	IIISE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Alters vaginal pH	IIISE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Astringent	IIISE	Withdraw	n/a
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/ psoriasis	IIE	IIE	310.545(a)(7)
Miscellaneous external	External analgesic	Astringent	n/a	n/a	n/a
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)(A)
Oral cavity	Oral health care	Debriding agent	IISE	IISE	Pending
Sodium borate monohydrate					
Dental	Oral mucosal injury	Skin wound cleanser	IISE	IISE	Pending
Sodium bromide					
Sedative	Nighttime sleep aid	Sleep aid	IISE	IISE	[54 FR 6826]
Sedative	Daytime sedative	Sedative	IIS	IISE	310.519(a)
Sodium caprylate					
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(ii)
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	Pending
Sodium carbonate					
Antacid	Antacid	Antacid	I	I	331.11(k)(1)
Contraceptive/vaginal	Vaginal	Alters vaginal pH	IIISE	Withdraw	n/a
Internal analgesic	Internal analgesic	Corrective	I	n/a	n/a
Sodium caseinate					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Sodium chloride					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Ophthalmic	Ophthalmic	Hypertonic agent	I	I	349.16
Sodium citrate					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Dental	Relief of oral discomfort	Tooth desensitizer (in combination only)	IIIE	IIIE	Pending
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIIE	IIIE	310.545(a)(8)(i)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIIE	IIIE	310.545(a)(8)(i)
Sodium citrate in solution					
Miscellaneous internal	Overindulgence in alcohol/food	Overindulgence remedies (hangover)	I	I	Pending
Miscellaneous internal	Overindulgence in alcohol/food	Overindulgence remedies (hangover)	I	I	Pending

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Sodium diacetate					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Sodium dichromate					
Oral cavity	Oral health care	Antimicrobial	IIS	IISE	Pending
Sodium dihydrogen phosphate [see sodium phosphate, monobasic]					
====	====	====	====	====	====
Sodium fluoride					
Dental	Anticaries	Anticavity dentrifrice	I	I	355.10(a)(2)
Dental	Anticaries	Anticavity dental rinse	I	I	355.10(a)(3)(iv)
Dental	Anticaries	Anticavity dental rinse	I	I	355.10(a)(3)(v)
Dental	Anticaries	Anticavity dentrifrice	I	I	355.10(a)(1)
Dental	Anticaries	Anticavity dental rinse	I	I	355.10(a)(3)(iii)
Dental	Relief of oral discomfort	Tooth desensitizer (in combination only)	IISE	IISE	Pending
Dental	Relief of oral discomfort	Tooth desensitizer	IIIE	IIIE	Pending
Sodium lactate					
Contraceptive/vaginal	Vaginal	Alters vaginal pH	IIIE	Withdraw	n/a
Sodium lauryl sulfate					
Contraceptive/vaginal	Vaginal	Lowers surface tension mucolytic effects	I	Withdraw	n/a
Sodium monoflurorophosphate					
Dental	Anticaries	Anticavity dentrifrice	I	I	355.10(b)(1)
Dental	Anticaries	Anticavity dental rinse	IIS	IIS	310.545(a)(2)(i)
Dental	Relief of oral discomfort	Tooth desensitizer	IIIE	IIIE	Pending
Dental	Anticaries	Anticavity dentrifrice	I	I	355.10(b)(2)
Sodium nitrate					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Sodium oleate					
Laxative	Laxative	Stimulant laxative	IIIE	IIIE	310.545(a)(12)(iv)(A)
Sodium perborate					
Contraceptive/vaginal	Vaginal	Alters vaginal pH	IIISE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Astringent	IIISE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Lowers surface tension mucolytic effects	IIISE	Withdraw	n/a
Contraceptive/vaginal	Vaginal	Minor irritations	IIISE	Withdraw	n/a
Oral cavity	Oral health care	Debriding agent	IIISE	IIISE	Pending
Sodium perborate monohydrate					
Dental	Oral health care	Wound cleanser	IISE	I	Pending
Sodium phosphate [see sodium phosphate, dibasic]					
====	====	====	====	====	====
Sodium phosphate, dibasic					
Dental	Anticaries	Anticavity agent	IIE	IIE	310.545(a)(2)(ii)
Laxative	Laxative	saline laxative	I	I	Pending
Sodium phosphate, dibasic anhydrous reagent [see sodium phosphate, dibasic]					
====	====	====	====	====	====
Sodium phosphate, monobasic					
Dental	Anticaries	Anticavity agent	IIE	IIE	310.545(a)(2)(ii)
Laxative	Laxative	Saline laxative	I	I	Pending
Sodium picosulfate					
n/a	TEA	Laxative	n/a		
Sodium potassium tartrate					
Antacid	Antacid	Antacid	I	I	331.11(j)(2) 331.11(k)(2)
Sodium potassium tartrate [see potassium sodium tartrate]					
====	====	====	====	====	====
Sodium propionate					
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(ii)
Contraceptive/vaginal	Vaginal	Minor irritations	I	Withdraw	n/a
Miscellaneous external	Antifungal	Diaper rash	Defer	IISE	310.545(a)(22)(ii)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	IIISE	Pending

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Sodium salicylate					
Contraceptive/vaginal	Vaginal	Minor irritations	IISE	Withdraw	n/a
Internal analgesic	Internal analgesic	Analgesic	I	I	Pending
Internal analgesic	Internal analgesic	Antipyretic	I	I	Pending
Internal analgesic	Internal analgesic	Antirheumatic	I	Not OTC	n/a
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/ psoriasis	IIIE	IIIE	310.545(a)(7)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Miscellaneous internal	Menstrual/diuretic	Analgesic	I	I	Pending
Miscellaneous internal	Menstrual/diuretic	Diuretic	IIIE	IIIE	310.545(a)(24)(i)
Miscellaneous internal	Overindulgence in alcohol/food	Overindulgence remedies (hangover)	I	I	Pending
Sodium salicylate acid phenolate					
Hemorrhoidal	Anorectal	Antiseptic (intrarectal)	IISE	IISE	310.545(a)(26)(ii)
Hemorrhoidal	Anorectal	Antiseptic (external)	IISE	IISE	310.545(a)(26)(ii)
Contraceptive/vaginal	Vaginal	Minor irritations	IISE	Withdraw	n/a
Sodium sulfide					
Miscellaneous external	Ingrown toenail	Ingrown toenail	n/a	I	538.310
Miscellaneous external	Ingrown toenail	Ingrown toenail	IIIE	IIIE	310.538(a) [removed 68 FR 24348]
Sodium thiosulfate					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Sorbitan monostearate					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Sorbitan sesquioleate					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Sorbitol					
Laxative	Laxative	Hyperosmotic laxative	I	I	Pending
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	IIE	IIE	310.545(a)(8)(i)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	IIE	IIE	310.545(a)(8)(i)
Oral cavity	Oral health care	Oral health care nonantimicrobial	n/a	n/a	310.545(a)(14)
Soyasterol					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Soybean oil, hydrogenated					
Miscellaneous internal	Cholecystokinetic	Cholecystokinetic	n/a	n/a	357.210(b)
Soybean protein					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Soymeal					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Spermaceti					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Squill					
Cough/cold	Cough/cold (expectorant)	Expectorant	IISE	IISE	310.545(a)(6)(iii)
Squill extract					
Cough/cold	Cough/cold (expectorant)	Expectorant	IISE	IISE	310.545(a)(6)(iii)
Stannous fluoride					
====	Antigingivitis	Antigingivitis	I	=====	Pending
Dental	Anticaries	Anticavity dental gel	I	I	355.10(c)(2)
Dental	Anticaries	Anticavity dentrifrice	I	I	355.10(c)(1)
Dental	Anticaries	Anticavity dental rinse	I	I	355.10(c)(3)
Dental	Relief of oral discomfort	Tooth desensitizer	IIIE	IIIE	Pending
Stannous pyrophosphate and zinc citrate					
====	Gingivitis/plaque	Antiplaque/gingivitis	n/a	IIIE	Pending

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Stearly alcohol					
====	Insect bite/sting	Insect bite/sting	n/a	n/a	310.545(a)(18)(v)(B)
====	Poison ivy/oak/sumac	Poison ivy/oak/ sumac	n/a	n/a	310.545(a)(18)(vi)(B)
====	Skin protectant	Skin protectant	n/a	n/a	310.545(a)(18)(i)(B)
Stem bromelain					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Strawberry					
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Strontium chloride					
Dental	Relief of oral discomfort	Tooth desensitizer (in combination only)	IISE	IISE	Pending
Dental	Relief of oral discomfort	Tooth desensitizer	IIIE	IIIE	Pending
Strychnine					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Miscellaneous internal	Digestive aid	Digestive aid (ippuad)	n/a	n/a	310.545(a)(18)(ii)
Sucrose					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Sucrose octaacetate					
Miscellaneous external	Nailbiting/thumbsucking	Nailbiting/ thumbsucking deterrent	IIIE	IIIE	310.536(a)
Sugars					
Oral cavity	Oral health care	Oral health care nonantimicrobial	n/a	n/a	310.545(a)(14)
Sulfacetamide sodium					
Miscellaneous external	Hair growth/loss	Hair grower	n/a	n/a	310.527(a)
Ophthalmic	Ophthalmic	Anti-infective	IIS	IIS	310.545(a)(21)(ii)
Sulfur					
====	External analgesic	Poison ivy/oak/ sumac	n/a	IIE	310.545(a)(10)(vii)
====	Skin protectant	Wound healing agent	n/a	n/a	310.545(a)(18)(i)(A)
Antimicrobial II	Acne	Acne	I	I	333.310(d)
Antimicrobial II	Acne	Acne	I	I	333.310(e)
Miscellaneous external	Boil treatment	Boil treatment	n/a	IIISE	310.531(a)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff	I	I	358.710(a)(7)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IISE	310.545(a)(18)(iii)
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	IISE	310.545(a)(18)(iv)
Topical analgesic	Skin protectant	Skin protectant	IISE	IISE	310.545(a)(18)(i)(A)
Sulfur (paraffinic hydrocarbons)					
Miscellaneous external	Hair growth/loss	Hair grower	n/a	IIE	310.527(a)
Sulfur, precipitated					
Hemorrhoidal	Anorectal	Keratolytic (external)	IIIE	IIIE	310.545(a)(26)(v)
Hemorrhoidal	Anorectal	Keratolytic (intrarectal)	IIE	IIE	310.545(a)(26)(v)
Sulfur, sublimed					
Hemorrhoidal	Anorectal	Keratolytic (intrarectal)	IIE	IIE	310.545(a)(26)(v)
Hemorrhoidal	Anorectal	Keratolytic (external)	IIIE	IIIE	310.545(a)(26)(v)
Miscellaneous external	Pediculicide	Pediculicide	IISE	IISE	310.545(a)(25)(i)
Sulfurated oils of turpentine					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Sulisobenzone					
Topical analgesic	Sunscreen	Sunscreen	I	I	352.10(o)
Sweet spirits of nitre					
Miscellaneous external	Sweet spirits of nitre	All indications	IISE	n/a	310.502(a)(12)
Syrup of pine tar [see pine tar syrup]					
====	====	====	====	====	====
Talc					
====	Antimicrobial	Diaper rash	n/a	n/a	Pending
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	I	Pending

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Talcum powder					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Tannic acid					
====	Skin protectant	Diaper rash	n/a	IISE	310.545(a)(18)(iii)
====	Skin protectant	Wound healing agent	n/a	n/a	310.545(a)(18)(i)
Antimicrobial II	Antifungal	Antifungal	IIE	IIE	310.545(a)(22)(ii)
Hemorrhoidal	Anorectal	Astringent (external)	IISE	IISE	310.545(a)(26)(iii)
Hemorrhoidal	Anorectal	Anorectal (intrarectal)	IISE	IISE	310.545(a)(26)(iii)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIISE	310.545(a)(10)(v)
Miscellaneous external	External analgesic	Insect bite/sting	n/a	IIIE	Pending
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IIIE	310.545(a)(10)(vii)
Miscellaneous external	Ingrown toenail	Ingrown toenail	IIIE	IIIE	310.538(a)
Miscellaneous external	Ingrown toenail	Astringent(external)	IIIE	IIIE	310.538(a)
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	IIISE	310.545(a)(18)(iv)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(8)(ii)
Topical analgesic	Skin protectant	Skin protectant	IISE	IISE	310.545(a)(18)(i)(A)
Tannic acid glycerite					
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Tar oil					
Miscellaneous external	Hair growth/loss	Hair grower	IISE	n/a	310.527(a)
Taraxacum officinale					
Miscellaneous external	Menstrual/diuretic	Dysmenorrhea	IIE	IIE	310.545(a)(24)(i)
Tartaric acid					
Antacid	Antacid	Antacid	I	I	331.11(m)
Contraceptive/vaginal	Vaginal	Alters vaginal pH	IIIE	Withdraw	n/a
Laxative	Laxative	Saline laxative	IIISE	IIISE	310.545(a)(12)(ii)
Terpin hydrate					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Terpin hydrate elixir					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Testosterone					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IIS	IIS	310.528(a)
Tetracaine					
====	External analgesic	Poison ivy/oak/sumac	n/a	I	Pending
Hemorrhoidal	Anorectal	Anesthetic (external)	IIIE	I	346.10(h)
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIIE	IIIE	[55 FR 1779]
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	IISE	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	IIS	IIS	310.545(a)(14)
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Tetracaine hydrochloride					
====	External analgesic	Poison ivy/oak/sumac	n/a	I	Pending
Antimicrobial II	Acne	Acne	IISE	IISE	310.545(a)(1)
Hemorrhoidal	Anorectal	Anesthetic (external)	IIIE	I	346.10(i)
Hemorrhoidal	Anorectal	Anesthetic (intrarectal)	IIIE	IIIE	[55 FR 1779]
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	I	Pending
Miscellaneous external	Hair growth/loss	Hair grower	IIE	IIE	310.527(a)
Oral cavity	Oral health care	Analgesic/anesthetic	IIS	IIS	310.545(a)(14)
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Tetracycline hydrochloride					
Antimicrobial II	Antibiotic	First aid antibiotic	n/a	I	333.110(f)
Antimicrobial II	Antibiotic	Skin wound antibiotic	IIIE	Defer	n/a
Antimicrobial II	Antibiotic	Skin wound protectant	I	Defer	n/a
Tetrahydrozoline hydrochloride					
Ophthalmic	Ophthalmic	Vasoconstrictor	I	I	349.18(d)
Thenyldiamine hydrochloride					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	IIIE	IIIE	310.545(a)(6)(i)(A)&(B)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	IIIE	IIIE	[59 FR 43408]

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Theobromine sodium salicylate					
Miscellaneous internal	Menstrual/diuretic	Diuretic	IIIE	IIIE	310.545(a)(24)(i)
Theophylline					
Miscellaneous internal	Menstrual/diuretic	Diuretic	IIIE	IIIE	310.545(a)(24)(i)
Theophylline (all combinations)					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	n/a	n/a	310.545(a)(6)(iv)(B)
Theophylline anhydrous [see theophylline, anhydrous]					
====	====	====	====	====	====
Theophylline anhydrous [see theophylline]					
====	====	====	====	====	====
Theophylline calcium salicylate					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	I	IIS	310.545(a)(6)(iv)(A)
Theophylline sodium glycinate					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	I	IIS	310.545(a)(6)(iv)(A)
Theophylline, anhydrous					
Cough/cold	Cough/cold (bronchodilator)	Bronchodilator	I	IIS	310.545(a)(6)(iv)(A)
Thiamine					
Miscellaneous internal	Oral insect repellant	Insect repellent	IIE	IIE	310.529(a)
Thiamine hydrochloride					
Miscellaneous external	Hair growth/loss	Hair grower	n/a	n/a	310.527(a)
Miscellaneous internal	Menstrual/diuretic	Menstrual	n/a	IISE	310.545(a)(24)(i)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Sedative	Nighttime sleep aid	Sleep aid	IIE	IIE	[54 FR 6826]
Sedative	Daytime sedative	Sedative	IIE	IISE	310.519(a)
Thiamine mononitrate					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Thimerosal					
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Miscellaneous external	Mercury	First aid antiseptic	n/a	IISE	310.545(a)(27)(i)
Thiocyanoacetate					
====	Pediculicide	Pediculicide	n/a	n/a	310.545(a)(25)(i)
Thonzylamine hydrochloride					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	I	I	341.12(l)
Threonine					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Thyme oil, white					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Thymol					
====	External analgesic	Poison ivy/oak/sumac	n/a	IIIE	310.545(a)(10)(vii)
Antimicrobial II	Acne	Acne	IIE	IIIE	310.545(a)(1)
Antimicrobial II	Antifungal	Antifungal	IIISE	IIISE	310.545(a)(22)(ii)
Cough/cold	Cough/cold (antihistamine)	Antitussive (topical/inhalant)	IIIE	IIIE	[52 FR 30055]
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (inhalant room spray)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (lozenge)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (mouthwash)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Dental	Relief of oral discomfort	Toothache relief	IIIE	IIIE	Pending
Dental	Relief of oral discomfort	Oral mucosal analgesic	IIIE	IIIE	Pending

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Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/ psoriasis	IIIE	IIIE	310.545(a)(7)
Miscellaneous external	External analgesic	Astringent	IISE	n/a	n/a
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIISE	310.545(a)(10)(v)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous internal	Smoking deterrent	Smoking deterrent	IIE	IIE	310.544(d)
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	Pending
Oral cavity	Oral health care	Analgesic/anesthetic	IIIE	IIIE	310.545(a)(14)
Topical analgesic	External analgesic	Analgesic/anesthetic	IIIE	IIIE	310.545(a)(10)(i)
Thymol iodide					
Dental	Relief of oral discomfort	Oral mucosal analgesic	IIIE	IIIE	Pending
Dental	Relief of oral discomfort	Toothache relief	IIIE	IIIE	Pending
Oral cavity	Oral health care	Antimicrobial	IIISE	IIISE	Pending
Tincture of impatiens bi-flora [see impatiens bi-flora tincture]					
====	====	====	====	====	====
Tincture of iodine [see iodine tincture]					
====	====	====	====	====	====
Titanium dioxide					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	v	n/a
Topical analgesic	Sunscreen		I	I	352.10(p)
Tolindate					
Antimicrobial II	Antifungal	Antifungal	IISE	IISE	310.545(a)(22)(ii)
Tolnaftate					
Antimicrobial II	Antifungal	Antifungal	I	I	333.210(e)
Tolu					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Tolu balsam					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Oral cavity	Oral health care	Antimicrobial	IIIE	IIIE	Pending
Oral cavity	Oral health care	Expectorant	IIIE	n/a	310.545(a)(6)(iii)
Tolu balsam tincture					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
Topical starch					
====	Skin protectant	Poison ivy/oak/ sumac	n/a	IIIE	310.545(a)(18)(vi)(A)
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(9)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(9)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Astringent	IISE	IISE	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	I	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	IIISE	310.545(a)(18)(iv)
Topical analgesic	Skin protectant	Skin protectant	I	Defer	347.10(q)
Triacetin					
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(ii)
Tribromsalan					
Antimicrobial I	Antimicrobial	Antimicrobial	IIS	n/a	310.502(a)(5)
Tricalcium phosphate					
Antacid	Antacid	Antacid	n/a	n/a	331.11(i)(3)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Tricalcium phosphate [see calcium phosphate, tribasic]					
====	====	====	====	====	====

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Triclocarban					
Antimicrobial I	Antimicrobial	Skin antiseptic	n/a	IIIE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	IISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IISE	IISE	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IISE	IISE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IISE	IISE	Pending
Antimicrobial I	Antimicrobial	Skin protectant	IISE	IISE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IIISE	IIISE	Pending
Triclosan					
Antimicrobial I	Antimicrobial	Skin antiseptic	n/a	IIIE	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin protectant	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IISE	IIISE	Pending
Miscellaneous external	Antimicrobial	Diaper rash	Defer	IIISE	Pending
Miscellaneous external	Boil treatment	Boil treatment	n/a	n/a	310.531(a)
n/a	TEA	Acne	n/a		
n/a	TEA	Antigingivitis	n/a		
Trillium					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Tripelennamine hydrochloride					
====	External analgesic	Poison ivy/oak/sumac	n/a	I	Pending
Cough/cold	Cough/cold (antihistamine)	Antihistamine	n/a	n/a	[57 FR 58373]
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIIE	310.545(a)(10)(v)
Topical analgesic	External analgesic	Analgesic/anesthetic	I	I	Pending
Triple dye					
Antimicrobial I	Antimicrobial	Skin antiseptic	n/a	IIISE	Pending
Antimicrobial I	Antimicrobial	Antimicrobial soap	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin protectant	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	n/a	IIISE	Pending
Triprolidine hydrochloride					
Cough/cold	Cough/cold (antihistamine)	Antihistamine	n/a	I	341.12(m)
Triticum					
Miscellaneous internal	Menstrual/diuretic	Menstrual	n/a	IISE	310.545(a)(24)(i)
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Trolamine					
Miscellaneous external	External analgesic	Insect bite/sting	IIIE	IISE	Pending
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	n/a	Pending
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	IIIE	310.545(a)(18)(iv)(A)
Miscellaneous external	Skin protectant	Insect bite/sting	IIIE	IIIE	310.545(a)(18)(v)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IIIE	310.545(a)(18)(vi)(A)
Trolamine salicylate					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIIE	310.545(a)(10)(v)
Miscellaneous external	External analgesic	Insect bite/sting	n/a	IIIE	310.545(a)(10)(vi)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	n/a	IIIE	310.545(a)(10)(vii)
Topical analgesic	External analgesic	Analgesic/anesthetic	IIIE	IIIE	Pending
Topical analgesic	Sunscreen	Sunscreen	I	I	352.10(q)
Tryptophan					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)

Review Panel	Report	Drug Category	ANPR	PR	FR
Turpentine oil					
Cough/cold	Cough/cold (antitussive)	Antitussive (oral)	IISE	IISE	Pending
Cough/cold	Cough/cold (antitussive)	Antitussive (topical/inhalant)	IIIE	IIIE	[52 FR 30055]
Cough/cold	Cough/cold (expectorant)	Expectorant (topical/inhalant)	IIIE	IIIE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (expectorant)	Expectorant (oral)	IISE	IISE	310.545(a)(6)(iii)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (oral)	IISE	IISE	310.545(a)(6)(ii)(A)
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant (topical/inhalant)	IIIE	IIIE	310.545(a)(6)(ii)(A)
Topical analgesic	External analgesic	Counterirritant	I	I	Pending
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIIE	310.545(a)(10)(v)
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)(A)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Turpentine oil, rectified					
Hemorrhoidal	Anorectal	Counterirritant (intrarectal)	IISE	IISE	310.545(a)(26)(iv)
Hemorrhoidal	Anorectal	Counterirritant (external)	IISE	IISE	310.545(a)(26)(iv)
Turpentine, venice					
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Tyrosine					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Undecoylilum chlorideiodine complex [see undecoyliumchloride iodine complex]					
====	====	====	====	====	====
Undecoylium chlorideiodine complex					
Antimicrobial I	Antimicrobial	Antimicrobial soap	n/a	IISE	Pending
Antimicrobial I	Antimicrobial	Skin wound cleanser	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Surgical hand scrub	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin protectant	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Skin antiseptic	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Preoperative skin prep	IIISE	IIISE	Pending
Antimicrobial I	Antimicrobial	Health care personnel handwash	IIIE	IIIE	Pending
Undecylenic acid					
Antimicrobial II	Antifungal	Antifungal	I	I	333.210(f)
Miscellaneous external	Antifungal	Diaper rash	Defer	IISE	310.545(a)(22)(i)
Undecylenic acid monoethanolamine sulfosuccinate sodium					
Miscellaneous external	Dandruff/seborrheic dermatitis/psoriasis	Dandruff/seborrheic dermatitis/psoriasis	IIIE	IIIE	310.545(a)(7)
Urea					
Miscellaneous external	Hair growth/loss	Hair grower	n/a	IIE	310.527(a)
Miscellaneous external	Ingrown toenail	Ingrown toenail	IISE	IISE	310.538(a)
Miscellaneous internal	Menstrual/diuretic	Diuretic	n/a	IISE	310.545(a)(24)(i)
Uva ursi, extract					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Valine					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Vegetable					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Vegetable oil					
Miscellaneous external	Hair growth/loss	Hair grower	IISE	n/a	310.527(a)
Vitamin A					
Contraceptive/vaginal	Vaginal	Minor irritations	IIIE	Withdraw	n/a
Hemorrhoidal	Anorectal	Wound healing agent (external)	IIIE	IIIE	310.545(a)(26)(x)
Hemorrhoidal	Anorectal	Wound healing agent (intrarectal)	IIIE	IIIE	310.545(a)(26)(x)

Review Panel	Report	Drug Category	ANPR	PR	FR
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	Pending
Miscellaneous external	Corn/callus remover	Corn/callus remover	IISE	IISE	[55 FR 33261]
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Vitamin A acetate					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Vitamin A palmitate					
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Antimicrobial	Diaper Rash	Defer	n/a	Pending
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Vitamin B					
Miscellaneous external	Hair growth/loss	Hair grower	n/a	IIE	310.527(a)
Vitamin D [see cholecalciferol]					
====	====	====	====	====	====
Vitamin D2 [see ergocalciferol]					
====	====	====	====	====	====
Vitamin E					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Hair growth/loss	Hair grower	IIE	n/a	310.527(a)
Miscellaneous external	Skin protectant	Diaper rash	Defer	Withdraw	n/a
Miscellaneous internal	Leg muscle cramp	Nocturnal leg muscle cramps	n/a	IIISE	310.546
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Sedative	Stimulant	Stimulant	IIE	IIE	[39 FR 6104]
Vitamins					
Miscellaneous external	Hair growth/loss	Hair grower	IISE	n/a	310.527(a)
Miscellaneous internal	Aphrodisiac	Aphrodisiac	n/a	IISE	310.528(a)
Vitromersal					
Miscellaneous external	Mercury	First aid antiseptic	n/a	IISE	310.545(a)(27)(i)
Miscellaneous external	Mercury	Antiseptic	IISE	IISE	310.545(a)(27)(i)
Water and additives					
====	Ophthalmic	Emergency first aid eyewash	n/a	I	Pending
Water, purified					
====	Ophthalmic	Eyewash	n/a	n/a	349.20
Wax, candelilla					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Wax, carnauba					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Wax, white					
Ophthalmic	Ophthalmic	Emollient	I	I	349.14(b)(6)
Wax, yellow					
Ophthalmic	Ophthalmic	Emollient	n/a	I	349.14(b)(7)
Wheat germ					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Wheat germ glycerides					
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	n/a	n/a
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	n/a	n/a
Wheat germ oil					
Miscellaneous external	Hair growth/loss	Hair grower	IIE	IIE	310.527(a)
White ointment					
Ophthalmic	Ophthalmic	Emollient	I	I	349.14(b)(8)
White petrolatum					
====	Skin protectant	Skin protectant	n/a	n/a	347.10(r)
White pine					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)
White pine extract, compound					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIIE	IIIE	310.545(a)(6)(iii)

Review Panel	Report	Drug Category	ANPR	PR	FR
White pine syrup, compound					
Cough/cold	Cough/cold (expectorant)	Expectorant	IIISE	IIIE	310.545(a)(6)(iii)
White thyme oil [see thyme oil, white]					
====	====	====	====	====	====
Wintergreen oil [see methyl salicylate]					
====	====	====	====	====	====
Witch hazel					
Hemorrhoidal	Anorectal	Astringent (external)	I	I	346.18 (b)
Hemorrhoidal	Anorectal	Astringent (intrarectal)	I	I	346.18 (b)
Miscellaneous external	External analgesic	Astringent	I	n/a	n/a
Miscellaneous external	Skin protectant	Astringent	I	I	347.12(c)
Witch hazel water [see hamamelis water of xi]					
====	====	====	====	====	====
Woodruff					
Miscellaneous internal	Digestive aid	Digestive aid (intestinal distress)	n/a	n/a	310.545(a)(18)(ii)
Wool alcohols [see lanolin alcohols]					
====	====	====	====	====	====
Xanthan gum					
Miscellaneous internal	Weight control	Anorectic	IIIE	IISE	310.545(a)(20)
Xylometazoline hydrochloride					
Cough/cold	Cough/cold (nasal decongestant)	Nasal decongestant	I	I	341.20(b)(10)
Yeast					
Miscellaneous internal	Weight control	Anorectic	IISE	IISE	310.545(a)(20)
Yeast cell derivative, live					
Hemorrhoidal	Anorectal	Wound healing agent (external)	IIISE	IIISE	310.545(a)(26)(vii)
Hemorrhoidal	Anorectal	Wound healing agent (intrarectal)	IIISE	IIISE	310.545(a)(26)(vii)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Diaper rash	Defer	IIISE	Pending
Topical analgesic	Skin protectant	Wound healing agent	IIIE	IIIE	Pending
Yohimbine					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Yohimbine hydrochloride					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	IISE	IISE	310.528(a)
Yohimbinum					
Miscellaneous internal	Aphrodisiac	Aphrodisiac	n/a	n/a	310.528(a)
Zinc acetate					
====	Skin protectant	Diaper rash	n/a	n/a	310.545(a)(18)(iii)
Miscellaneous external	Skin protectant	Poison ivy/oak/sumac	Defer	I	347.10(s)
Miscellaneous external	External analgesic	Poison ivy/oak/sumac	Defer	IISE	Pending
Topical analgesic	Skin protectant	Wound healing agent	IIIE	IIIE	310.545(a)(18)(i)(A)
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(s)
Zinc caprylate					
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(ii)
Zinc carbonate					
====	Skin protectant	Diaper rash	Defer	IIISE	310.545(a)(18)(iii)
====	Skin protectant	Poison ivy/oak/sumac	n/a	I	347.10(t)
Topical analgesic	Skin protectant	Skin protectant	I	I	347.10(t)
Zinc chloride					
Miscellaneous external	Corn/callus remover	Corn/callus remover	IIIE	IIIE	[55 FR 33261]
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Oral cavity	Oral health care	Astringent	I	I	Pending
Zinc citrate					
====	Gingivitis/plaque	Antiplaque/gingivitis	n/a	IIIE	Pending

Review Panel	Report	Drug Category	ANPR	PR	FR
Zinc oxide					
====	n/a	Sunscreen	n/a	I	352.10(r)
====	Skin protectant	Poison ivy/oak/ sumac	n/a	I	347.10(u)
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Hemorrhoidal	Anorectal	Astringent (external)	I	I	346.18 (c)
Hemorrhoidal	Anorectal	Astringent (intrarectal)	I	I	346.18 (c)
Hemorrhoidal	Anorectal	Protectant (external)	I	I	346.14(b)(4)
Hemorrhoidal	Anorectal	Protectant (intrarectal)	I	I	346.14(b)(4)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Boil treatment	Boil treatment	IISE	IISE	310.531(a)
Miscellaneous external	External analgesic	Astringent	IISE	IISE	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	I	Pending
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(18)(v)(A)
Miscellaneous external	Skin protectant	Protectant	I	I	Pending
Topical analgesic	Skin protectant	Skin protectant	I	I	Pending
Zinc phenolsulfonate					
Laxative	Antidiarrheal	Antidiarrheal	IIE	IIE	310.545(a)(3)(i)
Laxative	Antiemetic	Antiemetic	IIIE	IIE	[52 FR 15891]
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Zinc propionate					
Antimicrobial II	Antifungal	Antifungal	IIIE	IIIE	310.545(a)(22)(ii)
Zinc pyrithione [see pyrithione zinc]					
====	====	====	====	====	====
Zinc stearate					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Miscellaneous external	Antifungal	Diaper rash	Defer	n/a	310.545(a)(22)(i)
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	External analgesic	Diaper rash	Defer	n/a	310.545(a)(10)(iv)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Diaper rash	Defer	n/a	Pending
Miscellaneous external	Antimicrobial	Diaper rash	Defer	n/a	Pending
Zinc sulfate					
Contraceptive/vaginal	Vaginal	Astringent	IIIE	Withdraw	n/a
Miscellaneous external	External analgesic	Astringent	IISE	n/a	Pending
Miscellaneous external	External analgesic	Fever blister (topical)	Defer	IIISE	310.545(a)(10)(v)
Miscellaneous external	Skin protectant	Astringent	IISE	IISE	310.545(a)(18)(ii)
Miscellaneous external	Skin protectant	Fever blister (topical)	Defer	IIIE	310.545(a)(18)(iv)
Miscellaneous internal	Poison treatment	Emetic	n/a	IISE	310.545(a)(16)
Ophthalmic	Ophthalmic	Astringent	I	I	349.10
Zinc sulfide					
Antimicrobial II	Acne	Acne	IIE	IIE	310.545(a)(1)
Zinc undecylenate					
Antimicrobial II	Antifungal	Antifungal	I	I	333.210(f)
Zirconium oxide					
Miscellaneous external	External analgesic	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	Skin protectant	Insect bite/sting	IISE	IISE	310.545(a)(10)(vi)
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(18)(vi)(A)
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	n/a	IISE	310.545(a)(10)(vii)
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)
Zyloxin					
Miscellaneous external	External analgesic	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(10)(vii)
Miscellaneous external	Mercury	First aid antiseptic	IISE	n/a	310.545(a)(27)(i)
Miscellaneous external	Skin protectant	Poison ivy/oak/ sumac	Defer	IISE	310.545(a)(18)(vi)(A)

Appendix II Unproven Safety of OTC Ingredients

(1) Topical acne drug products.
Alcloxa
Alkyl isoquinolinium bromide
Aluminum chlorohydrex
Aluminum hydroxide
Benzocaine
Benzoic acid
Boric acid
Calcium polysulfide
Calcium thiosulfate
Camphor
Chloroxylenol
Cloxyquin
Coal tar
Dibenzothiophene
Estrone
Magnesium aluminum silicate
Magnesium sulfate
Phenol
Phenolate sodium
Phenyl salicylate
Povidone-iodine
Pyrilamine maleate
Resorcinol (as single ingredient)
Resorcinol monoacetate (as single ingredient)
Salicylic acid (over 2% up to 5%)
Sodium borate
Sodium thiosulfate
Tetracaine hydrochloride
Thymol
Vitamin E
Zinc oxide
Zinc stearate
Zinc sulfide
(2) Anticaries drug products—(i) Approved as of May 7, 1991.
Hydrogen fluoride
Sodium carbonate
Sodium monofluorophosphate (6% rinse)
Sodium phosphate
(ii) Approved as of October 7, 1996.
Calcium sucrose phosphate
Dicalcium phosphate dihydrate
Disodium hydrogen phosphate[1]
Phosphoric acid
Sodium dihydrogen phosphate
Sodium dihydrogen phosphate monohydrate
Sodium phosphate, dibasic anhydrous reagent
(3) Antidiarrheal drug products—(i) Approved as of May 7, 1991.
Aluminum hydroxide
Atropine sulfate
Calcium carbonate
Carboxymethylcellulose sodium
Glycine
Homatropine methylbromide
Hyoscyamine sulfate
Lactobacillus acidophilus
Lactobacillus bulgaricus
Opium, powdered
Opium tincture
Paregoric
Phenyl salicylate
Scopolamine hydrobromide
Zinc phenolsulfonate
(ii) Approved as of April 19, 2004; April 18, 2005, for products with annual sales less than $25,000.
Attapulgite, activated
Bismuth subnitrate
Calcium hydroxide
Calcium polycarbophil
Charcoal (activated)
Pectin
Polycarbophil
Potassium carbonate
Rhubarb fluidextract
(4) Antiperspirant drug products—(i) Ingredients—Approved as of May 7, 1991.
Alum, potassium
Aluminum bromohydrate
Aluminum chloride (alcoholic solutions)
Aluminum chloride (aqueous solution) (aerosol only)
Aluminum sulfate
Aluminum sulfate, buffered (aerosol only)
Sodium aluminum chlorohydroxy lactate
(ii) Approved as of December 9, 2004; June 9, 2005, for products with annual sales less than $25,000.
Aluminum sulfate buffered with sodium aluminum lactate
(5) [Reserved]
(6) Cold, cough, allergy, bronchodilator, and antiasthmatic drug products—(i) Antihistamine drug products—(A) Ingredients.
Methapyrilene hydrochloride
Methapyrilene fumarate
Thenyldiamine hydrochloride
(B) Ingredients.
Phenyltoloxamine dihydrogen citrate
Methapyrilene hydrochloride
Methapyrilene fumarate
Thenyldiamine hydrochloride
(ii) Nasal decongestant drug products—(A) Approved as of May 7, 1991.
Allyl isothiocyanate
Camphor (lozenge)
Creosote, beechwood (oral)
Eucalyptol (lozenge)
Eucalyptol (mouthwash)
Eucalyptus oil (lozenge)
Eucalyptus oil (mouthwash)
Menthol (mouthwash)
Peppermint oil (mouthwash)
Thenyldiamine hydrochloride
Thymol
Thymol (lozenge)
Thymol (mouthwash)
Turpentine oil
(B) Approved as of August 23, 1995.
Bornyl acetate (topical)
Cedar leaf oil (topical)
Creosote, beechwood (topical)
Ephedrine (oral)
Ephedrine hydrochloride (oral)
Ephedrine sulfate (oral)
Racephedrine hydrochloride (oral/topical)
(C) Approved as of April 11, 2007; October 11, 2007, for products with annual sales less than $25,000. Any ingredient(s) labeled with claims or directions for use for sinusitis or for relief of nasal congestion associated with sinusitis.
(iii) Expectorant drug products.
Ammonium chloride

Antimony potassium tartrate
Beechwood creosote
Benzoin preparations (compound tincture of benzoin, tincture of benzoin)
Camphor
Chloroform
Eucalyptol/eucalyptus oil
Horehound
Iodides (calcium iodide anyhydrous, hydroidic acid syrup, iodized lime, potassium iodide)
Ipecac
Ipecac fluidextract
Ipecac syrup
Menthol/peppermint oil
Pine tar preparations (extract white pine compound, pine tar, syrup of pine tar, compound white pine syrup, white pine)
Potassium guaiacolsulfonate
Sodium citrate
Squill preparations (squill, squill extract)
Terpin hydrate preparations (terpin hydrate, terpin hydrate elixir)
Tolu preparations (tolu, tolu balsam, tolu balsam tincture)
Turpentine oil (spirits of turpentine)
(iv) Bronchodilator drug products—(A) Approved as of October 2, 1987.
Aminophylline
Belladonna alkaloids
Euphorbia pilulifera
Metaproterenol sulfate
Methoxyphenamine hydrochloride
Pseudoephedrine hydrochloride
Pseudoephedrine sulfate
Theophylline, anhydrous
Theophylline calcium salicylate
Theophylline sodium glycinate
(B) Approved as of January 29, 1996. Any combination drug product containing theophylline (e.g., theophylline and ephedrine, or theophylline and ephedrine and phenobarbital).
(C) Approved as of June 19, 1996. Any ingredient(s) in a pressurized metered-dose inhaler container.
(D) Approved as of October 29, 2001. Any oral bronchodilator active ingredient (e.g., ephedrine, ephedrine hydrochloride, ephedrine sulfate, racephedrine hydrochloride, or any other ephedrine salt) in combination with any analgesic(s) or analgesic-antipyretic(s), anticholinergic, antihistamine, oral antitussive, or stimulant active ingredient.
(7) Dandruff/seborrheic dermatitis/psoriasis drug products.
Alkyl isoquinolinium bromide
Allantoin
Benzalkonium chloride
Benzethonium chloride
Boric acid
Calcium undecylenate
Captan
Chloroxylenol
Colloidal oatmeal
Cresol, saponated
Ethohexadiol
Eucalyptol
Juniper tar
Lauryl isoquinolinium bromide
Menthol
Mercury oleate
Methylbenzethonium chloride
Methyl salicylate
Phenol
Phenolate sodium
Pine tar
Povidone-iodine
Resorcinol
Sodium borate
Sodium salicylate
Thymol
Undecylenic acid
(8) Digestive aid drug products—(i) Approved as of May 7, 1991.
Bismuth sodium tartrate
Calcium carbonate
Cellulase
Dehydrocholic acid
Dihydroxyaluminum sodium carbonate
Duodenal substance
Garlic, dehydrated
Glutamic acid hydrochloride
Hemicellulase
Homatropine methylbromide
Magnesium hydroxide
Magnesium trisilicate
Ox bile extract
Pancreatin
Pancrelipase
Papain
Peppermint oil
Pepsin
Sodium bicarbonate
Sodium citrate
Sorbitol
(ii) Approved as of November 10, 1993.
Alcohol
Aluminum hydroxide
Amylase
Anise seed
Aromatic powder
Asafetida
Aspergillus oryza enzymes (except lactase enzyme derived from *Aspergillus oryzae*)
Bacillus acidophilus
Bean
Belladonna alkaloids
Belladonna leaves, powdered extract
Betaine hydrochloride
Bismuth subcarbonate
Bismuth subgallate
Black radish powder
Blessed thistle (cnicus benedictus)
Buckthorn
Calcium gluconate
Capsicum
Capsicum, fluid extract of
Carbon
Cascara sagrada extract
Catechu, tincture
Catnip
Chamomile flowers
Charcoal, wood
Chloroform
Cinnamon oil
Cinnamon tincture
Citrus pectin
Diastase
Diastase malt

Dog grass
Elecampane
Ether
Fennel acid
Galega
Ginger
Glycine
Hydrastis canadensis (golden seal)
Hectorite
Horsetail
Huckleberry
Hydrastis fluid extract
Hydrochloric acid
Iodine
Iron ox bile
Johnswort
Juniper
Kaolin, colloidal
Knotgrass
Lactic acid
Lactose
Lavender compound, tincture of
Linden
Lipase
Lysine hydrochloride
Mannitol
Mycozyme
Myrrh, fluid extract of
Nettle
Nickel-pectin
Nux vomica extract
Orthophosphoric acid
Papaya, natural
Pectin
Peppermint
Peppermint spirit
Phenacetin
Potassium bicarbonate
Potassium carbonate
Protease
Prolase
Rhubarb fluid extract
Senna
Sodium chloride
Sodium salicylate
Stem bromelain
Strawberry
Strychnine
Tannic acid
Trillium
Woodruff

(iii) Charcoal, activated

(9) [Reserved]

(10) External analgesic drug products—(i) Analgesic and anesthetic drug products.
Aspirin
Chloral hydrate
Chlorobutanol
Cyclomethycaine sulfate
Eugenol
Hexylresorcinol
Methapyrilene hydrochloride
Salicylamide
Thymol

(ii) Counterirritant drug products.
Chloral hydrate
Eucalyptus oil

(iii) Male genital desensitizer drug products.
Benzyl alcohol
Camphorated metacresol
Ephedrine hydrochloride

(iv) Diaper rash drug products. Any ingredient(s) labeled with claims or directions for use in the treatment and/or prevention of diaper rash.

(v) Fever blister and cold sore treatment drug products.
Allyl isothiocyanate
Aspirin
Bismuth sodium tartrate
Camphor (exceeding 3%)
Capsaicin
Capsicum
Capsicum oleoresin
Chloral hydrate
Chlorobutanol
Cyclomethycaine sulfate
Eucalyptus oil
Eugenol
Glycol salicylate
Hexylresorcinol
Histamine dihydrochloride
Menthol (exceeding 1%)
Methapyrilene hydrochloride
Methyl nicotinate
Methyl salicylate
Pectin
Salicylamide
Strong ammonia solution
Tannic acid
Thymol
Tripelennamine hydrochloride
Trolamine salicylate
Turpentine oil
Zinc sulfate

(vi) Insect bite and sting drug products.
Alcohol
Alcohol, ethoxylated alkyl
Benzalkonium chloride
Calamine
Ergot fluidextract
Ferric chloride
Panthenol
Peppermint oil
Pyrilamine maleate
Sodium borate
Trolamine salicylate
Turpentine oil
Zinc oxide
Zirconium oxide

(vii) Poison ivy, poison oak, and poison sumac drug products.
Alcohol
Aspirin
Benzethonium chloride
Benzocaine (0.5–1.25%)
Bithionol
Calamine
Cetalkonium chloride
Chloral hydrate
Chlorobutanol
Chlorpheniramine maleate
Creosote, beechwood
Cyclomethycaine sulfate
Dexpanthenol

Diperodon hydrochloride
Eucalyptus oil
Eugenol
Glycerin
Glycol salicylate
Hectorite
Hexylresorcinol
Hydrogen peroxide
Impatiens biflora tincture
Iron oxide
Isopropyl alcohol
Lanolin
Lead acetate
Merbromin
Mercuric chloride
Methapyrilene hydrochloride
Panthenol
Parethoxycaine hydrochloride
Phenyltoloxamine dihydrogen citrate
Povidone-vinylacetate copolymers
Pyrilamine maleate
Salicylamide
Salicylic acid
Simethicone
Sulfur
Tannic acid
Thymol
Trolamine salicylate
Turpentine oil
Zirconium oxide
Zyloxin
(11) [Reserved]
(12) Laxative drug products—(i)(A) Bulk laxatives.
Agar
Carrageenan (degraded)
Carrageenan (native)
Guar gun
(i)(B) Bulk laxatives—Approved as of March 29, 2007.
Granular dosage forms containing psyllium (hemicellulose), psyllium hydrophilic mucilloid, psyllium seed, psyllium seed (blond), psyllium seed husks, plantago husks, or plantago seed including, but not limited to, any granules that are:
(1) swallowed dry prior to drinking liquid;
(2) dispersed, suspended, or partially dissolved in liquid prior to swallowing;
(3) chewed, partially chewed, or unchewed, and then washed down (or swallowed) with liquid; or
(4) sprinkled over food.
(ii) Saline laxative.
Tartaric acid
(iii) Stool softener.
Poloxamer 188
(iv)(A) Stimulant laxatives—Approved as of May 7, 1991.
Aloin
Bile salts/acids
Calcium pantothenate
Calomel
Colocynth
Elaterin resin
Frangula
Gamboge
Ipomea
Jalap
Ox bile
Podophyllum resin
Prune concentrate dehydrate
Prune powder
Rhubarb, Chinese
Sodium Oleate
(iv)(B) Stimulant laxatives—Approved as of January 29, 1999.
Danthron
Phenolphthalein
(C) Stimulant laxatives—Approved as of November 5, 2002.
Aloe ingredients (aloe, aloe extract, aloe flower extract)
Cascara sagrada ingredients (casanthranol, cascara fluidextract aromatic, cascara sagrada bark, cascara sagrada extract, cascara sagrada fluidextract).
(13) [Reserved]
(14) Oral health care drug products (nonantimicrobial).
Antipyrine
Camphor
Cresol
Dibucaine
Dibucaine hydrochloride
Eucalyptol
Lidocaine
Lidocaine hydrochloride
Methly salicylate
Myrrh tincture
Pyrilamine maleate
Sorbitol
Sugars
Tetracaine
Tetracaine hydrochloride
Thymol
(15) Topical otic drug products—(i) For the prevention of swimmer's ear and for the drying of water-clogged ears, approved as of May 7, 1991.
Acetic acid
(ii) For the prevention of swimmer's ear, approved as of August 15, 1995.
Glycerin and anhydrous glycerin
Isopropyl alcohol
(16) Poison treatment drug products.
Ipecac fluidextract
Ipecac tincture
Zinc sulfate
(17) Skin bleaching drug products.
Mercury, ammoniated
(18) Skin protectant drug products—(i)(A) Ingredients—Approved as of May 7, 1991.
Allantoin (wound healing claims only)
Sulfur
Tannic acid
Zinc acetate (wound healing claims only)
(B) Ingredients—Approved as of June 4, 2004; June 6, 2005, for products with annual sales less than $25,000.
Beeswax
Bismuth subnitrate
Boric acid
Cetyl alcohol
Glyceryl stearate
Isopropyl palmitate
Live yeast cell derivative
Shark liver oil
Stearyl alcohol
(ii) Astringent drug products.
Acetone
Alcohol
Alum, ammonium
Alum, potassium
Aluminum chlorhydroxy complex

Aromatics
Benzalkonium chloride
Benzethonium chloride
Benzocaine
Benzoic acid
Boric acid
Calcium acetate
Camphor gum
Clove oil
Colloidal oatmeal
Cresol
Cupric sulfate
Eucalyptus oil
Eugenol
Ferric subsulfate (Monsel's Solution)
Honey
Isopropyl alcohol
Menthol
Methyl salicylate
Oxyquinoline sulfate
p-*t*-Butyl-*m*-cresol
Peppermint oil
Phenol
Polyoxeythylene laurate
Potassium ferrocyanide
Sage oil
Silver nitrate
Sodium borate
Sodium diacetate
Talc
Tannic acid glycerite
Thymol
Topical starch
Zinc chloride
Zinc oxide
Zinc phenolsulfonate
Zinc stearate
Zinc sulfate

(iii) Diaper rash drug products.
Aluminum hydroxide
Cocoa butter
Cysteine hydrochloride
Glycerin
Protein hydrolysate
Racemethionine
Sulfur
Tannic acid
Zinc acetate
Zinc carbonate

(iv) Fever blister and cold sore treatment drug products.
Bismuth subnitrate
Boric acid
Pyridoxine hydrochloride
Sulfur
Tannic acid
Topical starch
Trolamine
Zinc sulfate

(v) Insect bite and sting drug products—(A) Ingredients—Approved as of November 10, 1993.
Alcohol
Alcohol, ethoxylated alkyl
Ammonia solution, strong
Ammonium hydroxide
Benzalkonium chloride
Camphor
Ergot fluid extract
Ferric chloride
Menthol
Peppermint oil
Phenol
Pyrilamine maleate
Sodium borate
Trolamine
Turpentine oil
Zirconium oxide

(B) Ingredients—Approved as of June 4, 2004; June 6, 2005, for products with annual sales less than $25,000.
Beeswax
Bismuth subnitrate
Boric acid
Cetyl alcohol
Glyceryl stearate
Isopropyl palmitate
Live yeast cell derivative
Shark liver oil
Stearyl alcohol

(vi) Poison ivy, poison oak, and poison sumac drug products—(A) Ingredients—Approved as of November 10, 1993.
Alcohol
Anion and cation exchange resins buffered
Benzethonium chloride
Benzocaine
Benzyl alcohol
Bismuth subnitrate
Bithionol
Boric acid
Camphor
Cetalkonium chloride
Chloral hydrate
Chlorpheniramine maleate
Creosote
Diperodon hydrochloride
Diphenhydramine hydrochloride
Eucalyptus oil
Ferric chloride
Glycerin
Hectorite
Hydrogen peroxide
Impatiens biflora tincture
Iron oxide
Isopropyl alcohol
Lanolin
Lead acetate
Lidocaine
Menthol
Merbromin
Mercuric chloride
Panthenol
Parethoxycaine hydrochloride
Phenol
Phenyltoloxamine dihydrogen citrate
Povidone-vinylacetate copolymers
Salicylic acid
Simethicone
Tannic acid
Topical starch
Trolamine
Turpentine oil
Zirconium oxide

Zyloxin
(B) Ingredients—Approved as of June 4, 2004; June 6, 2005, for products with annual sales less than $25,000.
Beeswax
Bismuth subnitrate
Boric acid
Cetyl alcohol
Glyceryl stearate
Isopropyl palmitate
Live yeast cell derivative
Shark liver oil
Stearyl alcohol
(19) [Reserved]
(20) Weight control drug products.
Alcohol
Alfalfa
Alginic acid
Anise oil
Arginine
Ascorbic acid
Bearberry
Biotin
Bone marrow, red
Buchu
Buchu, potassium extract
Caffeine
Caffeine citrate
Calcium
Calcium carbonate
Calcium caseinate
Calcium lactate
Calcium pantothenate
Carboxymethylcellulose sodium
Carrageenan
Cholecalcierol
Choline
Chondrus
Citric acid
Cnicus benedictus
Copper
Copper gluconate
Corn oil
Corn syrup
Corn silk, potassium extract
Cupric sulfate
Cyanocobalamin (vitamin B12)
Cystine
Dextrose
Docusate sodium
Ergocalciferol
Ferric ammonium citrate
Ferric pyrophosphate
Ferrous fumarate
Ferrous gluconate
Ferrous sulfate (iron)
Flax seed
Folic acid
Fructose
Guar gum
Histidine
Hydrastis canadensis
Inositol
Iodine
Isoleucine
Juniper, potassium extract
Karaya gum
Kelp
Lactose
Lecithin
Leucine
Liver concentrate
Lysine
Lysine hydrochloride
Magnesium
Magnesium oxide
Malt
Maltodextrin
Manganese citrate
Mannitol
Methionine
Methylcellulose
Mono- and di-glycerides
Niacinamide
Organic vegetables
Pancreatin
Pantothenic acid
Papain
Papaya enzymes
Pepsin
Phenacetin
Phenylalanine
Phosphorus
Phytolacca
Pineapple enzymes
Plantago seed
Potassium citrate
Pyridoxine hydrochloride (vitamin B6)
Riboflavin
Rice polishings
Saccharin
Sea minerals
Sesame seed
Sodium
Sodium bicarbonate
Sodium caseinate
Sodium chloride (salt)
Soybean protein
Soy meal
Sucrose
Thiamine hydrochloride (vitamin B1)
Thiamine mononitrate (vitamin B1 mononitrate)
Threonine
Tricalcium phosphate
Tryptophan
Tyrosine
Uva ursi, potassium extract
Valine
Vegetable
Vitamin A
Vitamin A acetate
Vitamin A palmitate
Vitamin E
Wheat germ
Xanthan gum
Yeast
(21) Ophthalmic drug products. (i) Ophthalmic anesthetic drug products.
Antipyrine
Piperocaine hydrochloride
(ii) Ophthalmic anti-infective drug products.
Boric acid
Mild silver protein

Yellow mercuric oxide
(iii) Ophthalmic astringent drug products.
Infusion of rose petals
(iv) Ophthalmic demulcent drug products.
Polyethylene glycol 6000
(v) Ophthalmic vasoconstrictor drug products.
Phenylephrine hydrochloride (less than 0.08%)
(22) Topical antifungal drug products. (i) Diaper rash drug products. Any ingredient(s) labeled with claims or directions for use in the treatment and/or prevention of diaper rash.
(ii) Ingredients.
Alcloxa
Alum, potassium
Aluminum sulfate
Amyltricresols, secondary
Basic fuchsin
Benzethonium chloride
Benzoic acid
Benzoxiquine
Boric acid
Camphor
Candicidin
Chlorothymol
Coal tar
Dichlorophen
Menthol
Methylparaben
Oxyquinoline
Oxyquinoline sulfate
Phenol
Phenolate sodium
Phenyl salicylate
Propionic acid
Propylparaben
Resorcinol
Salicylic acid
Sodium borate
Sodium caprylate
Sodium propionate
Sulfur
Tannic acid
Thymol
Tolindate
Triacetin
Zinc caprylate
Zinc propionate
(iii) Any ingredient(s) labeled with claims or directions for use on the scalp or on the nails.
(iv) Ingredients.
Camphorated metacresol
Chloroxylenol
m-cresol
Nystatin
(23) Internal analgesic drug products—(i) Approved as of November 10, 1993.
Aminobenzoic acid
Antipyrine
Aspirin, aluminum
Calcium salicylate
Codeine
Codeine phosphate
Codeine sulfate
Iodoantipyrine
Lysine aspirin
Methapyrilene fumarate
Phenacetin
Pheniramine maleate
Pyrilamine maleate
Quinine
Salsalate
Sodium aminobenzoate
(ii) Approved as of February 22, 1999.
Any atropine ingredient
Any ephedrine ingredient
(24) Orally administered menstrual drug products—
(i) Approved as of November 10, 1993.
Alcohol
Alfalfa leaves
Aloes
Asclepias tuberosa
Asparagus
Barosma
Bearberry (extract of uva ursi)
Bearberry fluidextract (extract of bearberry)
Blessed thistle (cnicus benedictus)
Buchu powdered extract (extract of buchu)
Calcium lactate
Calcium pantothenate
Capsicum oleoresin
Cascara fluidextract, aromatic (extract of cascara)
Chlorprophenpyridamine maleate
Cimicifuga racemosa
Codeine
Collinsonia (extract stone root)
Corn silk
Couch grass
Dog grass extract
Ethyl nitrite
Ferric chloride
Ferrous sulfate
Gentiana lutea (gentian)
Glycyrrhiza (licorice)
Homatropine methylbromide
Hydrangea, powdered extract (extract of hydrangea)
Hydrastis canadensis (golden seal)
Hyoscyamine sulfate
Juniper oil (oil of juniper)
Magnesium sulfate
Methapyrilene hydrochloride
Methenamine
Methylene blue
Natural estrogenic hormone
Niacinamide
Nutmeg oil (oil of nutmeg)
Oil of erigeron
Parsley
Peppermint spirit
Pepsin, essence
Phenacetin
Phenindamine tartrate
Phenyl salicylate
Piscidia erythrina
Pipsissewa
Potassium acetate
Potassium nitrate
Riboflavin
Saw palmetto
Senecio aureus
Sodium benzoate
Sodium nitrate
Sucrose
Sulferated oils of turpentine

Taraxacum officinale
Theobromine sodium salicylate
Theophylline
Thiamine hydrochloride
Triticum
Turpentine, venice (venice turpertine)
Urea
(ii) Approved as of February 22, 1999.
Any atropine ingredient
Any ephedrine ingredient
(25) Pediculicide drug products—(i) Approved as of November 10, 1993.
Benzocaine
Benzyl alcohol
Benzyl benzoate
Chlorophenothane (dichlorodiphenyl trichloroethane)
Coconut oil soap, aqueous
Copper oleate
Docusate sodium
Formic acid
Isobornyl thiocyanoacetate
Picrotoxin
Propylene glycol
Sabadilla alkaloids
Sulfur, sublimed
Thiocyanoacetate
(ii) Approved as of June 14, 1994. The combination of pyrethrum extract (formerly named pyrethrins) and piperonyl butoxide in an aerosol dosage formulation.
(26) Anorectal drug products—(i) Anticholinergic drug products.
Atropine
Belladonna extract
(ii) Antiseptic drug products.
Boric acid
Boroglycerin
Hydrastis
Phenol
Resorcinol
Sodium salicylic acid phenolate
(iii) Astringent drug products.
Tannic acid
(iv) Counterirritant drug products.
Camphor (greater than 3–11%)
Hydrastis
Menthol (1.25–16%)
Turpentine oil (rectified) (6–50%)
(v) Keratolytic drug products.
Precipitated sulfur
Sublimed sulfur
(vi) Local anesthetic drug products.
Diperodon
Phenacaine hydrochloride
(vii) Other drug products.
Collinsonia extract
Escherichia coli vaccines
Lappa extract
Leptandra extract
Live yeast cell derivative
Mullein
(viii) Protectant drug products.
Bismuth oxide
Bismuth subcarbonate
Bismuth subgallate
Bismuth subnitrate
Lanolin alcohols
(ix) Vasoconstrictor drug products.
Epinephrine undecylenate
(x) Wound-healing drug products.
Cholecalciferol
Cod liver oil
Live yeast cell derivative
Peruvian balsam
Shark liver oil
Vitamin A
(xi) Combination drug products. Any combination drug product containing hydrocortisone and pramoxine hydrochloride.
(27) Topical antimicrobial drug products—(i) First aid antiseptic drug products .
Ammoniated mercury
Calomel (mercurous chloride)
Merbromin (mercurochrome)
Mercufenol chloride (ortho-chloromercuriphenol, ortho-hydroxyphenylmercuric chloride)
Mercuric chloride (bichloride of mercury, mercury chloride)
Mercuric oxide, yellow
Mercuric salicylate
Mercuric sulfide, red
Mercury
Mercury oleate
Mercury sulfide
Nitromersol
Para-chloromercuriphenol
Phenylmercuric nitrate
Thimerosal
Vitromersol
Zyloxin
(ii) Diaper rash drug products.
Para-chloromercuriphenol
Any other ingredient containing mercury
(28) Vaginal contraceptive drug products—(i) Approved as of October 22, 1998.
Dodecaethylene glycol monolaurate (polyethylene glycol 600 monolaurate)
Laureth 10S
Methoxypolyoxyethyleneglycol 550 laurate
Phenylmercuric acetate
Phenylmercuric nitrate
Any other ingredient containing mercury
(ii) Approved as of November 5, 2002.
Octoxynol 9
(29) Sunscreen drug products.
Diethanolamine methoxycinnamate
Digalloyl trioleate
Ethyl 4-[bis(hydroxypropyl)] aminobenzoate
Glyceryl aminobenzoate
Lawsone with dihydroxyacetone
Red petrolatum

Part II

Manufacturing Formulations

Pharmaceutical Manufacturing Formulations

Acetaminophen and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Acetaminophen (fine powder)	500.00
65.00	2	Anhydrous caffeine	65.00
15.00	3	Maize starch	15.00
10.00	4	Povidone (PVP K-30)	10.00
5.00	5	Croscarmellose sodium (Ac-Di-Sol)	5.00
33.00	6	Maize starch	33.00
8.00	7	Povidone (PVP K-90)	8.00
1.00	8	Polysorbate 80 (Tween 80)	1.00
10.00	9	Microcrystalline cellulose (Avicel™ PH102)	10.00
7.00	10	Sodium starch glycolate (Primojel®)	7.00
5.00	11	Croscarmellose sodium (Ac-Di-Sol)	5.00
2.00	12	Stearic acid (fine powder)	2.00
4.00	13	Talc (fine powder)	4.00
–	14	Purified water	155.00

Manufacturing Directions

1. Sift items 1 to 5 through a stainless steel 630-μm sieve. Load into mixer. Mix for 5 minutes at low speed.
2. Dissolve items 7 and 8 in 115 g of purified water (80–90°C) in a vessel.
3. Prepare slurry of item 6 in 40 g of purified water (25–30°C).
4. Add the slurry to the vessel to make a translucent paste. Cool to 45°C to 50°C.
5. Add the binder (item 4) to the paste.
6. Mix at low speed over a period of 3 minutes. Scrape sides and blades. Mix and chop at low speed for 1 to 2 minutes.
7. Check the end point of granulation. If required, add additional purified water to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Unload the wet granules into stainless steel trays for drying.
8. Dry the wet granules at 55°C for 8 hours. After 2 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying. Check the loss on drying (LOD limit: 1.5–2.0%). If required, dry further at 55°C for 1 hour.
9. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed. Collect in stainless steel drums.
10. Load the granules into blender. Sift items 9, 10, and 11 through a 500-μm sieve using a suitable sifter and add it to the blender. Mix for 2 minutes.
11. Sift items 12 and 13 through a 500-μm sieve.
12. Add 5 to 10 g granules from bulk. Mix in.
13. Check temperature and humidity before start of compression (recommended: relative humidity [RH] 55–60% at a temperature not exceeding 27°C).
14. Compress the granules using a rotary tableting machine. Average weight of tablet is 665 mg.

Acetaminophen and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Acetaminophen (crystalline)	500
50.00	2	Caffeine (Knoll)	50
90.00	3	Avicel™ PH101	90
10.00	4	Kollidon® 30	10
20.00	5	Kollidon® CL	20
10.00	6	Polyethylene glycol (PEG-6000) (powder)	10

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with high compression force.
2. Compress into 683-mg tablets using 12-mm biplanar punches.
3. If the flowability of the powder mixture for tableting is not high enough, some Aerosil 200 should be added.

Acetaminophen and Diphenhydramine Hydrochloride Hot Therapy Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
1650.00	1	Acetaminophen (micronized)	1650.00
250.00	2	Diphenhydramine hydrochloride	250.00
0.90	3	FD&C yellow dye No. 10 lake	0.90
0.0005	4	FD&C red dye No. 40	0.0005
18081.10	5	Castor sugar	18081.10
200.00	6	Aspartame	200.00
250.00	7	Maize starch (dried)	250.00
180.00	8	Citric acid	180.00
38.00	9	Sodium citrate	38.00
200.00	10	Sodium chloride	200.00
240.00	11	Honey flavor (dry)	240.00
100.00	12	Lemon flavor (dry)	100.00
QS	13	Purified water	QS

Manufacturing Directions

1. Mix items 1 and 2 well, then pass through 0.8-mm sieves.
2. Mix items 3, 5, and 13 to make a clear solution.
3. Add mixture of items 1 and 2 to second step mixture and mix well.
4. Add this mixture to item 4 and mix. Take care to avoid lump formation.
5. Dry in an oven and maintain a constant temperature.
6. Sieve and add items 6 to 12. Mix well. Make sure all the solids added are in fine powder form.
7. Fill 20 g of powder into sachets and seal.

Acetaminophen and Pseudoephedrine Hydrochloride Hot Therapy Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
650.00	1	Acetaminophen (micronized)	650.00
260.00	2	Pseudoephedrine hydrochloride	260.00
0.90	3	FD&C yellow dye No. 10 lake	0.90
18081.10	4	Castor sugar	18081.10
200.00	5	Aspartame	200.00
250.00	6	Maize starch (dried)	250.00
180.00	7	Citric acid	180.00
38.00	8	Sodium citrate	38.00
200.00	9	Sodium chloride	200.00
240.00	10	Apple flavor (dry)	240.00
100.00	11	Cinnamon flavor (dry)	100.00
QS	12	Purified water	QS

Manufacturing Directions

1. Mix item 1 and 2 well, pass through a 0.8-mm sieve, and add to items 3 and 12 which have been mixed together.
2. Make into a clear solution. Take care to avoid lump formation.
3. Dry in an oven and maintain constant moisture.
4. Using a 500-mm sieve, add items 6 to 11. Mix well. Make sure all the solids added are in fine powder form.
5. Fill 20 g of powder into sachets and seal.

Acetaminophen and Diphenhydramine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
325.00	1	Acetaminophen (fine powder)	325.00
26.00	2	Diphenhydramine HCl	26.00
50.00	3	Maize starch	50.00
07.00	4	Povidone (PVP K-30)	7.00
50.00	5	Microcrystalline cellulose (Avicel PH101)	50.00
42.00	6	Cornstarch	42.00
10.00	7	Povidone (PVP K-30)	10.00
09.50	8	Cellulose (powdered)	9.50
65.50	9	Cellulose (microcrystalline) (Avicel PH102)	65.50
20.00	10	Sodium starch glycolate (Primojel)	20.00
08.00	11	Stearic acid (fine powder)	8.00
05.00	12	Talc (fine powder)	5.00
02.00	13	Magnesium stearate	2.00
–	14	Purified water	180.00

Manufacturing Directions

1. Sift items 1 to 5 through a 630-μm stainless steel sieve.
2. Load into mixer. Mix for 5 minutes at low speed.
3. Dissolve item 7 in 135 g of purified water (80–90°C) in a vessel.
4. Prepare a slurry of item 6 in 45 g of purified water (25–30°C).
5. Add the slurry to the vessel to make a translucent paste.
6. Cool to 45°C to 50°C.
7. Add the binder (item 4).
8. Mix at low speed over a period of 3 minutes. Scrape sides and blades. Mix and chop at low speed for 1 to 2 minutes. Check the end point of granulation. If required, add additional purified water to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.)

9. Unload the wet granules into stainless steel trays for drying.
10. Dry the wet granules in an oven at 55°C for 10 hours. After 2 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying. Check the LOD (limit: 1–2%). If required, dry further at 55°C for 1 hour.
11. Grind the dried granules through a 1.25-mm sieve at medium speed.
12. Collect in stainless steel drums. Load the granules into blender.
13. Sift items 8, 9, and 10 through a 500-μm sieve using a suitable sifter and add mixture to blender. Mix for 2 minutes.
14. Sift items 11, 12, and 13 through a 500-μm sieve. Add 5 to 10 g of granules from bulk.
15. Mix in polyethylene bag for 1 minute. Add to blender. Blend for 1 minute.
16. Check temperature and humidity before start of compression (limit: temperature not exceeding 27°C, RH 55–65%).
17. Compress the granules using a rotary tableting machine. Compress average tablet weight of 620 mg.
18. Disintegration time is not more than (NMT) 15 minutes; friability NMT is 1%.
19. Coating: Use one of the HPMC aqueous formulations in the part III, such as yellow opadry.

Acetaminophen Sustained-Release Tablets

Manufacturing Directions

1. 300 g acetaminophen and 60 g hydroxypropylmethylcellulose were dissolved in a mixture of 720 g methanol and 720 g dichloromethane.
2. 300 g Celphere 102 (mean particle diameter of approximately 127 μm, particle diameter of approximately 50–150 μm) were introduced to a fluidized bed granulator and coated with the solution by the side-spraying method (spraying liquid volume 14 g/min, spraying air pressure 3 kg/cm^2, product temperature 32°C, inlet temperature 45°C) to obtain acetaminophen particles.
3. Separately, 48 g ethyl cellulose and 12 g hydroxypropylmethylcellulose were dissolved in a mixture of 57 g purified water and 1083 g methanol.
4. 300 g acetaminophen particles were introduced to a fluidized bed granulator and coated with this solution by side spraying (spraying liquid volume 8 g/min, spraying air pressure 3 kg/cm^2, product temperature 38°C, inlet temperature 67°C) to obtain sustained-release fine particles.
5. 66.00 g of these sustained-release fine particles and 314.25 g mannitol that had been pulverized by a pin-mill pulverizing device were granulated (spraying liquid volume 15 g/min, spraying air pressure 1.1 kg/cm^2, product temperature 30°C, inlet temperature 38°C, spraying cycle 30 seconds spraying/30 seconds drying) with an aqueous 30% w/w solution containing 67.5 g maltose in a fluidized bed granulator to obtain the final composition.
6. After further mixing 2.25 g magnesium stearate with the composition that was obtained, 450-mg tablets containing 25 mg acetaminophen per tablet were made under a tableting pressure of 25 kg/punch and an initial hardness of 2 kp using a rotary tableting machine.
7. Next, these tablets were kept for 24 hours while heating and humidifying at 25°C and 75% RH using a thermostatic chamber at constant humidity. Then they were dried for 3 hours at 30°C and 40% RH.
8. The tablets that were obtained showed a hardness of 3.5 kp and disintegration time in the buccal cavity of 12 seconds.

Acetaminophen and Pseudoephedrine Hydrochloride Tablets

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Qty/1000 Caplets (g)
325.00	1	Acetaminophen (fine powder)	325.00
31.50	2	Pseudoephedrine HCl	31.50
50.00	3	Cornstarch	50.00
7.00	4	Povidone (PVP K-30)	7.00
50.00	5	Microcrystalline cellulose (Avicel PH101)	50.00
42.00	6	Cornstarch	42.00
10.00	7	Povidone (PVP K-30)	10.00
9.50	8	Cellulose (powdered)	9.50
60.00	9	Cellulose (microcrystalline) (Avicel PH102)	60.00
20.00	10	Sodium starch glycolate (Primojel)	20.00
8.00	11	Stearic acid (fine powder)	8.00
5.00	12	Talc (fine powder)	5.00
2.00	13	Magnesium stearate	2.00
–	14	Purified water	180.00

Manufacturing Directions

1. Sift items 1 to 5 through a stainless steel 630-μm sieve.
2. Load into mixer. Mix for 5 minutes at low speed.
3. Dissolve item 7 in 135 g of purified water (80–90°C) in a vessel.
4. Prepare a slurry of item 6 in 45 g of purified water (25–30°C).
5. Add the slurry to the vessel to make a translucent paste. Cool to 45°C to 50°C. Add the binder (item 4).
6. Mix at low speed over a period of 3 minutes. Scrape sides and blades. Mix and chop at low speed for 1 to 2 minutes. Check the end point of granulation. If required, add additional purified water to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Unload the wet granules into stainless steel trays for drying.
7. Dry the wet granules in oven at 55°C for 10 hours.
8. After 2 hours of drying, scrape the semidried granules to break up the lumps for uniform drying.
9. Check the LOD (limit: 1–2%). If required, dry further at 55°C for 1 hour.
10. Transfer the dried granules to stainless steel drums.
11. Grind the dried granules through a 1.25-mm sieve using granulator at medium speed. Collect in stainless steel drums. Load the granules into blender.
12. Sift items 8, 9, and 10 through a 500-μm sieve using a suitable sifter and add to blender. Mix for 2 minutes.
13. Sift items 11, 12, and 13 through a 500-μm sieve.
14. Add 5 to 10 g of granules.
15. Mix in polyethylene bag for 1 minute. Add to blender. Blend for 1 minute. Unload in stainless steel drums.
16. Compress 620 mg in 6-mm capsule-shaped punches.
17. Coat. The formula for the coating solution is determined to obtain a weight gain of 10 mg per caplet, considering evaporation and loss during the coating operation.

Acetaminophen Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
300.00	1	Acetaminophen, milled (Hoechst)	300.00
600.00	2	Sucrose, milled	600.00
550.00	3	Kollidon® CL-M	550.00
30.00	4	Orange flavor (FDO)	30.00
30.00	5	Strawberry flavor (FDO)	30.00
60.00	6	Kollidon 30	60.00
QS	7	Ethanol (96%)	~425.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with solution of items 6 and 7, pass through a sieve, and press with medium compression force.
2. Average weight of tablet is 1620 mg using a 20-mm biplanar punch.
3. Taste is sweet, fruity, and only slightly bitter.

Acetaminophen, Chlorpheniramine, and Pseudoephedrine Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
24.00	1	Acetaminophen (fine powder)	24.00
3.00	2	Pseudoephedrine HCl	3.00
0.44	3	Chlorpheniramine maleate (10% excess)	0.44
14.00	4	Ascorbic acid	14.00
2.40	5	Sodium hydroxide	2.40
1.00	6	Edetate disodium (sodium EDTA)	1.00
0.50	7	Saccharin sodium	0.50
2.00	8	Sodium metabisulfite (sodium disulfite)	2.00
80.00	9	Alcohol (ethanol, 95%)	80.00
100.00	10	Propylene glycol	100.00
100.00	11	Sorbitol (70% solution)	100.00
250.00	12	Glycerin (glycerol)	250.00
300.00	13	Sucrose	300.00
0.04	14	Quinoline yellow	0.04
0.25	15	Pineapple flavor	0.25
QS	16	Purified water	QS to 1 L

Manufacturing Directions

1. Add 200 g of item 16 to the manufacturing vessel and heat to 90°C to 95°C.
2. Add item 13 while mixing at slow speed at a temperature of 90°C to 95°C.
3. Mix for 1 hour at high speed.
4. Add items 10, 11, and 12 to the manufacturing vessel while mixing at high speed. Mix for 10 minutes.
5. Cool the temperature to 50°C while mixing at slow speed.
6. Add 70 g of item 9 to the syrup solution while mixing at slow speed.
7. Load item 1 into the manufacturing vessel while mixing at high speed.
8. Mix for 30 minutes to obtain a clear solution. Check the clarity of the solution.
9. Flush the solution with nitrogen gas for 5 minutes at 1 bar.
10. Add items 2, 4, 6, and 8 to the manufacturing vessel while mixing at slow speed.
11. Dissolve item 3 in 2 g of item 16 (25°C) and check that the solution is complete.
12. Add the solution to the manufacturing vessel while mixing at slow speed.
13. Dissolve item 15 in 10 g of item 9 in a stainless steel container and add to the manufacturing vessel while mixing at slow speed.
14. Dissolve items 5 and 7 in 20 g of item 16 (25°C) and add to the manufacturing vessel while mixing at slow speed.
15. Dissolve item 14 in 2 g of item 16 (25°C).
16. Transfer the color solution to the manufacturing vessel while mixing at slow speed.
17. Rinse the container of color solution with 2 g of item 16 (25°C), then transfer the rinsing to the manufacturing vessel and mix for 5 minutes at high speed.
18. Bring the volume up to 1 L with item 16 and finally mix for 15 to 20 minutes at high speed.
19. Check and record the pH (limit: 5.1–5.2). If required, adjust pH with 10% citric acid or 10% sodium citrate solution.
20. Assemble the filter press with 13.1 T 1000 12 sheets (K 800 14 sheets). Use changeover plate. Wash the filters using purified water (25°C) by passing through filters at 0.2 bar. Discard the washings. Filter the syrup at 1.5 bar. Recirculate approximately 20 to 30 mL syrup.
21. Connect the hose to the manufacturing vessel and transfer the filtered syrup to the storage vessel.

Acetaminophen, Chlorpheniramine Maleate, and Pseudoephedrine Caplets

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Qty/1000 Caplets (g)
325.00	1	Acetaminophen (fine powder)	325.00
31.50	2	Pseudoephedrine HCl	31.50
2.10	3	Chlorpheniramine maleate	2.10
50.00	4	Cornstarch	50.00
7.00	5	Povidone (PVP K-30)	7.00
50.00	6	Cellulose (microcrystalline) (Avicel PH101)	50.00
42.00	7	Cornstarch	42.00
10.00	8	Povidone (PVP K-30)	10.00
9.50	9	Powdered cellulose	9.50
77.90	10	Cellulose (microcrystalline) (Avicel PH102)	77.90
20.00	11	Sodium starch glycolate (Primojel)	20.00
8.00	12	Stearic acid (fine powder)	8.00
5.00	13	Talc (fine powder)	5.00
2.00	14	Magnesium stearate	2.00
–	15	Purified water	180.00

Manufacturing Directions

1. Sift items 1 to 6 through a 630-μm stainless steel sieve.
2. Load into mixer. Mix for 5 minutes at low speed.
3. Dissolve item 8 in 135 g of item 15 (80–90°C) in a vessel.
4. Prepare a slurry of item 7 in 45 g of item 15 (25–30°C). Add the slurry to the vessel to make a translucent paste. Cool to 45°C to 50°C.
5. Add the binder (item 5) to step above.
6. Mix at low speed over a period of 3 minutes. Scrape sides and blades.
7. Mix and chop at low speed for 1 to 2 minutes. Check the end point of granulation. If required, add additional item 15 to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Unload the wet granules in stainless steel trays for drying.
8. Dry the wet granules at 55°C for 10 hours. After 2 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying. Check the LOD (limit: 1.0–2.0%). If required, dry further at 55°C for 1 hour.
9. Grind the dried granules through a 1.25-mm sieve at medium speed. Collect in stainless steel drums.
10. Load the granules into blender.
11. Sift items 9, 10, and 11 through a 500-μm sieve using suitable sifter and add mixture to blender. Mix for 2 minutes.
12. Sift items 12, 13, and 14 through a 500-μm sieve.
13. Add 5 to 10 g of granules from bulk. Mix in polyethylene bag for 1 minute.
14. Add to blender. Blend for 1 minute.
15. Check temperature and humidity before start of compression. Temperature should not exceed 27°C and recommended RH is 55% to 65%.
16. Compress the granules using rotary tableting machine. Tablet weight is 640 mg.
17. Coating: Select an appropriate coating, such as opadry HPMC. The formula for the coating solution is determined to obtain a weight gain of 10 mg per caplet, considering evaporation and loss during coating operation.

Acetaminophen, Dextromethorphan, and Pseudoephedrine Caplets

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Qty/1000 Caplets (g)
325.00	1	Acetaminophen (fine powder)	325.00
31.50	2	Pseudoephedrine HCl	31.50
15.50	3	Dextromethorphan HBr	15.50
50.00	4	Cornstarch	50.00
7.00	5	Povidone (PVP K-30)	7.00
50.00	6	Cellulose (microcrystalline) (Avicel PH101)	50.00
42.00	7	Cornstarch	42.00
10.00	8	Povidone (PVP K-30)	10.00
9.50	9	Cellulose (powdered)	9.50
64.50	10	Cellulose (microcrystalline) (Avicel PH102)	64.50
20.00	11	Sodium starch glycolate (Primojel)	20.00
8.00	12	Stearic acid (fine powder)	8.00
5.00	13	Talc (fine powder)	5.00
2.00	14	Magnesium stearate	2.00
–	15	Purified water	180.00

Manufacturing Directions

Follow manufacturing directions provided for acetaminophen, chlorpheniramine, and pseudoephedrine caplets.

Acetaminophen, Doxylamine, and Caffeine Effervescent Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
500.00	1	Acetaminophen (powder)	500.00
5.00	2	Doxylamine succinate	5.00
33.00	3	Caffeine (Knoll)	33.00
391.00	4	Tartaric acid	391.00
417.00	5	Sodium hydrogen carbonate	417.00
6.00	6	Kollidon 30	6.00
–	7	Isopropanol (or ethanol)	QS
30.00	8	Sodium citrate	30.00
707.00	9	Sugar	707.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with solution of items 6 and 7, dry at 60°C under vacuum conditions through 0.8-mm sieve, and mix with items 8 and 9.
2. Fill 2.1 g in sachets at maximum relative atmospheric humidity of 30%.
3. Granules are free flowing.
4. If the solvent isopropanol is replaced by water, the granulation should be done in a fluidized bed.

Acetaminophen Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
739.00	1	Propylene glycol	739.00
90.00	2	Acetaminophen	90.00
17.50	3	Saccharin sodium	17.50
8.75	4	Sodium chloride	8.75
0.05	5	FD&C red dye No. 40[a]	0.05
2.50	6	Purified water, USP	2.50
2.00	7	Wild cherry artificial flavor	2.00
65.00	8	Alcohol (ethanol, 190 proof, nonbeverage), USP	65.00
QS	9	Deionized purified water, USP	QS to 1 L

[a]Check for local regulatory allowance to use red dyes.

Manufacturing Directions

Caution: Ensure that solution in tank never exceeds 65°C.

1. Add 739 g of propylene glycol to jacketed mixing tank and start heating with slow mixing.
2. Dissolve dye in 2.5 mL of purified water and add to tank while mixing.
3. Rinse container with small amount of purified water and add to tank.
4. While mixing, add acetaminophen, saccharin sodium, and sodium chloride.
5. Hold at 60°C to 65°C with continued moderate mixing until all are in solution.
6. Force cool to less than 30°C with slow mixing.
7. Blend flavor with alcohol and add to tank with slow mixing.
8. Add purified water with mixing QS to make 1 L.
9. Mix well with moderate agitation until uniform.
10. Filter through an 8-μm millipore membrane (or equivalent).

Acetaminophen Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Acetaminophen (powder <300 μm)	500.00
500.00	2	Sodium bicarbonate	500.00
430.00	3	Tartaric acid (powder)	430.00
200.00	4	Dextrose	200.00
QS	5	Flavoring	QS
20.00	6	Kollidon 30	20.00
—	7	Isopropanol	100.00 mL
60.00	8	PEG-6000 (powder)	60.00

Manufacturing Directions

1. Granulate the mixture of items 1 to 5 with solution of items 6 and 7.
2. Pass through a 0.8-mm sieve, add item 8, mix.
3. Press to tablets (average weight, 1700 mg; 16-mm diameter biplanar tablet).

Acetaminophen Fast-Dissolving Tablets

Manufacturing Directions

1. To the vortex of a rapidly stirred vessel containing 2.85 kg of deionized water is added 300 g of croscarmellose sodium, forming slurry. This slurry is mixed for 10 minutes.
2. Concurrently, 5 kg of powdered acetaminophen is placed in the bowl of a mixer.
3. At the conclusion of the mixing time for the slurry of croscarmellose sodium, the slurry is added slowly to the acetaminophen in the mixer bowl, forming a granulation, which is then placed in trays and dried in a 70°C oven for 3 hours.
4. The dry granulation is then passed through a U.S. standard 14-mesh screen (1410 μm).
5. Dry granulation (4796 g) is then placed in a twin shell blender and to it is added 1584 g of Avicel AC-815 [85% microcrystalline cellulose coprocessed with 15% of calcium, sodium alginate complex, and 1584 g of microcrystalline cellulose (Avicel PH-302)].
6. This is thoroughly blended for 10 to 15 minutes after which 36.24 g of magnesium stearate is added and mixed for an additional 5 minutes.
7. Prior to being added to the blender magnesium stearate had been passed through a U.S. standard 30-mesh screen.
8. The resulting blend is compressed into caplet-shaped tablets with average weight of 0.884 g and an average thickness of 7.869 mm (0.3098 in).
9. The hardness of these tablets averaged 11.98 kp. Friability of these tablets is measured at 0.433% after 10 minutes and 0.847% after 19 minutes.
10. The average disintegration time is 26 seconds in 10 mL of deionized water, forming a suspension with minimal shaking.

Acetaminophen, Ibuprofen, and Orphenadrine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Acetaminophen (powder <300 μm)	250.00
200.00	2	Ibuprofen	200.00
100.00	3	Orphenadrine hydrochloride	100.00
200.00	4	Ludipress®	200.00
5.00	5	Magnesium stearate	5.00
5.00	6	Aerosil® 200	5.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve. Mix.
2. Press with high compression force.
3. Tablet weight is 761 mg for each 12-mm biplanar tablet.

Acetaminophen Instant Granules

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
166.66	1	Acetaminophen (fine powder)	166.66
426.64	2	Sucrose (fine powder)	426.64
300.00	3	Kollidon CL-M	300.00
23.33	4	Aspartame	23.33
16.66	5	Orange flavor	16.66
16.66	6	Strawberry flavor	16.66
40.00	7	Kollidon 30	40.00
250.00	8	Ethanol (96%)	250.00

Manufacturing Directions

1. Granulate items 1 to 6 with solution made from items 7 and 8 and pass through a 0.8-mm sieve.
2. Fill 1.5 or 3.0 g in sachets (for 250- or 500-mg strength respectively).
3. The free-flowing granules disperse well in cold water.
4. Suspend 1.5 or 3.0 g of the granules (=250 or 500 mg acetaminophen) in a glass of water.

Acetaminophen Instant Granules

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
192.30	1	Acetaminophen (fine powder)	192.30
500.00	2	Sorbitol (instant) (Merck)	500.00
192.30	3	Kollidon CL-M	192.30
27.00	4	Aspartame	27.00
19.23	5	Orange flavor	19.23
19.23	6	Strawberry flavor	19.23
11.53	7	Sodium citrate	11.53
11.53	8	Citric acid	11.53
30.76	9	Kollidon® 90 F	30.76
192.30	10	Ethanol (96%)	192.30

Manufacturing Directions

1. Granulate items 1 to 8 with solution made from items 9 and 10 and pass through a 0.8-mm sieve.
2. Fill 1.3 or 2.6 g in sachets (for 250- or 500-mg strength respectively).
3. The free-flowing granules disperse well in cold water.
4. Suspend 1.2 or 2.6 g of the granules (=250 or 500 mg acetaminophen) in a glass of water.

Acetaminophen Instant Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
500.00	1	Acetaminophen fine powder	500.00
1300.00	2	Sorbitol instant (Merck)	1300.00
500.00	3	Lutrol F 127	500.00
30.00	4	Citric acid (powder)	30.00
30.00	5	Sodium citrate	30.00
80.00	6	Kollidon 90 F	80.00
500.00	7	Ethanol (96%)	500.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 in solution of item 6 in item 7.
2. Fill 2.44 g in sachets (=500 mg acetaminophen).
3. The free-flowing granules disperse well in cold water.
4. The taste of the suspension is only slightly bitter (2.44 g in a glass of water).

Acetaminophen Microsphere Tablets

Manufacturing Directions

1. Formulation: Acetaminophen (APAP) powder (melting point 169–170.5°C), 85%; carnauba wax, 7.5%; Pluronic F68, 7.5%.
2. The Pluronic is milled through a Fitz mill using a 40-mesh screen.
3. All of the ingredients are blended at 60 Hz slow speed with chopper for 10 minutes.
4. The blend is then subjected to liquiflash processing at 60 Hz and 37% nominal power using the 5 in V-groove heater head.
5. The collected microspheres are sieved.
6. The fraction passing through a 40-mesh and retained on 120-mesh sieve is coated.
7. The microspheres selected are coated in a fluid-bed coater for taste masking at a 30% coating level with a coating solution containing a 1:1 ethyl cellulose/hydroxypropyl cellulose blend in acetone:isopropyl alcohol solvent.
8. A preblend of 78.25% sucrose, 11.00% sorbitol, 10.00% xylitol, and 0.75% Tween (polysorbate) 80 is prepared.
9. The floss preblend is processed using the 5-in crown head at a temperature of 250°C and rotational speed of 60 Hz (3600 rpm).
10. The floss collected is chopped with 2% lactose (2% w/w of the floss) for 2 minutes at 100 rpm with the choppers on 200 proof ethanol (0.5% based on weight of the floss) is sprayed on the chopped floss and mixed.
11. The floss is then dried at 45°C for 90 minutes with intermittent mixing.

12. The dried floss is screened through a 20-mesh screen.
13. APAP taste-masked microspheres (step 5), 47.97; floss (step 6), 48.88; grape flavor, 0.70; citric acid, 1.50; acesulfame potassium, 0.20; silicon dioxide, 0.25; sodium stearyl fumarate, 0.50 are processed.
14. The coated APAP microspheres are blended with the sieved floss for 5 minutes in a mixer, followed by the addition of flavors, sweeteners, and citric acid for another 3 minutes.
15. Thereafter, silicon dioxide is added and the mix blended for another 2 minutes. The final addition, sodium stearyl fumarate, is followed by blending for an additional 2 minutes.
16. The blend is then tableted using flat-faced bevel edge punches (tablet weights are 255 mg for 9-mm punch tooling, equivalent to 80 mg APAP, and 510 mg for 12-mm tooling, equivalent to 160 mg APAP dose).
17. The hardness values ranged from 0.5 to 2.0 lb.

Acetaminophen, Norephedrine, and Phenyltoloxamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
300.00	1	Acetaminophen (crystalline) (Merck)	300.00
25.00	2	Norephedrine hydrochloride (Knoll)	25.00
22.00	3	Phenyltoloxamine	22.00
200.00	4	Cornstarch	200.00
25.00	5	Kollidon 30	25.00
–	6	Ethanol (96%)	QS
25.00	7	Kollidon CL	25.00
5.00	8	Magnesium stearate	5.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with solution of items 5 and 6.
2. Dry, pass through a 0.8-mm sieve, add items 7 and 8.
3. Press with high compression force.
4. Tablet weight is 601 mg for 12-mm biplanar tablet.

Acetaminophen Oral Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
250.00	1	Acetaminophen (micronized) (2% excess)	51.00
2500.00	2	Sucrose	500.00
5.00	3	Methyl paraben	1.00
1.50	4	Propyl paraben	0.30
0.30	5	Sodium citrate	0.06
35.00	6	Glycerin (glycerol)	7.00
400.00	7	Glycerin (glycerol)	80.00
2000.00	8	Sorbitol (70%)	400.00
10.00	9	Xanthan gum (Keltrol® F)	2.00
0.50	10	Dye	0.10
22.50	11	Flavor	4.50
3.50	12	Strawberry flavor	0.70
–	13	Purified water	QS to 1 L

Manufacturing Directions

Note: Acetaminophen dispersion should be uniformly mixed. If acetaminophen dispersion is either added to hot syrup base or homogenized for a long time, flocculation may appear. While handling the syrup or mucilage or drug dispersion, the handling loss should not be more than 1%. If it exceeds 1%, a poor suspension may result.

1. Add 180 g of purified water to the mixer and heat to 90°C.
2. Dissolve item 3 and item 4 while mixing.
3. Add and dissolve item 2 while mixing.
4. Cool down to approximately 50°C to 55°C.
5. Add and dissolve item 5 while mixing.
6. Filter the syrup through T-1500 filters washed with purified water.
7. Collect the syrup in a clean stainless steel tank.

8. Disperse item 9 in item 6 in a separate stainless steel container.
9. Add 40 g of hot purified water (90°C) at once while mixing.
10. Mix for 20 minutes to make a homogeneous smooth mucilage.
11. Mix item 7 in 10 g of purified water (25°C) in a separate stainless steel container.
12. Add item 1 while mixing with stirrer.
13. Mix for 25 minutes to make uniform suspension.
14. Add sugar syrup and mucilage to the mixer.
15. Rinse the container of mucilage with 15 g of purified water and add the rinsings to the mixer.
16. Cool to 25°C while mixing.
17. Add item 1 dispersion to the mixer.
18. Rinse the container of dispersion with 15 g of purified water and add rinsings to the mixer.
19. Check the suspension for uniformity of dispersion.
20. Mix for additional 5 minutes at 18 rpm and a vacuum of 0.5 bar, if required.
21. Add item 8 to the mixer and mix for 10 minutes.
22. Dissolve item 10 in 7 g of purified water and add to the mixer.
23. Disperse item 11 in 7 g of purified water and add to the mixer.
24. Add item 12 to the mixer.
25. Add cold purified water (25°C) to bring the volume up to 1 L.
26. Homogenize for 5 minutes at low speed under a vacuum of 0.5 bar, 18 rpm, and temperature of 25°C.
27. Check the dispersion for uniformity.
28. Check the pH (limit: 5.7±0.5 at 25°C). If required, adjust the pH with a 20% solution of citric acid or sodium citrate.
29. Transfer the suspension through a 630-μm sieve to the stainless steel storage tank, after mixing for 5 minutes at 18 to 20 rpm at room temperature.

Acetaminophen, Phenylpropanolamine, Dextromethorphan, and Chlorpheniramine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Acetaminophen	200.00
12.50	2	Phenylpropanolamine hydrochloride (10% excess)	13.75
10.00	3	Dextromethorphan hydrobromide (10% excess)	11.00
1.00	4	Chlorpheniramine maleate (10% excess)	1.10
64.65	5	Cellulose (microcrystalline) (Avicel PH101)	121.72
28.00	6	Sodium starch glycolate (pH 5.5–7.5)	28.00
17.00	7	Povidone (PVP K-29–32)	17.5
–	8	Distilled purified water	~80.0 mL
2.00	9	Magnesium stearate	2.00
125.00	10	Acetaminophen	125.00
50.00	11	Ascorbic acid; use item 12	–
56.25	12	Sodium ascorbate (special grade) (20% excess)	67.50
24.00	13	Sodium starch glycolate (pH 5.5–7.5)	24.00
15.00	14	Povidone (PVP K-29–32)	~15.00
–	15	Alcohol SD 3A (200 proof)	75.0 mL

Manufacturing Directions

1. Dissolve chlorpheniramine and povidone (item 7) in the purified water.
2. Pass phenylpropanolamine, dextromethorphan, and an equal portion of Avicel (item 5) through a 790-μm screen to break up any agglomerates.
3. Blend the screened items in a suitable mixer for 5 minutes.
4. Load the acetaminophen (item 1), sodium starch glycolate (item 6), remaining Avicel (item 5), and blended items from previous step into a suitable planetary mixer.
5. Blend for 10 minutes.
6. Granulate the blend from the solution above.
7. Add the granulating solution in three equal portions, massing for 5 minutes after each addition.
8. Pass the wet mass through a 4.2-mm screen onto paper-lined trays.
9. Dry at 50°C until the granule LOD is 1% to 1.5%.
10. Pass the dried granules through an oscillating granulator fitted with a 790-μm screen.
11. Load the dried granules into a suitable blender.
12. Pass the magnesium stearate through a 600-μm screen and add to the blender.
13. Blend for 5 minutes.
14. Compress to the following specifications: tablet weight 291 mg and tablet thickness 4.2 to 4.4 mm.

Acetaminophen, Propoxyphenazone, and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Acetaminophen powder	250.00
150.00	2	Propoxyphenazone (isopropyl antipyrine)	150.00
50.00	3	Anhydrous caffeine	50.00
120.00	4	Avicel PH102	120.00
5.00	5	Pharmacoat® 603	5.00
3.25	6	Magnesium stearate	3.25
9.75	7	Talcum	9.75
1.30	8	Silicic acid	1.30
7.00	9	Methocel E-15	7.00
32.50	10	Esmaspreng fine	32.50
21.20	11	Maize starch	21.20
–	12	Water purified	QS

Manufacturing Directions

1. Place into a suitable vessel 5 g of Pharmacoat and 74 g of purified water. Stir until homogeneous aqueous mucilage is obtained.
2. Mix in another vessel 250 g acetaminophen powder and 17.50 g Esmaspreng fine. Add the above granulating solution and knead for approximately 10 minutes until an evenly moist mass of soft lumps is obtained.
3. Granulate by means of centrifugal granulator with 10-mm screen. Dry the moist granulate overnight on trays in drying oven at 45°C (RH: 20–30%).
4. Crush the dried cake through an oscillator with a 1.5-mm perforated plate.
5. In a suitable container, add 65 g deionized water and 7 g Methocel.
6. Stir until homogeneous aqueous mucilage is obtained.
7. Mix into another vessel 150 g isopropyl antipyrine, 50 g caffeine, 15 g Esmespreng fine, and 5 g maize starch.
8. Pass through a centrifugal granulator with 1-mm screen. Place mixture into another vessel and knead for approximately 10 minutes until an evenly moist mass of small lumps is obtained.
9. Granulate through centrifugal granulator with 10-mm perforated screen.
10. Dry moist granulate overnight on trays in drying oven at 45°C (RH: 10–20%).
11. Crush the dried granules through oscillator with a 1.5-mm perforated plate. Store in airtight container.
12. Mix into a tumbling mixer 4.875 g talc, 1.625 g magnesium stearate, 0.65 kg silicic acid, and 60.00 g Avicel PH102.
13. Pass through a 0.5-mm round sieve and load acetaminophen granulate and isopropyl antipyrine/caffeine granulate. Add premixture of talc into blender.
14. Mix the mixture well for 30 minutes (RH: 30–35%).
15. Store mix in airtight container.
16. Compress 650-mg tablet to 12.8 to 13.2 mm, hardness 6 to 20, disintegration time 5 minutes.

Acetaminophen, Pseudoephedrine Hydrochloride, and Chlorpheniramine Hot Therapy Sachet

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
650.00	1	Acetaminophen (micronized)	650.00
60.00	2	Pseudoephedrine hydrochloride	60.00
4.00	3	Chlorpheniramine maleate	4.00
1.20	4	Dispersed orange	1.20
18081.10	5	Castor sugar	18081.10
200.00	6	Aspartame	200.00
250.00	7	Maize starch (dried)	250.00
180.00	8	Citric acid	180.00
38.00	9	Sodium citrate	38.00
200.00	10	Sodium chloride	200.00
400.00	11	Blood orange flavor (dry)	400.00
QS	12	Purified water	QS

Manufacturing Directions

See manufacturing directions for acetaminophen and pseudoephedrine hydrochloride hot therapy sachets.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
80.00	1	Acetaminophen (micronized)	80.00
836.80	2	Hard fat (Suppocire AM)	836.80
3.20	3	Sorbitan monostearate (Crill-3)	3.20

Manufacturing Directions

1. Fill weight is 920 mg per suppository. The molten suppository mass must be stirred throughout the storage period and during manufacturing and filling to avoid sedimentation of the active drug.
2. Load items 2 and 3 into the fat-melting vessel and heat to 50°C±3°C.
3. Transfer the molten mass to a mixer through filter sieves.
4. Set the temperature at 45°C±2°C.
5. Load item 1 into the mixer containing molten item 2.
6. Carefully mix the powder with molten item 2 for 20 minutes at 10 rpm, at a temperature of 45°C±2°C, and at a vacuum of 0.4 to 0.5 bar, then homogenize for 10 minutes at low speed.
7. Continue mixing at 10 rpm.
8. Heat the storage vessel and set the temperature at 45°C±2°C.
9. Transfer the molten mass from the mixer to the storage vessel.
10. Hold the mass at 45°C±2°C, with continuous mixing at low speed.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
125.00	1	Acetaminophen (micronized) (5% excess)	131.25
785.54	2	Hard fat (Suppocire AM)	785.54
3.21	3	Sorbitan monostearate (Crill-3)	3.21

Manufacturing Directions

Fill weight is 920 mg per suppository. See manufacturing directions for acetaminophen suppositories.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
250.00	1	Acetaminophen (micronized)	250.00
1140.00	2	Hard fat (Suppocire AM)	1140.00

Manufacturing Directions

Fill weight is 1390 mg per suppository. See manufacturing directions for acetaminophen suppositories.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
150.00	1	Acetaminophen (fine powder), excess	150.00
20.00	2	Aerosil 200	20.00
1290.00	3	Lutrol E 1500	1290.00
554.00	4	Lutrol E 4000	554.00

Manufacturing Directions

1. Melt the mixture of items 1 and 2 in a mixture of items 3 and 4.
2. Fill the molten mass in suppository molds.
3. Average weight is 2 g.

Acetaminophen Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
500.00	1	Acetaminophen (fine powder)	500.00
100.00	2	Lutrol E 400	100.00
600.00	3	Lutrol E 1500	600.00
800.00	4	Lutrol E 4000	800.00

Manufacturing Directions

1. Fill weight is 2.09 g. Melt items 2 through 4 and add and dispense item 1.
2. Fill the molten mass in suppository molds.

Acetaminophen Suspension

Bill of Materials			
Scale (mg/10 mL)	Item	Material Name	Qty/L (g)
500.00	1	Acetaminophen (powder)	50.00
50.00	2	Citric acid (powder)	5.00
50.00	3	Sodium citrate	5.00
500.00	4	Kollidon CL-M	50.00
10.00	5	Orange flavor	1.00
3000.00	6	Dextrose	300.00
QS	7	Water	589.00

Manufacturing Directions

1. Prepare the solution of dextrose in water and add the other solid ingredients with stirring in the following sequence: citric acid, sodium citrate, orange flavor, Kollidon CL-M, and acetaminophen.
2. A white, homogeneous suspension is obtained that is a practically tasteless, stable suspension showing almost no sedimentation over 24 hours and good redispersibility (easily homogenized by shaking 2 to 3 times).

Acetaminophen Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
569.00	1	Sucrose (granulated sugar), NF	560.00
2.00	2	Sodium citrate (dihydrate powder), USP	2.00
1.00	3	Citric acid (anhydrous powder), USP	1.00
1.00	4	Saccharin sodium (powder), USP	1.00
1.00	5	Sodium chloride (powder), USP	1.00
204.00	6	Propylene glycol, USP	204.00
35.00	7	Acetaminophen, USP	35.00
77.11	8	Alcohol (ethanol, 190 proof), USP	77.112
0.12	9	Cherry flavor (artificial), N59456/A	0.12
0.12	10	FD&C red dye No. 40	0.10
QS	11	Deionized purified water, USP	400.00
–	12	HyFlo filter aid	QS

Manufacturing Directions

1. Add 300 mL of purified water to a jacketed stainless steel mixing tank. Start heating.
2. Add sugar with mixing.
3. Heat to 60°C to 65°C and hold. Mix for complete solution.
4. Add, while mixing, sodium citrate, citric acid, saccharine sodium, and sodium chloride. Mix for complete solution.
5. Add propylene glycol with mixing.
6. Add acetaminophen powder with moderate mixing.
7. Continue mixing at 60°C to 65°C for complete solution.
8. Force cool to 25°C to 30°C with slow mixing.
9. Blend cherry flavor with approximately twice its volume of alcohol and add with mixing.
10. Rinse the container with several portions of alcohol and add. Mix until uniform.
11. Dissolve red dye in approximately 4 g of slightly warmed (50–60°C) purified water and add with mixing.
12. Rinse the container twice with approximately 1.5 g purified water and add. Mix until uniform.
13. Adjust volume to 1 L with purified water. Mix well.
14. Add a small amount of HyFlo filter aid to the mixing tank and continue to mix slowly while filtering.
15. Filter through press until sparkling clear.
16. Use clarifying pad backed by lint-free filter paper.

Acetaminophen Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Acetaminophen (Merck)	50.00
50.00	2	Sorbitol (crystalline)	50.00
40.00	3	Cyclamate sodium	40.00
1.00	4	Strawberry flavor	1.00
200.00	5	Kollidon® 25	200.00
150.00	6	Glycerol	150.00
200.00	7	1,2-Propylene glycol	200.00
310.00	8	Water	310.00

Manufacturing Directions

1. First dissolve Kollidon 25 and then the other solid components in the solvent mixture of glycerol, propylene glycol, and water.
2. The clear solution has a slightly bitter taste.
3. The solution remains clear for more than 1 week at 6°C and for more than 3 months at 25°C and 40°C.
4. The color of the solution changes only a little during 3 months at 25°C and 40°C.
5. To prevent discoloration during storage, 0.2% to 0.5% of cysteine could be added as antioxidant.

Acetaminophen Syrup for Children

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
25.00	1	Acetaminophen (crystalline)	25.00
300.00	2	Kollidon 25 or Kollidon 30	300.00
60.00	3	Glycerol	600.00
40.00	4	Sodium cyclamate	40.00
QS	5	Orange flavor	<01.0
QS	6	Raspberry flavor	2.00
QS	7	Water	575.00

Manufacturing Directions

1. Dissolve Kollidon in water, add acetaminophen and cyclamate, heat to 50°C, and stir to obtain a clear solution.
2. Dissolve the flavors and mix with glycerol.
3. The obtained syrup is a viscous, clear, sweet, and only slightly bitter liquid.

Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Acetaminophen (fine powder)	500.00
44.15	2	Maize starch	44.15
0.84	3	Potassium sorbate	0.84
18.00	4	Povidone (PVP K-30)	18.00
4.00	5	Aerosil 200	4.00
12.00	6	Gelatin (powder)	12.00
4.00	7	Glycerol	4.00
30.00	8	Cellulose (powder)	30.00
12.00	9	Primojel	12.00
8.00	10	Stearic acid (fine powder)	8.00
2.00	11	Magnesium stearate	2.00
5.00	12	Talc (fine powder)	5.00
QS	13	Purified water	QS

Manufacturing Directions

1. Binder solution: Prepare in several batches. Add items 3 to 5 with approximately 50% quantity of water, dissolve item 1 in water, add item 4, and dissolve at medium speed. Avoid foaming.
2. Add item 5 and mix for 3 minutes.
3. Dissolve item 6 in 70°C to 80°C purified water and mix until clear. Avoid foaming.
4. Add item 7 and mix gently. Add to mixture from previous step.
5. Mix items 1 and 2 for 5 minutes.
6. Add binding solution and mix at slow speed until granules form. Add extra water if necessary.
7. Dry in fluid-bed dryer at 55°C for 30 minutes. After 15 minutes, scrape granules to break up lumps to promote uniform drying. Dry to LOD 1% to 1.5%.
8. Grind through a 3-mm sieve and then through a 1-mm sieve. Load into double-cone blender.
9. Pass cellulose powder, Primojel, and stearic acid through a 500-μm sieve; bag-mix magnesium stearate and fine talc powder and pass through a 250-μm sieve; add portion of granules from the bulk to the bag and mix for 1 minute.
10. Add both of these parts to the granules.
11. Compress 17.6-mm × 7.2-mm caplet punches to 10- to 14-kp hardness and 5.8- to 6.0-mm thickness.

Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Acetaminophen (crystalline)	500.00
137.00	2	Avicel PH102	137.00
35.00	3	Kollidon® VA 64	35.00
21.00	4	Kollidon CL	21.00
3.00	5	Magnesium stearate	3.00
4.00	6	Aerosil 200	4.00

Manufacturing Directions

1. Pass the lubricant through a 200-mm sieve. Mix all other components.
2. Pass through 0.8-mm sieve and add the lubricant and press with a high compression force of 25 to 30 KN.
3. Fill 699 mg.

Acetaminophen Tablets

Bill of Materials			
Scale (g/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500	1	Acetaminophen (crystalline)	500
150	2	Avicel PH102	150
20	3	Kollidon VA 64	20
15	4	Kollidon CL	15
15	5	PEG-6000 (powder)	15
2	6	Aerosil 200	2

Manufacturing Directions

1. Pass the lubricant through a 200-μm sieve. Mix all other components.
2. Pass through a 0.8-mm sieve, add the lubricant, and press with a high compression force of 25 to 30 kN.
3. Weight should be 703 mg.

Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Acetaminophen (powder)	500.00
30.00	2	Dicalcium phosphate	30.00
12.00	3	Kollidon CL	12.00
20.00	4	Kollidon VA 64	20.00
10.00	5	Kollidon 90 F	10.00
–	6	Ethanol (96%)	70 mL (max.)
12.00	7	Kollidon CL	12.00
10.00	8	Polyethylene glycol (powder)	10.00

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with solution of item 5 and 6.
2. Dry, sieve, and mix with items 7 and 8.
3. Press with high compression force of 25 to 30 kN.
4. Tablet weight is 587 mg for an 11-mm biconvex tablet.

Acetaminophen Tablets for Children

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
210.00	1	Acetaminophen (Merck)	210.00
168.00	2	Avicel PH101	168.00
13.00	3	Kollidon VA 64	13.00
6.00	4	Kollidon CL	6.00
2.00	5	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium compression force.
2. Tablet weight is 401 mg for each 12-mm biplanar tablet.

Acetylcysteine Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
66.66	1	Acetylcysteine BP (200 mg/sachet)	66.66
914.16	2	Sugar (18–60 mesh)	914.16
3.33	3	Saccharin sodium	3.33
0.66	4	Silicon dioxide (colloidal)	0.66
0.16	5	FD&C yellow dye No. 6	0.16
QS	6	Mandarin flavor (e.g., Naarden)	~13.0 mL

Manufacturing Directions

1. Load the acetylcysteine and half the amount of sugar and saccharin sodium into a suitable blender and premix for 30 minutes.
2. Sift the premix through a 0.8-mm screen.
3. Load again into the blender.
4. Add the remaining amount of sugar and colloidal silicon dioxide and blend until uniform (typically, this is achieved on the PK processor by heating the envelope to 40°C and mixing until the product cools to 30–35°C).
5. Dissolve the dye in 13 mL of distilled water.
6. Continue mixing the blended powders and slowly add the solution from step above.
7. When addition of the solution is complete, continue massing until the granulation is evenly wetted and colored. If necessary, complete massing by adding additional quantities of distilled water (in approximately 1-mL increments).
8. Verify that massing is adequate and note the total quantity of added water. Record the total quantity of water added. Do not overmass.
9. Spread the wet granules on trays and dry at 50°C until LOD is NMT 1% (3 hours at 60°C at 5 mmHg).
10. Allow the granules to cool, then sift on an oscillating granulator fitted with 1.18-mm aperture screen.
11. Load the granules from step above into a suitable blender, add the flavor, and blend until uniform (15 minutes), passing it through a 1.18-mm screen if necessary.
12. Fill into suitable approved sachets at a theoretical fill weight of 3 g per sachet.

Acetylsalicylic Acid, Acetaminophen and Caffeine Tablets (250 mg + 250 mg + 50 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Acetaminophen (Merck)	250.00
50.00	2	Caffeine powder	50.00
250.00	3	Acetylsalicylic acid	250.00
60.00	4	Kollidon VA 64	60.00
20.00	5	Kollidon CL	20.00
3.00	6	Aerosil 200	3.00
4.00	7	Magnesium stearate	4.00

Manufacturing Directions

1. The active ingredients and Kollidon VA 64 are granulated in a roller compactor.
2. Pass the granules together with magnesium stearate, Aerosil 200, and Kollidon CL through an 800-μm sieve.
3. Blend for 10 minutes in a mixer.
4. Compress into tablets with a force of approximately 12 kN.

Acetylsalicylic Acid + Paracetamol (= Acetaminophen) Tablets (250 mg + 250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Acetylsalicylic acid	250.00
250.00	2	Acetaminophen	250.00
60.00	3	Avicel PH101	60.00
15.00	4	Kollidon VA 64	15.00
3.00	5	Macrogel 6000 powder	3.00

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with medium compression force.

Acetylsalicylic Acid + Vitamin C Tablets (400 mg + 250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
400.00	1	Acetylsalicylic acid crystalline	400.00
250.00	2	Ascorbic acid	250.00
100.00	3	Ludipress	100.00
20.00	4	Kollidon CL	20.00
3.00	5	Macrogol 6000 powder	3.00

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with medium compression force.

Acetylsalicylic Acid Tablets (500 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Acetylsalicylic acid crystalline	500.00
200.00	2	Avicel PH101	200.00
15.00	3	Kollidon 30	15.00
25.00	4	Kollidon CL	25.00
3.00	5	Magnesium stearate	3.00

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with low compression force.

Acetylsalicylic Acid, Acetaminophen, and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Acetylsalicylic acid (crystalline)	250.00
250.00	2	Acetaminophen (crystalline)	250.00
50.00	3	Caffeine	50.00
50.00	4	Kollidon 90 F	50.00
—	5	Isopropanol	QS
5.00	6	Magnesium stearate	5.00
16.00	7	Kollidon CL	16.00

Manufacturing Directions

1. Granulate items 1 to 3 with solution of items 4 and 5. Dry and sieve through a 0.8-mm screen.
2. Add items 5 and 6 and press with low compression force (hardness 45 N). Each 12-mm biplanar tablet has an average weight of 670 mg.

Acetylsalicylic Acid, Acetaminophen, and Caffeine Tablets (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
400.00	1	Acetylsalicylic acid (crystalline)	400.00
100.00	2	Acetaminophen (crystalline)	100.00
30.00	3	Caffeine	30.00
100.00	4	Ludipress	100.00
20.00	5	Kollidon CL	20.00
30.00	6	PEG-6000 (powder)	30.00
5.00	7	Stearic acid	5.00

Manufacturing Directions

1. Mix all components. Pass through a 0.8-mm sieve.
2. Press with compression force of 116 N. Each 12-mm biplanar tablet has an average weight of 683 mg.

Acetylsalicylic Acid and Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Acetylsalicylic acid (crystalline)	250.00
250.00	2	Acetaminophen (crystalline)	250.00
60.00	3	Avicel PH101	60.00
15.00	4	Kollidon 30 (or Kollidon VA 64)	15.00
25.00	5	Kollidon CL	25.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve. Mix.
2. Press with medium compression force.
3. Tablet weight is 605 mg for each 12-mm biplanar tablet.

Acetylsalicylic Acid and Acetaminophen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Acetylsalicylic acid (40 mesh)	250.00
250.00	2	Acetaminophen (40 mesh)	250.00
15.00	3	Avicel PH102	15.00
7.20	4	Croscarmellose sodium (Ac-Di-Sol)	7.20
7.20	5	Stearic acid	7.20
4.00	6	Fumed silica	4.00

Manufacturing Directions

1. Screen all ingredients through a 0.8-mm sieve.
2. Blend all ingredients in a V-blender and mix for 10 minutes.
3. Compress to 670-mg tablet weight using appropriate tooling.

Acetylsalicylic Acid and Ascorbic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
325.00	1	Acetylsalicylic acid (crystalline) (Merck)	325.00
250.00	2	Ascorbic acid (powder) (BASF)	250.00
120.00	3	Sorbitol (crystalline)	120.00
40.00	4	Avicel PH101	40.00
25.00	5	Kollidon VA 64	25.00
20.00	6	Kollidon CL	20.00
2.00	7	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve. Mix.
2. Press with medium to high compression force (hardness 92 N). Each 12-mm biplanar tablet has an average weight of 790 mg.

Acetylsalicylic Acid and Ascorbic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
325.00	1	Acetylsalicylic acid (crystalline) (Merck)	325.00
250.00	2	Ascorbic acid (powder) (BASF)	250.00
100.00	3	Avicel PH101	100.00
12.00	4	Kollidon VA 64	12.00
30.00	5	Kollidon CL	30.00
3.00	6	Magnesium stearate	3.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve. Mix.
2. Press with medium to high compression force (hardness 100 N). Each 12-mm biplanar tablet has an average weight of 726 mg.

Acetylsalicylic Acid Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
100.00	1	Acetylsalicylic acid	100.00
400.00	2	Suppocire AM	400.00

Manufacturing Directions

1. Heat item 2 to 50°C. Allow to cool to 40°C.
2. Add item 1 while stirring with a turbine mixer. Cool molds to –5°C to 0°C.
3. Continue mixing and cooling and pour into molds at 35°C.
4. Remove suppositories from molds after 7 minutes.
5. Fill to appropriate weight for strength desired.

Acetylsalicylic Acid Tablets (Buffered)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
400.00	1	Acetylsalicylic acid (40 mesh)	400.00
40.00	2	Magnesium hydroxide	40.00
40.00	3	Aluminum hydroxide	40.00
135.00	4	Cellulose (microcrystalline) (Avicel PH101)	135.00
15.30	5	Stearic acid	15.30
15.30	6	Croscarmellose sodium (Ac-Di-Sol)	15.30
18.50	7	Hydroxy coatings	18.50

Manufacturing Directions

1. Screen all ingredients except the item 7 through a 40-mesh sieve.
2. Blend items 2 and 3 in a V-blender for 10 minutes.
3. Coat items 2 and 3 using Aquacoat (FMC) aqueous polymer dispersion in a fluid-bed column using a 10% by weight formula.
4. Blend 50% of item 1 with items 4 and 5 for 10 minutes in a V-blender.
5. Add remaining item 1 and blend again for 10 minutes.
6. Blend item 7 with the mixture from the previous step for 10 minutes.
7. Add item 6 and blend for 7 minutes.
8. Compress 625 mg to the desired hardness using appropriate tooling.

Acetylsalicylic Acid Tablets (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
400.00	1	Acetylsalicylic acid (crystalline) (Merck)	400.00
99.00	2	Ludipress	99.00
1.00	3	Stearic acid	1.00
15.00	4	Kollidon CL	15.00

Manufacturing Directions

1. Mix all components. Pass through a 0.8-mm sieve.
2. Press with low compression force (hardness 90 N). Each 12-mm biplanar tablet has an average weight of 516 mg.

Acetylsalicylic Acid Tablets (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
400.00	1	Acetylsalicylic acid (40 mesh)	400.00
55.60	2	Cellulose (microcrystalline) (Avicel PH101)	55.60
21.40	3	Starch (pregelatinized)	21.40
2.20	4	Stearic acid	2.20
10.00	5	Croscarmellose sodium (Ac-Di-Sol)	10.00
3.20	6	Fumed silica	3.20

Manufacturing Directions

1. Screen approximately half of item 1 through a mill using 12-mesh screen with knives forward.
2. Preblend items 2 to 6 with 25% of item 1 and pass the mixture through the mill.
3. Pass the balance of item 1 through the mill.
4. Mix all the ingredients in a V-blender for 10 minutes and compress using 13/32-in tooling.
5. For enteric coating, coat with Aquateric (FMC) dispersion.

Acetylsalicylic Acid Tablets (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Avicel PH101	200.00
15.00	2	Kollidon 30	15.00
25.00	3	Kollidon CL	25.00
3.00	4	Magnesium stearate	3.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve. Mix.
2. Press with low compression force of (hardness 61 N). Each 12-mm biplanar tablet has an average weight of 707 mg.

Acne Cover Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
37.00	1	Glyceryl stearate S/E	37.00
46.00	2	Mineral oil/Lanolin alcohol (liquid base CB3939)	46.00
9.00	3	Polawax GP2000	9.00
18.00	4	Stearic acid	18.00
QS	5	Deionized water	QS
36.00	6	Propylene glycol	36.00
2.00	7	Carboxymethyl cellulose (CMC-7HF)	2.00
9.00	8	Magnesium aluminum silicate (regular) (Veegum)	9.00
9.00	9	Triethanolamine (99%)	9.00
120.00	10	Titanium dioxide	120.00
QS	11	Iron oxides	QS
50.00	12	Actives	50.00
QS	13	Perfume, preservative	QS

Manufacturing Directions

1. Disperse CMC in propylene glycol and triethanolamine and add warm water (60–65°C) while stirring, until the gum is hydrated.
2. Add Veegum and stir until hydrated.
3. Heat oil phase to 60°C to 65°C.
4. Add water phase to oil phase while stirring.
5. Add pigments and stir to cool, adding the actives at 30°C.
6. Homogenize using suitable equipment.
7. Fill. [Note that active ingredients may be added as required to this base formula.]

Acne Scrub

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Magnesium aluminum silicate magnabrite HV	20.00
582.00	2	Water	582.00
100.00	3	Propylene glycol	100.00
150.00	4	Mineral oil and acetylated lanolin alcohol	150.00
30.00	5	Glyceryl stearate and PEG-100 stearate	30.00
14.00	6	Myristyl propionate	14.00
100.00	7	PEG-600	100.00
4.00	8	Eucalyptus oil	4.00
QS	9	Preservatives	QS

Manufacturing Directions

1. Slowly sift item 1 into water, mixing until smooth.
2. Heat to 75°C.
3. Heat items 3 to 6 separately. Mix and heat to 70°C.
4. Add this portion to item 1 dispersion and mix well until smooth.
5. Add item 7 to mixture and mix.
6. Finally, add items 8 and 9 and mix until cool.
7. *Note*: If using parabens, prepare a solution in a portion of water and add before adding item 8 and after allowing parabens to cool to 50°C.

Acne Treatment Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Polychol 10 (Laneth-10)	20.00
5.00	2	Lanolin alcohols (Super Hartolan)	5.00
55.00	3	Cetyl alcohol C90	55.00
60.00	4	Polawax, NF	60.00
14.00	5	Sulfur	14.00
QS	6	Deionized water	QS
40.00	7	Veegum® (regular)	40.00
20.00	8	Propylene glycol	20.00
20.00	9	Resorcinol	20.00
QS	10	Perfume, preservative	QS

Manufacturing Directions

1. Hydrate Veegum in water.
2. Add rest of the water-phase ingredients and heat to 70°C.
3. Heat oil phase to 70°C.
4. Disperse sulfur in the oil phase.
5. Add oil phase to water phase while stirring.
6. Stir to cool. Fill.

Alginic Acid + Aluminium Hydroxide + Magnesium Silicate Tablets (500 mg+100 mg+25 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Alginic acid	500.00
100.00	2	Aluminum hydroxide dried gel (Giulini)	100.00
25.00	3	Magnesium trisilicate	25.00
170.00	4	Sodium bicarbonate	170.00
160.00	5	Sorbitol crystalline	160.00
627.00	6	Sucrose crystalline	627.00
900.00	7	Ludipress	900.00
70.00	8	Kollidon VA 64	70.00
50.00	9	Magnesium stearate	50.00
5.00	10	Vanillin	5.00

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with high compression force.

Aloe Vera Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
4.00	1	Aloe vera extract (200-fold)	4.00
50.00	2	Propylene glycol	50.00
QS	3	Preservative	QS
736.00	4	Water	736.00
11.00	5	Cremophor RH 40	11.00
QS	6	Perfume	QS
200.00	7	Lutrol F 127	200.00

Manufacturing Directions

1. Prepare solutions I (items 1–4) and II (items 5 and 6) separately and add I into II.
2. Cool this mixture to <10°C (or heat to 70–80°C) and dissolve item 7.
3. Maintain the temperature until air bubbles escape.
4. Appearance is clear, viscosity is approximately 60 Pa, and pH is approximately 5.5.

Alpha-Bisabolol Aqueous Mouthwash Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
2.00	1	Alpha-bisabolol, natural (BASF)	2.00
QS	2	Flavor	QS
25.00	3	Cremophor RH 40	25.00
50.00	4	Glycerol	50.00
1.00	5	Saccharin sodium	1.00
QS	6	Preservative	QS
922.00	7	Water	922.00

Manufacturing Directions

1. Heat mixture of items 1 to 3 to approximately 60°C and slowly add the warm solution of items 4 to 7 (60°C).
2. The clear, colorless liquid has a low viscosity.

Alpha-Bisabolol Buccal or Topical Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1.20	1	Alpha-bisabolol (racemic) (BASF)	1.20
10.00	2	Cremophor RH 40	10.00
0.10	3	Butylhydroxytoluene (BHT)	0.10
QS	4	Preservative	QS
990.00	5	Water	990.00

Manufacturing Directions

Heat mixture of items 1 to 3 to approximately 60°C, stir well and slowly add the warm solution of items 4 in 5 to obtain a clear solution.

Alpha-Bisabolol Ethanolic Mouthwash Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Alpha-bisabolol, racemic (BASF)	10.00
100.00	2	Flavor	100.00
60.00	3	Cremophor RH 40	60.00
10.00	4	Glycerol	10.00
2.00	5	Saccharin sodium	2.00
818.00	6	Ethanol (96%)	818.00

Manufacturing Directions

1. Heat mixture of items 1 to 3 to approximately 60°C and slowly add the warm solution of items 4 to 6.
2. The clear, colorless liquid can be diluted with water.

Alpha-Bisabolol Mouthwash Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
5.00	1	(–)Alpha-bisabolol, natural (BASF)	5.00
50.00	2	Lutrol F 127	50.00
QS	3	Flavor	QS
100.00	4	Propylene glycol (pharma)	100.00
300.00	5	Ethanol (96%)	300.00
545.00	6	Water	545.00

Manufacturing Directions

1. Prepare solution of items 1 to 5 and slowly add the water.
2. The clear, colorless solution has pH 8.

Aluminum Acetylsalicylate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Aluminum acetylsalicylate, excess	255.00
213.00	2	Mannitol	213.00
28.00	3	Cornstarch	28.00
10.00	4	Kollidon 90 F	10.00
5.00	5	Lutrol E 6000	5.00
–	6	Isopropanol, QS	50.00 mL
23.00	7	Kollidon CL	23.00
5.00	8	Magnesium stearate	5.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with solution of items 4 to 6.
2. Dry, pass through a 0.8-mm sieve, mix with items 7 and 8.
3. Compress with medium compression force. Each 12-mm biplanar tablet has an average weight of 540 mg.

Aluminium Hydroxide + Magnesium Silicate Chewable Tablets (120 mg+250 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
120.00	1	Aluminum hydroxide dried gel (Giulini)	120.00
250.00	2	Magnesium trisilicate	250.00
232.00	3	Ludipress	232.00
6.00	4	Aerosil 200	6.00
6.00	5	Magnesium stearate	6.00
12.00	6	Cyclamate sodium	12.00
1.50	7	Menthol	1.50

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, and press with a compression force of 20 kN at 640 mg.

Aluminum Hydroxide and Magnesium Carbonate Dry Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
200.00	1	Aluminum hydroxide dry gel (Giulini)	200.00
200.00	2	Basic magnesium carbonate	200.00
240.00	3	Kollidon CL-M	240.00
211.50	4	Sorbitol (crystalline)	211.50
41.30	5	Orange flavor	41.30
82.60	6	Kollidon 30	82.60
3.30	7	Coconut flavor	3.30
4.13	8	Banana flavor	4.13
4.13	9	Saccharin sodium	4.13
8.26	10	Water	8.26

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with solution of items 6 to 10, pass through a sieve, and dry.
2. Shake 58 g of the granules with 100 mL of water.
3. Product remains homogeneous and without sedimentation for more than 24 hours.

Aluminum Hydroxide and Magnesium Hydroxide Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Aluminum hydroxide (Rorer)	200.00
200.00	2	Magnesium hydroxide (Rorer)	200.00
100.00	3	Lactose monohydrate	100.00
30.00	4	Kollidon VA 64	30.00
QS	5	Water	260.00 mL
315.00	6	Sucrose (crystalline)	315.00
100.00	7	Sorbitol (crystalline) (Merck)	100.00
60.00	8	PEG-6000 (powder)	60.00
12.00	9	Aerosil 200	12.00
6.00	10	Talc	6.00
6.00	11	Magnesium stearate	6.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with solution of items 4 to 5.
2. Dry and pass through a 0.8-mm sieve, add items 6 to 11, and press with high compression force (20 kN).
3. Each 16-mm biplanar tablet has an average weight of 1013 mg.

Aluminum Hydroxide and Magnesium Hydroxide Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
320.00	1	Aluminum hydroxide (dried gel)	320.00
320.00	2	Magnesium hydroxide powder	320.00
32.00	3	Sucrose	32.00
288.40	4	Mannitol	288.40
QS	5	Povidone (Plasdone®) (10% solution in equal parts water and alcohol)	QS
12.90	6	Glycerin	12.90
19.20	7	Magnesium stearate	19.20
6.40	8	Fumed silica	6.40
0.30	9	Oil of peppermint	0.30

Manufacturing Directions

1. Mix items 1 to 4 in a suitable blender, add item 6 to item 5, and use this combination to moisten the mix of items 1 to 4.
2. Granulate by passing through a 20-mesh screen.
3. Add and thoroughly mix items 7 to 9 and compress using 0.5-in flat-face, beveled-edge punches.

Aluminum Hydroxide and Magnesium Hydroxide Antacid Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
5.00	1	Purified bentonite (Veegum® HS)	5.00
2.00	2	Xanthan gum (Rhodigel)	2.00
401.00	3	Water	401.00
200.00	4	Sorbitol (70%)	200.00
360.00	5	Aluminum hydroxide gel	360.00
320.00	6	Magnesium hydroxide, USP	320.00
QS	7	Preservative, flavor	QS

Manufacturing Directions

1. Slowly add a dry blend of item 1 and 2 to item 3, agitating with maximum available shear until a smooth and uniform mix is obtained.
2. Mix items 4 to 6 together in another vessel until uniform and then add to previous mix.
3. Agitate until uniform.
4. Add item 7 and mix until uniform.

Aluminum Hydroxide and Magnesium Hydroxide Antacid Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
200.00	1	Magnesium aluminum silicate (Magnabrite S) (5% suspension)	200.00
2.00	2	Methyl paraben	2.00
1.00	3	Propyl paraben	1.00
0.50	4	Saccharin sodium	0.50
500.00	5	Aluminum hydroxide/Magnesium hydroxide fluid gel	500.00
3.00	6	Polysorbate 80	3.00
2.00	7	Flavor	2.00
291.50	8	Deionized water	291.50

Manufacturing Directions

1. Add the parabens and saccharin to item 1 with stirring until dissolved (may heat to 80°C to dissolve).
2. Add item 5 with mixing.
3. Finally, add items 6 and 7. Mix well.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
405.00	1	Aluminum hydroxide gel	290.00
100.00	2	Magnesium hydroxide paste (30%)	67.00
0.21	3	Ammonia solution (25%)	0.04
0.05	4	Ammonia solution (25%)	0.01
10.00	5	Methyl paraben	2.00
0.25	6	Menthol	0.05
3.00	7	Propyl paraben	0.60
1.00	8	Peppermint oil	0.20
50.00	9	Propylene glycol	10.00
1.25	10	Saccharin sodium	0.25
150.00	11	Sorbitol (70% solution)	30.00
4.50	12	Sodium hypochlorite (5%)	0.90
1.25	13	Sodium hypochlorite (5%)	0.25
15.00	14	Magnesium aluminum silicate (Veegum® HV)	3.00
QS	15	Purified water	QS to 1 L

Note: The quantity of the sodium hypochlorite solution should be adjusted according to the assay.

Manufacturing Directions

1. Disperse item 14 in 60 g of hot purified water (70–80°C) in stainless steel vessel, using stirrer. Continue stirring for 30 minutes.
2. Transfer the dispersion into mixer (e.g., Krieger) vessel by vacuum and mix for 30 minutes at 16/32 mixer speed.
3. Cool down to 30°C.
4. Add 200 g of hot purified water (70–80°C) to the mixer.
5. Mix and homogenize at 1420 rpm, mixer speed 16/32, and vacuum 0.5 bar for 30 minutes.
6. Cool down to 30°C.
7. Add 1 kg of purified water (70°C) to a suitable vessel and heat to 85°C to 90°C for 1 hour.
8. Cool to 20°C to 25°C.
9. Mix items 13 and 4 and immediately add to purified water (20–25°C) in the storage vessel.
10. Mix for 2 minutes. Store in a previously cleaned storage vessel.
11. Load item 2 and 100 g of purified water (25–30°C) in a stainless steel mixing vessel with lid and stirrer.
12. Mix for 5 minutes at medium speed.
13. Transfer by vacuum into mixer.
14. Load 80 g of item 1 and 80 g of purified water (25–30°C) from step above in a stainless steel mixing vessel with lid and stirrer. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer.
15. Load 50 g of item 1 and 50 g of purified water (25–30°C) from step above in a stainless steel mixing vessel with lid and stirrer.
16. Mix for 5 minutes at medium speed. Transfer by vacuum into mixer.
17. Transfer item 11 into mixer by vacuum.
18. Dissolve item 10 in 2 g of purified water (25–30°C) and transfer to mixer.
19. Mix and homogenize for 30 minutes at 1420 rpm under vacuum 0.5 bar.
20. Dissolve items 5 and 7 in item 9 (50–60°C) by stirring in stainless steel container in a water bath.
21. Dissolve items 6 and 8 and add to parabens/glycol solution. Mix well. Add to mixer.
22. Mix and homogenize for 10 minutes under vacuum 0.5 bar.
23. Mix items 3 and 12 and 2 g of purified water and immediately add to the mixer.
24. Mix for 10 minutes without vacuum.
25. Add cold purified water to bring the volume up to 1 L. Mix for 15 minutes.
26. Transfer the suspension through 630-μm sieve to the stainless steel storage tank. (Final pH is 7.5–8.0 and density is 1.04–1.06.)

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
200.00	1	Aluminum hydroxide gel	214.00
80.00	2	Magnesium hydroxide paste (30%)	54.20
150.00	3	Sorbitol (70% solution)	30.00
10.00	4	Methyl paraben	2.00
1.00	5	Propyl paraben	0.20
2.00	6	Saccharin sodium	0.40
15.00	7	Magnesium aluminum silicate (Veegum HV)	3.00
0.20	8	Ammonia solution (25%)	0.04
4.50	9	Sodium hypochlorite (5%)	0.90
100.00	10	Propylene glycol	20.00
0.75	11	Lemon mint flavor	0.15
QS	12	Purified water	QS to 1 L

Manufacturing Directions

See manufacturing directions for aluminum hydroxide and magnesium hydroxide suspension.

Aluminum Hydroxide and Magnesium Hydroxide Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
40.00	1	Aluminum hydroxide	40.00
40.00	2	Magnesium hydroxide	40.00
50.00 g	3	Cremophor RH 40	50.00
1.00	4	Silicon oil DC 200 (Serva)	1.00
100.00	5	Kollidon CL-M	100.00
QS	6	Water	76.90

Manufacturing Directions

Mix Cremophor RH 40 well with the silicon oil, add the water, and suspend the solid substances.

Aluminum Hydroxide and Magnesium Hydroxide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
405.00	1	Aluminum hydroxide gel (dried)	405.00
100.00	2	Magnesium hydroxide powder	100.00
108.00	3	Mannitol	108.00
38.80	4	Sorbitol powder	38.80
2.50	5	Saccharin sodium	2.50
16.70	6	Povidone (PVP K-30)	16.70
7.00	7	Magnesium stearate	7.00
2.00	8	Mint flavor (dry)	2.00
299.00	9	Purified water	299.00

Manufacturing Directions

1. Dissolve items 4 and 5 in 59 g of purified water by using stirrer.
2. Add item 6 while mixing until clear solution is obtained.
3. Add items 1, 2, and 3 into mixer and mix for 5 minutes using mixer and chopper at high speed.
4. Dilute concentrate-binding solution with 240 g of purified water.
5. Add binding solution at a rate of 9 to 11 g/min to the dry powders in mixer while mixing at low speed. Mix for 2 to 3 minutes. Scrape the sides, blade, and lid of the mixer. Mix and chop at low speed for an additional 2 to 3 minutes or until the granules stop flying around the chopper. Add extra-purified water, if required, and continue mixing until a satisfactory mass is obtained. Record extra quantity of purified water added.
6. Unload the wet mass into a clean Aeromatic bowl for drying. Avoid big lump formation, as this leads to nonuniform drying.
7. Dry the wet mass in an Aeromatic fluid-bed dryer at 60°C for 120 minutes. After 30 minutes of drying, scrape the semidried granules to break the lumps for uniform drying. Check the LOD (limit: NMT 5.5%).
8. Pass the dried granules through 1.5-mm sieve using granulator at medium speed. Collect in stainless steel drums. Set aside 7 to 9 g granules for later step.
9. Load the rest of the granules into blender. Pass items 8 and 7 through a sifter using a 250-μm sieve. Collect in a polyethylene bag.
10. Add approximately 7 to 9 g of granules and mix gently.
11. Load into blender and blend for 3 minutes.
12. Check temperature and humidity of the room before beginning compression (humidity limit: NMT 60%, temperature 25°C±1°C).
13. Compress the granules using a rotary tableting machine. Compress 680-mg tablets using 12.7-mm flat, beveled-edge punches.

Aluminum Hydroxide and Magnesium Silicate Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
120.00	1	Aluminum hydroxide dried gel (Giulini)	120.00
250.00	2	Magnesium trisilicate	250.00
232.00	3	Ludipress	232.00
6.00	4	Aerosil 200	6.00
6.00	5	Magnesium stearate	6.00
12.00	6	Cyclamate sodium	12.00
1.50	7	Menthol	1.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with a compression force of 20 kN.
2. Because of the poor flowability of the powder, the tableting machine should be equipped with a special technical device to provide a continuous and homogeneous filling of the dies.
3. Each 16-mm biplanar tablet has an average weight of 640 mg.

Aluminum Hydroxide, Magnesium Carbonate (or Oxide), and Simethicone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
576.00	1	Sucrose	576.00
157.00	2	Aluminum hydroxide	157.00
160.00	3	Magnesium carbonate (or oxide)	160.00
97.00	4	Magnesium oxide	97.00
45.00	5	Kollidon 90 F	45.00
22.00	6	Aerosil 200	22.00
300.00	7	Simethicone suspension (30%)	300.00
9.00	8	Menthol	9.00
1.00	9	Saccharin sodium	1.00
49.00	10	Talc	49.00
13.00	11	Magnesium stearate	13.00

Manufacturing Directions

1. Granulate mixture of items 1 to 6 with the simethicone suspension, dry, sieve through a 0.8-mm screen, add items 8 to 11, and press with high compression force.
2. Tablet has an average weight of 1295 mg.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
27.00	1	Simethicone 30%	27.00
30.00	2	Cremophor RH 40	30.00
70.00	3	Water	70.00
80.00	4	Aluminum hydroxide dry gel (Giulini)	80.00
80.00	5	Magnesium hydroxide	80.00
90.00	6	Kollidon CL-M	90.00
100.00	7	Sorbitol (crystalline)	100.00
4.00	8	Banana flavor	4.00
5.00	9	Coconut flavor	5.00
1.00	10	Saccharin sodium	1.00
QS	11	Water	QS to 1 L
QS	12	Citric acid (to adjust pH)	QS

Manufacturing Directions

1. Mix Cremophor RH 40 with simethicone and heat to approximately 50°C, stirring well.
2. Add warm water.
3. Dissolve the flavors and saccharin in water and suspend aluminum hydroxide, magnesium hydroxide, and Kollidon CL-M.
4. Add emulsion of items 1 to 3 to the stirred suspension of items 4 to 11 and adjust the pH to approximately 9 with item 12, if needed.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
215.00	1	Aluminum hydroxide gel	217.00
80.00	2	Magnesium hydroxide paste (30%)	56.00
25.00	3	Simethicone emulsion (Simethicone Antifoam M30)	18.50
150.00	4	Sorbitol (70% solution)	30.00
0.20	5	Ammonia solution 25%	0.04
10.00	6	Methyl paraben	2.00
1.00	7	Propyl paraben	0.20
28.00	8	Methyl cellulose 4000 (Methocel A4M)	5.60
2.00	9	Saccharin sodium	0.40
4.50	10	Sodium hypochlorite (5%)	0.90
1.00	11	Lemon mint flavor	0.20
QS	12	Purified water	QS to 1 L

Manufacturing Directions

See manufacturing directions for aluminum and magnesium hydroxide suspension.

Aluminum Hydroxide, Magnesium Hydroxide, and Simethicone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Aluminum hydroxide gel (dried)	260.00
200.00	2	Magnesium hydroxide powder	200.00
200.00	3	Mannitol	200.00
45.00	4	Sorbitol powder	45.00
65.00	5	Dextrose (glucose) monohydrate	65.00
16.50	6	Povidone (PVP K-30)	16.50
2.50	7	Saccharin sodium	2.50
1.00	8	FD&C yellow dye No.10 lake	1.00
2.50	9	Mint flavor (dry)	2.50
1.50	10	Lemon flavor (dry)	1.50
25.00	11	Simethicone GS granules	84.00
315.00	12	Dextrates (Emdex®)	315.00
1.00	13	Colloidal silicon dioxide (Aerosil 200)	1.00
6.00	14	Magnesium stearate	6.00
–	15	Purified water	160.00

Manufacturing Directions

1. Processing should be done at RH 50%±5% and temperature of 26°C±1°C.
2. Dissolve items 4, 5, and 7 in cold purified water (25–30°C) by using stirrer, then add item 6 while mixing.
3. Add item 8 and disperse the color completely.
4. Check final weight; if required adjust with purified water.
5. Load items 1, 2, and 3 into mixer and mix for 5 minutes using mixer and chopper at high speed.
6. Add binding solution at a rate of 16 to 20 g/min to the dry powders in mixer while mixing at low speed. Mix for 2 to 3 minutes. Scrape the sides, blade, and lid of the mixer.
7. Mix and chop at low speed for an additional 2 to 3 minutes or until the granules stop flying around the chopper. Add extra-purified water, if required, and continue mixing until a satisfactory mass is obtained. Record extra quantity of purified water added.

8. Unload the wet mass into clean Aeromatic bowl for drying.
9. Avoid big lump formation, as this leads to nonuniform drying.
10. Dry the wet mass in an Aeromatic fluid-bed dryer at 60°C for 90 minutes.
11. After 30 minutes of drying, scrape the semidried granules to break up the lumps to promote uniform drying.
12. Pass the dried granules through a 1.5-mm sieve using a granulator at medium speed. Collect in stainless steel drums.
13. Load the granules into blender.
14. Add items 11 and 12 to stainless steel drum and mix for 2 minutes using drum mixer, then load into the blender and mix along with the granules for 2 minutes.
15. Pass items 9, 10, 13, and 14 through sifter using 250-μm sieve.
16. Load the sieved material into blender and mix for 2 minutes. Unload into stainless steel drums.
17. Check temperature and humidity of the room before beginning compression.
18. Compress 1.2 g per tablet using 15.8-mm flat punch at RH 50%±5% at a temperature of 26°C±1°C.

Analgesic Clear Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
25.00	1	Hydroxypropyl cellulose	25.00
QS	2	Deionized water	QS to 1 kg
400.00	3	Ethanol DEB 100	400.00
100.00	4	Menthol	100.00
150.00	5	Methyl salicylate	150.00
25.00	6	DEA-oleath-3-phosphate	25.00

Manufacturing Directions

1. Hydrate hydroxypropyl cellulose in water at 60°C to 65°C.
2. Stir to cool.
3. Add ethanol.
4. Add remaining ingredients and stir until homogeneous.

Analgesic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
130.00	1	Methyl salicylate	130.00
60.00	2	Menthol	60.00
20.00	3	Eucalyptus oil	20.00
5.00	4	Lanolin	5.00
1.00	5	Chloroxylenol	1.00
150.00	6	Glyceryl stearate and PEG-100 stearate	150.00
73.00	7	Cetearyl alcohol	73.00
70.00	8	Glyceryl stearate	70.00
QS	9	Deionized water	QS to 1 kg
QS	10	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 30°C.

Analgesic Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Methyl salicylate	150.00
70.00	2	Menthol	70.00
10.00	3	Lanolin oil	10.00
30.00	4	PEG-40 stearate	30.00
20.00	5	Glyceryl stearate	20.00
QS	6	Deionized water	QS
1.50	7	Carbopol® 980	1.50
10.00	8	Potassium hydroxide (10% aqueous solution)	10.00
QS	9	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases (except potassium hydroxide) separately to 65°C to 70°C.
2. Add water phase to oil phase while stirring.
3. Add potassium hydroxide solution to neutralize.
4. Stir to cool.
5. Fill at 30°C.

Anise Oil Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Anise oil	10.00
17.00	2	Cremophor RH 40	17.00
340.00	3	Ethanol	340.00
QS	4	Preservatives	QS
633.00	5	Water	633.00

Manufacturing Directions

1. Mix the anise oil with Cremophor RH 40, heat to approximately 65°C, stir strongly.
2. Slowly add the hot solution of items 3 to 5 to produce a clear or slightly opalescent, colorless liquid.

Antazoline and Xylometazoline Eye Drops

Bill of Materials			
Scale (mg/100 mL)	Item	Material Name	Qty/L (g)
500.00 g	1	Antazoline sulfate	5.00
50.00 g	2	Xylometazoline hydrochloride	0.50
0.15	3	Hydroxypropylmethylcellulose (4000 cps)	1.50
0.10	4	Benzalkonium chloride, use benzalkonium chloride solution (17%) (7% excess)	0.63 mL
0.10	5	Edetate disodium	1.00
0.843	6	Sodium chloride	8.43
QS	7	Water purified	QS to 1 L

Manufacturing Directions

Equipment used should be thoroughly cleaned and rinsed before proceeding. Use steam-jacketed, glass-lined, or stainless steel (No. 304 or better) tanks. The tank must be equipped with an agitator (preferably with speed control) and a cover to protect against air at all times during the manufacturing process, except when ingredients are being added or samples are being taken. Benzalkonium chloride markedly lowers the surface tension. During severe agitation or turbulent flow, substantial foaming will occur. This condition often exists in the processing equipment and in the overflow system of vacuum-filling machines. Benzalkonium chloride tends to concentrate in the foam. If the foam is not dissipated quickly and if it is allowed to accumulate, a substantial excess of benzalkonium chloride may result near the surface of the liquid after the foam condenses; therefore, it is advisable to design the processing and filling systems in such a way as to minimize foaming and ensure rapid dissipation of any unavoidable foaming.

1. Charge mixing tank to 90% of final volume with purified water.
2. Heat water to 90°C and, while agitating, add and dissolve the hydroxypropylmethylcellulose by slowly sprinkling onto the surface of the water.
3. Methyl cellulose must be dispersed evenly over a period of time to ensure complete wetting and dispersion.
4. The agitation rate should be adjusted to avoid excessive foaming.
5. Allow 15 minutes for hydration of the hydroxypropylmethylcellulose before cooling.
6. Discontinue heating and cool solution to approximately 40°C.
7. While agitating, add and dissolve antazoline sulfate, xylometazoline hydrochloride, benzalkonium chloride, edetate disodium, and sodium chloride.
8. Continue cooling to 25°C.
9. Turn off agitator and QS to final volume. Mix well.
10. Note: Methyl cellulose solutions filter at a slow rate. Recirculate the solution through filter assembly until clear.
11. Sterile filter and fill.

Antiacne Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
422.00	1	Witch hazel (distilled, 14% alcohol)	422.00
5.00	2	Salicylic acid	5.00
5.00	3	Aloe vera gel	5.00
10.00	4	Sorbitol	10.00
500.00	5	Polyglycerylmethacrylate	500.00
10.00	6	Propylene glycol	10.00
0.80	7	Methyl paraben	0.80
0.20	8	Propyl paraben	0.20

Manufacturing Directions

1. Premix items 1 to 4.
2. Add item 5 with low-shear mixing until homogeneous.
3. Mix together items 6 to 8 and add them to the formulation.

Antifungal Foot Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Dichlorobenzyl alcohol (Myacide SF)	5.00
5.00	2	Allantoin	5.00
200.00	3	Cornstarch	200.00
790.00	4	Talc	790.00

Manufacturing Directions

Mix all ingredients using geometric dilution technique.

Antiseptic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Polawax GP200	50.00
10.00	2	Lanolin	10.00
150.00	3	Mineral oil (70 cS)	150.00
70.00	4	Cetearyl alcohol	70.00
30.00	5	Dimethicone	30.00
QS	6	Deionized water	QS to 1 kg
5.00	7	Cetrimonium bromide	5.00
0.50	8	Chlorhexidine gluconate	0.50
QS	9	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases to 65°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Fill.

Antiseptic Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
30.00	1	Cetearyl alcohol and ceteareth-20	30.00
50.00	2	Mineral oil (70 cS)	50.00
2.00	3	Lanolin alcohol	2.00
QS	4	Deionized water	QS to 1 kg
5.00	5	Cetrimonium bromide (as 40% cetermide solution BP)	5.00
20.00	6	Glycerin	20.00
QS	7	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Fill at 30°C.

Antiseptic Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
30.00	1	Cetearyl alcohol and ceteareth-20	30.00
45.00	2	Mineral oil (70 cS)	45.00
25.00	3	Stearyl alcohol	25.00
10.00	4	Lanolin	10.00
5.00	5	Polysorbate 60	5.00
15.00	6	Laneth-15	15.00
QS	7	Deionized water	QS to 1 kg
5.00	8	Cetrimonium bromide (as 40% ceterimide solution BP)	5.00
20.00	9	Glycerin	20.00
QS	10	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Fill at 30°C.

Antiseptic Wet Wipes

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
3.75	1	Cetrimonium bromide	3.75
0.15	2	Chlorhexidine gluconate	0.15
10.0–20.0	3	Polysorbate 20	10.0–20.0
10.0–20.0	4	Glycerin	10.0–20.0
QS	5	Deionized water	QS to 1 L
QS	6	Perfume	QS

Manufacturing Directions

1. Preblend Polysorbate 20 and perfume.
2. Combine remaining components with stirring. Add perfume/Polysorbate 20 blend.
3. Stir until clear.
4. Package in wipes.

Asparagus Extract + Parsley Extract Tablets (200 mg+200 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Asparagus extract powder	200.00
200.00	2	Parsley extract powder	200.00
200.00	3	Sorbitol crystalline	200.00
20.00	4	Kollidon VA 64	20.00
10.00	5	Kollidon CL	10.00
4.00	6	Magnesium stearate	4.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve. Mix.
2. Press with low compression force at 636 mg.

Aspartame Effervescent Tablets (20 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
00.00	1	Aspartame	20.00
10.40	2	Sorbitol crystalline	10.40
14.30	3	Tartaric acid powder	14.30
18.70	4	Sodium carbonate	18.70
1.70	5	Kollidon 25	1.70
1.10	6	PEG-6000 powder	1.10

Manufacturing Directions

1. Mix and pass through a 0.5-mm sieve.
2. Press to tablets at 66 mg.

Aspartame Granules in Sachets

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachets (g)
30.00	1	Aspartame	30.00
2.00	2	Silicon dioxide (colloidal)	2.00
968.00	3	Cerelose powder N60[a]	1052.00

[a]Standard quantity of cerelose powder allows for LOD.

Manufacturing Directions

1. Protect from moisture. Maintain RH 40% and temperature 25°C.
2. Oven dry cerelose powder at 50°C overnight until LOD is NMT 3% (3 hours, vacuum at 60°C).
3. Pass dried cerelose powder through 595-μm aperture screen in oscillating granulator.
4. Charge the following ingredients into suitable blender: aspartame, half of the amount of dried cerelose powder (milled), and colloidal silicon dioxide.
5. Add the balance of the dried cerelose powder (for a total amount of dried powder of 968 g/kg) and blend for 15 minutes.
6. Pass blended powders through an 840-μm screen using an oscillating granulator and discharge into polyethylene-lined drums.
7. Fill weight is 1 g per sachet.

Aspartame Powder in Sachets

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
47.50	1	Aspartame	47.50
2.50	2	Silicon dioxide (colloidal)	2.50
950.00	3	Mannitol granules	950.00

Manufacturing Directions

1. Protect from humidity. Maintain RH 40% and temperature 25°C.
2. Pass mannitol granules and colloidal silicon dioxide through an 840-μm screen in oscillating granulator.
3. Charge the following ingredients into suitable blender: aspartame, half of the amount of mannitol granules, and colloidal silicon dioxide.
4. Add balance of mannitol granules and blend for 15 minutes.
5. Pass blended powders through an 840-μm screen using an oscillating granulator and discharge into polyethylene-lined drums.
6. Fill weight is 0.8 g per sachet.

Aspartame Tablets (25 mg), DC

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
27.00	1	Aspartame	27.00
76.00	2	Ludipress	76.00
12.00	3	Kollidon CL	12.00
1.00	4	Magnesium stearate	1.00
3.00	5	Lutrol F68	3.00

Manufacturing Directions

1. Mix all components and pass through a 0.8-mm sieve.
2. Press to tablets with low compression force at 120 mg.

Aspartame Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
20.00	1	Aspartame	20.00
4.00	2	Cellulose (microcrystalline) (Avicel PH101), NF	4.00
4.00	3	Sodium starch glycolate (pH 5.5–7.5), NF International	4.00
0.50	4	Silicon dioxide (colloidal)	0.50
0.50	5	Povidone (PVP K-29–32), USP	0.50
14.00	6	Anhydrous alcohol (isopropyl, refined) USP	~14.00
34.00	7	Lactose (granulated)	34.00
4.00	8	Leucine, USP	4.00
3.00	9	Sodium benzoate (powder), NF	3.00

Manufacturing Directions

1. Charge aspartame, cellulose microcrystalline, sodium starch glycolate, silicon dioxide, and povidone in a suitable mixer.
2. Blend for 20 minutes or until uniform.
3. While mixing, slowly add isopropyl alcohol to blended powders until a suitable granulating mass is obtained. Avoid overwetting.
4. Pass wet mass through a 2.38-mm screen on an oscillating granulator and spread onto paper-lined trays.
5. Oven dry at 45°C to 50°C until LOD is NMT 1.2%.
6. Pass dried granulation through an 840-μm screen on an oscillating granulator.
7. Charge dried granulation into a suitable mixer.
8. Add granulated lactose, leucine, and sodium benzoate and blend for approximately 10 minutes.
9. Discharge into polyethylene-lined drums.
10. Compress tablets in a low-humidity area not to exceed 40% RH at 23°C.
11. Compress, using 7/32-in concave punches, to the following specifications: weight of 10 tablets is 0.7 g, thickness of a tablet is 2.9 to 3.3 mm.

Aspartame Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
25	1	Aspartame	25
25	2	Dibasic calcium phosphate	25
3	3	Kollidon VA 64	3
10	4	Water	10
3	5	Kollidon CL	3
3	6	PEG-6000 (powder)	3

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with items 4 and 5.
2. Pass through a 0.8-mm sieve. Mix with item 6.
3. Press to tablets 60 mg in weight with a 5-mm biplanar shape.

Aspartame Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
25.00	1	Aspartame	27.00
76.00	2	Ludipress	76.00
12.00	3	Kollidon CL	12.00
1.00	4	Magnesium stearate	1.00
3.00	5	Lutrol F 68	3.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press to tablets with low compression force.
2. Each 8-mm biplanar tablet has an average weight of 120 mg.

Aspartame Tablets, Effervescent

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
20.00	1	Aspartame	20.00
10.40	2	Sorbitol (crystalline)	10.40
14.30	3	Tartaric acid (powder)	14.30
18.70	4	Sodium bicarbonate	18.70
1.70	5	Kollidon 25	1.70
1.10	6	PEG-6000 (powder)	1.10

Manufacturing Directions

1. Mix, pass through a 0.5-mm sieve, and press to tablets.
2. Each 6-mm biplanar tablet has an average weight of 66 mg.

Aspirin, Acetaminophen, and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
225.00	1	Aspirin (40 mesh)	225.00
250.00	2	Acetaminophen (20 mesh)	250.00
30.00	3	Caffeine (granular)	30.00
100.00	4	Cellulose (microcrystalline) (Avicel PH102)	100.00
45.00	5	Anhydrous lactose	45.00
10.00	6	Croscarmellose sodium (Ac-Di-Sol)	10.00
5.00	7	Fumed silica	5.00
10.00	8	Stearic acid	10.00

Manufacturing Directions

1. Mix items 1 to 6 in a suitable blender.
2. Pass the mixture through a mill using a 12-mesh screen with knives forward.
3. Add items 7 and 8 and blend the milled mixture for 20 minutes in a V-blender.
4. Compress to tablet weight of 675 mg.

Aspirin, Acetaminophen, Caffeine, and Salicylamide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Aspirin (40 mesh)	200.00
100.00	2	Salicylamide	100.00
100.00	3	Acetaminophen (40 mesh)	100.00
60.00	4	Caffeine (Granular)	60.00
150.00	5	Cellulose (microcrystalline) (Avicel PH101)	150.00
13.00	6	Stearic acid, USP	13.00
3.00	7	Fumed silica	3.00

Manufacturing Directions

1. Screen all ingredients through a 20-mesh sieve.
2. Blend all the ingredients in a V-blender for 20 minutes.
3. Compress 615-mg tablets using 5/8-in tooling.

Aspirin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
325.00	1	Aspirin	325.00
25.52	2	Starch 1500®	25.52
21.33	3	Microcrystalline cellulose (50 μm)	21.33
6.33	4	Powdered cellulose	6.33

Manufacturing Directions

1. Blend in a twin-shell blender.
2. Compress 378.00-mg tablets.

Aspirin-Coated Crystals

Formulation

Aqueous-based polymeric coating solution: Hydroxypropylmethylcellulose (HPMC E5), 6.0%; propylene glycol, 1.0%; FD&C red No. 3, 0.01%; and distilled water, QS to 100.

Manufacturing Directions

1. A standard coating pan and an air suspension 6-in column are used to coat aspirin crystals of 100 to 200 mesh using top-spray, bottom-spray, and tangential-spray fluid-bed coating processes.
2. Aspirin crystal load is placed in the product container.
3. The crystals are fluidized in an expansion chamber.
4. The spray nozzle is located low in the expansion chamber so that liquid is applied when the crystals are moving at a higher velocity.
5. This serves to minimize surface wetting and to inhibit agglomeration.
6. A filter is used to separate entrained crystals from the exiting process air stream.
7. The pump is calibrated with coating solution prior to start-up of the coating process.
8. The turbine is activated and the process air is heated to 55°C.
9. The spray and shake cycle is started and run continually until the coating solution is completely depleted.
10. The coated aspirin crystal bed is dried for 10 minutes and the product is cooled to 35°C.
11. The product is removed, weighed, and passed through a 20-mesh screen to remove any agglomerates.
12. Tablets are prepared containing five components: 50% by weight aspirin crystals (100–200 mesh) coated previously with 3% to 6% polyvinylpyrrolidone (PVP); 25% calcium carbonate buffer, 5% to 15% hydroxypropylmethylcellulose (K100LV) as the gel forming hydrophilic matrix material; 14.5% to 19.5% microcrystalline cellulose (Avicel PH101) as the excipient/binder; and 0.5% stearic acid as the hydrophobic lubricant.
13. The components of the tablet formulation are weighed and mixed.
14. 650-mg samples are compressed using 1/2-in punches.

Attapulgite Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
475.00	1	Attapulgite (regular)	475.00
275.00	2	Attapulgite (colloidal)	275.00
12.00	3	PVP K 30	12.00
7.00	4	Ac-Di-Sol	7.00
15.00	5	Kollidon CL	15.00
30.00	6	Sucrose	30.00
50.00	7	Klucel® EF	50.00
40.00	8	Sucrose	40.00
35.00	9	Ac-Di-Sol	35.00
25.00	10	Kollidon CL	25.00
14.00	11	Talc (fine powder)	14.00
5.00	12	Pectin	5.00
7.00	13	Glyceryl behenate	7.00
5.00	14	Aerosil 200	5.00
5.00	15	Magnesium stearate	5.00
–	16	Purified water	32.00
–	17	Ethanol (95%)	23.00

Manufacturing Directions

Use face mask, hand gloves, and clean uniform. Avoid dust and inhalation of powder.

1. Dissolve sucrose (item 6) in purified water by using an appropriate stirrer at slow speed in a stainless steel container.
2. Dissolve Klucel EF in the ethanol by using an appropriate stirrer at slow speed in stainless steel container.
3. Mix the two steps in a stainless steel drum by using an appropriate stirrer at slow speed.
4. Take item 8 (sucrose) and pass through a Fitz mill using sieve No. 24250 (impact forward, high speed). Collect in a stainless steel drum.
5. Add items 1 to 5 and sift the material through a 500-μm sieve using a Russell sifter.
6. Mix for 3 minutes.
7. Add the binding solution prepared earlier at a speed of 6 to 8 kg/min to the dry powder in an appropriate mixer at slow speed. After addition, scrape sides and blades, then mix and chop further for 1 minute at slow speed. Check for satisfactory wet mass. Add additional purified water, if required, to obtain satisfactory wet mass.

8. Spread the granules onto stainless steel trays to a thickness of one-fourth of the tray thickness and load the trays on the trolley.
9. Load the trolleys into the oven and dry the granules at 55°C for 16 hours.
10. After 4 hours of drying, stir the granules on the trays and change the position of the trays for uniform drying.
11. Check the LOD of dried granules (limit: 2.5–3.5%).
12. The LOD should be strictly maintained; otherwise, tablet hardness and friability are affected. If required, dry further to obtain the desired LOD.
13. Grind the dried granules first using a 2.5-mm sieve and then a 1.25-mm sieve.
14. Load the ground material into a double-cone blender.
15. Sift items 9, 10, 12, and 14 through a 500-μm sieve and add mixture to the double-cone blender.
16. Mix for 5 minutes.
17. Sift items 11, 13, and 15 through a 250-μm sieve and collect in a polyethylene bag.
18. Add approximately 2 to 3 kg bulk granules from earlier step, mix, and add to the double-cone blender.
19. Mix for 1 minute.
20. Compress the granules using an 18-mm × 8-mm oblong, capsule-shaped, parallel, concave plain punch for a 1-g tablet weight of hardness 12 to 18 kp.
21. Coat the tablets using one of the HPMC coating solutions (see appendix).

Azulene Solution (1%)

Manufacturing Directions

1. Mix 1 g azulene, 3 g Cremophor RH 40 and heat to approximately 60°C.
2. Add slowly the water (60°C) to 100 mL and cool to room temperature.

Baby Cream, Benzalkonium Chloride, and Zinc Oxide

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.002 mL	1	Benzalkonium chloride solution	2.30 mL
85.00 mg	2	Zinc oxide (powder)	85.00
100.00 mg	3	Polawax (emulsifying, nonionic wax)	100.00
16.00 mg	4	Alcohol cetostearyl	16.00
4.00 mg	5	Lanolin (acetylated/anhydrous, regular)	4.00
80.00 mg	6	Glycerin (96%)	80.00
10.00 mg	7	Oil (neutral, vegetable triglycerides mixture; Miglyol®)	10.00
0.50 mg	8	Propyl paraben (Aseptoform™ P)	0.50
1.00 mg	9	Methyl paraben (Aseptoform™ M)	1.00
0.80 mL	10	Purified water	QS to 800.00 mL
0.24 mg	11	Perfume (Diabolo 110.388/B)	0.24

Manufacturing Directions

Avoid mixing air into emulsion. Emulsify under vacuum to minimize air entrapment. Use jacketed tank with vacuum with high-speed agitator (adjustable, slow-speed, anchor type with Teflon sweep blades.

1. If necessary, mill zinc oxide in a Fitz mill or similar device (impact forward, maximum speed), fitted with a 250-μm screen.
2. Repeat 3 times.
3. Heat 800 mL of water to 75°C in a steam-jacketed mixing tank and dissolve methyl paraben.
4. Maintain temperature at 75°C.
5. Disperse milled zinc oxide in solution of previous step.
6. Maintain temperature at 75°C.
7. Dissolve benzalkonium chloride and glycerin in solution and maintain temperature at 75°C.
8. In a separate steam-jacketed tank, add Polawax, cetostearyl alcohol, acetylated lanolin, oil, and propyl paraben. Carefully melt at 70°C.
9. Adjust the turbomixer of the steam-jacketed tank containing the aqueous phase to maximum speed, keeping the temperature at 75°C.
10. Slowly add the oil phase to the aqueous phase.
11. Generate as much vacuum as possible and maintain it for the rest of the process.
12. Circulate cold water to allow for a slow temperature decrease (down to 60°C).
13. Stop the turbomixer and set the anchor-type agitator at minimum speed until 40°C to 45°C is reached.
14. The temperature decrease must be very slow.
15. Break the vacuum and add perfume to cream with anchor-type agitator set at slow speed.
16. Continue to mix until the perfume is completely dispersed.

Baby Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Alcohol (ethanol; natural cosmetic grade)	50.00
50.00	2	Propylene glycol	50.00
0.80	3	Ethoxylated nonyl phenol	0.80
0.005	4	FD&C red dye No. 40	5.70 mg
0.41	5	FD&C blue dye No. 1	0.41
0.70	6	FD&C yellow dye No. 5	0.70
0.40	7	Perfume essence (Nelandia)	0.40
QS	8	Hydrochloric acid (reagent-grade bottles)	~0.01
QS	9	Purified water	QS to 1 L

Manufacturing Directions

Use 316 or more resistant-grade stainless steel tank.

1. Charge approximately 800 mL of purified water in main mixing tank.
2. Add alcohol and propylene glycol and mix for 5 minutes.
3. Separately dissolve each dye in sufficient water to obtain 0.5% dye solutions.
4. Add color solutions to main tank and mix.
5. Rinse containers with small portions of purified water and add rinsings.
6. Dissolve perfume essence in ethoxylated nonyl phenol.
7. Add solution from previous step to main tank and mix for 5 minutes.
8. Determine pH of solution and adjust if necessary with 5% hydrochloric acid solution.
9. Mix well. pH should be 5.7 to 5.9.
10. QS to 1 L with purified water.

Baby Shampoo

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
250.00	1	Sodium alkyl ether sulfate/sulfonate	250.00
30.00	2	Monateric CAB surfactant	30.00
30.00	3	Cocamide DEA surfactant (Synotol CN 90)	30.00
1.00	4	Methyl paraben	1.00
0.52	5	Anhydrous citric acid	0.52
0.003	6	FD&C yellow dye No. 6	3.50 mg
0.01	7	FD&C yellow dye No. 5	15.00 mg
4.00	8	Ethoxylated nonyl phenol	4.00
3.00	9	Perfume I	3.00
1.00	10	Perfume II	1.00
8.50	11	Sodium chloride	8.50
QS	12	Purified water	QS to 1 kg

Manufacturing Directions

Use 315 or more resistant-grade stainless steel tank.

1. Add approximately 270 g of purified water to the main mixing tank.
2. With slow agitation, add cocamide DEA surfactant.
3. Add and dissolve methyl paraben and mix for approximately 10 minutes.
4. Add the following ingredients to tank: sodium alkyl sulfate/sodium alkyl ether sulfate/sulfonite, monateric CAB surfactant, and approximately 280 g of purified water.
5. Mix for 15 minutes until complete solution is obtained.
6. With constant stirring, slowly add citric acid (10% solution) until a pH of 6.9 to 7.1 is maintained constantly for 5 minutes after the last addition of the citric acid solution.
7. Separately dissolve FD&C yellow dyes No. 6 and 5 (if used) in sufficient purified water.
8. Add dye solution from step above to main tank and mix.
9. Rinse containers with a small portion of purified water and add rinsings.
10. Separately mix ethoxylated nonyl phenol with perfumes (perfume available from Firmenich; Plainsboro, NJ) and add to main mixing tank.

11. Rinse container with purified water and add rinsing.
12. Mix until completely dissolved.
13. Slowly add in small portions sodium chloride to adjust the viscosity to between 1500 and 3500 cps.
14. Mix for 15 minutes.
15. If necessary, QS to 1 kg with purified water.

Barium Sulfate Oral Suspension (23%)

Formulation

Barium sulfate, 100.0 g; Kollidon 90 F [1], 5.0 g; carboxymethyl cellulose sodium, 0.4 g; sodium bisulfite, <0.5 g; preservatives, QS; water, 320.0 g.

Manufacturing Directions

1. Dissolve the preservatives and the carboxymethyl cellulose sodium in the hot water.
2. Add Kollidon 90 F and sodium bisulfite.
3. In the obtained clear solution, suspend barium sulfate.

Basic Cream for Various Active Ingredients

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
70.00	1	Cetylstearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
120.00	4	Liquid paraffin	120.00
2.00	5	Paraben(s)	2.00
680.00	6	Water	680.00
80.00	7	Propylene glycol	80.00
1.00–20.00	8	Active ingredient	1.00–20.00

Manufacturing Directions

1. Separately heat a mixture of items 1 to 5 and the water to approximately 80°C.
2. Add the water to the obtained solution with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved, mix with aqueous solution, and continue to stir during cooling to room temperature.
4. This white basic cream can be readily used for active ingredients soluble in 1,2-propylene glycol.

Benzalkonium Chloride Contraceptive Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PEG-6, PEG-32, and glycol stearate (Tefose® 63)	50.00
30.00	2	Apricot kernel oil PEG-6 esters (Labrafil® M 1944 CS)	30.00
816.00	3	Deionized water	816.00
80.00	4	Hydroxyethylcellulose	80.00
24.00	5	Benzalkonium chloride (50 wt% in water)	24.00

Manufacturing Directions

1. Mix items 3 and 4 at room temperature.
2. Heat to 75°C and add items 1 and 2 while stirring.
3. Cool with gentle stirring to 30°C, then add item 5 and stir.

Benzoyl Peroxide and Alpha-Bisabolol Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
2.00	1	Alpha-Bisabolol, natural (BASF)	2.00
60.00	2	Propylene glycol	60.00
100.00	3	Triethanolamine	100.00
30.00	4	Cremophor RH 40	30.00
30.00	5	Kollidon 30	30.00
408.00	6	Water	408.00
10/00	7	Carbopol® 940	10.00
400.00	8	Water	400.00
50.00	9	Benzoyl peroxide	50.00

Manufacturing Directions

1. Prepare suspension of items 7 and 8. Let swell for 1 hour.
2. Add this suspension to the well-stirred solution of items 1 to 5.
3. Add item 9 to produce a colorless, transparent gel.

Benzoyl Peroxide Antiacne Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
460.50	1	Deionized water	460.50
5.00	2	Carbomer 940	5.00
10.00	3	Hydroxypropylmethylcellulose (HPMC, medium viscosity)	10.00
137.50	4	Deionized water	137.50
70.00	5	Purified bentonite (Polargel®, NF)	70.00
2.00	6	Methyl paraben	2.00
1.00	7	Propyl paraben	1.00
20.00	8	Glyceryl stearate	20.00
60.00	9	Propylene glycol	60.00
20.00	10	PEG-600	20.00
20.00	11	Myristyl propionate	20.00
50.00	12	Dimethicone	50.00
70.00	13	Purified bentonite (Polargel, NF)	70.00
10.00	14	Titanium dioxide	10.00
100.00	15	Benzoyl peroxide (70%)	100.00

Manufacturing Directions

1. Sift Carbomer 940 into vortex in water. When completely dispersed, sift in the HPMC.
2. Add parabens with stirring and heat to at least 80°C until dissolved.
3. Add glyceryl stearate.
4. Blend in propylene glycol and items 10 to 13 in order and mix well.
5. After addition of the Polargel, allow 15 minutes of mixing to complete hydration.
6. Blend propylene glycol portion into the first part.
7. Add benzoyl peroxide and titanium dioxide to the mixture and mill.

Benzoyl Peroxide Antiacne Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
2.50	1	Acrylates/C10-30 alkyl acrylate cross-polymer (Permulen TR1)	2.50
4.00	2	Carbopol 980	4.00
QS	3	Deionized water	QS to 1 kg
40.00	4	Isopropyl myristate	40.00
10.00	5	Cetyl alcohol	10.00
20.00	6	Glyceryl stearate	20.00
50.00	7	Sodium hydroxide (0.5 M)	50.00
15.00	8	Deionized water	15.00
50.00	9	Benzoyl peroxide	50.00
50.00	10	PEG-600	50.00
QS	11	Perfume, preservative	QS

Manufacturing Directions

1. Hydrate carbopol and permulen in warm water at 60°C.
2. When fully hydrated, heat to 70°C.
3. Heat oil phase to 70°C.
4. Add water phase to oil phase while stirring.
5. Add sodium hydroxide and continue stirring.
6. Combine benzoyl peroxide, PEG-600, and deionized water and add to the emulsion.
7. Homogenize at 35°C with caution, using suitable equipment.

Benzoyl Peroxide Antiacne Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Purified bentonite (Polargel, NF)	40.00
10.00	2	Hydroxypropylmethylcellulose (HPMC)	10.00
522.20	3	Water	522.20
190.00	4	Water	190.00
2.00	5	Methyl paraben	2.00
2.00	6	Propyl paraben	2.00
20.00	7	Glyceryl stearate	20.00
60.00	8	Propylene glycol	60.00
20.00	9	Myristyl propionate	20.00
5.00	10	Dimethicone	5.00
QS	11	Iron oxides	QS
10.00	12	Titanium dioxide	10.00
100.00	13	Benzoyl peroxide (77%)	100.00

Manufacturing Directions

1. Sift the Polargel into water with rapid mixing.
2. Allow to hydrate for 15 minutes.
3. Pass HPMC through a coarse sieve, add to the Polargel solution, and mix until all lumps are removed.
4. Add parabens to the water with stirring and heat to 90°C to dissolve the parabens.
5. Add items 4 to 10 and mix well, then add these to the HPMC mixture.
6. Mix well again.
7. Finally, add items 11 to 13 and mix.

Benzoyl Peroxide Antiacne Microemulsion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
470.00	1	Ethoxydiglycol (Transcutol®)	470.00
250.00	2	PEG-8 caprylic/Capric glycerides (Labrasol®)	250.00
150.00	3	Dipelargonate propylene glycol (DPPG)	150.00
80.00	4	Benzoyl peroxide	80.00
50.00	5	Propylene glycol laurate (Lauroglycol®)	50.00

Manufacturing Directions

1. Mix items 1 to 3.
2. Dissolve item 4 in this mixture with mixing for 1.5 to 2.0 hours.
3. Add item 5 to mixture and mix until uniform emulsion is obtained.

Benzyl Benzoate Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Benzyl benzoate	100.00
220.00	2	Cremophor RH 40	220.00
410.00	3	Ethanol (96%)	410.00
270.00	4	Water	270.00

Manufacturing Directions

1. Heat the mixture of benzyl benzoate and Cremophor RH 40 to approximately 60°C.
2. Stir strongly and slowly add the water.
3. Finally, add the ethanol to produce a clear, colorless liquid.

Berberine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
5.00	1	Berberine sulfate	5.70
54.10	2	Lactose monohydrate	54.10
54.10	3	Ludipress	54.10
1.20	4	Magnesium stearate	1.20

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compression force.
2. Each 6-mm biplanar tablet has an average weight of 115 mg.

Beta-Carotene + Vitamin C + Vitamin E Chewable Tablets (10 mg+500 mg+250 mg)

Formulation

Beta-carotene dry powder 10%, 100 g; ascorbic acid, crystalline (BASF), 250 g; sodium ascorbate, crystalline, 280 g; vitamin E acetate dry powder SD, 50, 500 g; (BASF) sorbitol, crystalline [10], 600 g; Ludipress, 500 g; fructose, 350 g; polyethylene glycol 6000, powder, 50 g.

Manufacturing Directions

Mix all components, pass through a sieve, and press with high compression force at 2600 mg.

Beta-Carotene + Vitamin C + Vitamin E Effervescent Tablets (12 mg+150 mg+25 mg)

Formulation

Lucarotene dry powder 10% CWD G/Y (BASF), 120 g; ascorbic acid, crystalline (BASF), 150 g; dry vitamin E acetate 50% DC (BASF), 50 g; Ludipress LCE [1], 705 g; Kollidon VA64 [1], 50 g; citric acid, anhydrous, 450 g; sodium bicarbonate, 320 g; polyethylene glycol 6000, powder [10], 75 g; orange flavor (Dragoco), 50 g; aspartame (Searle), 30 g.

Manufacturing Directions

1. Mix all components. Pass through a sieve.
2. Press with high compression force at a maximum of 30% of relative atmospheric humidity at 2.045 mg.

Beta-Carotene + Vitamin C + Vitamin E Tablets (7 mg+60 mg+25 mg)

Formulation

Betavit® dry powder 10% (BASF), 75 g; ascorbic acid, powder (BASF), 60 g; vitamin E acetate dry powder 50%, 50 g; sorbitol, crystalline [10], 240 g; Kollidon CL, 30 g; magnesium stearate, 5 g.

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with low compression force at 497 mg.

Beta-Carotene + Vitamin C + Vitamin E Tablets (12 mg+250 mg+125 mg)

Formulation

Beta-carotene dry powder 10%, 125 g; ascorbic acid, crystalline (BASF), 125 g; sodium ascorbate, crystalline (BASF), 141 g; vitamin E acetate dry powder SD 50, 250 g; (BASF) Ludipress or sorbitol, crystalline [10], 119 g; polyethylene glycol 6000, powder [10], 5 g; orange flavor (FDO), 15 g; sodium cyclamate, 10 g.

Manufacturing Directions

Mix all components, pass through a sieve, and press with medium compression force at 790 mg.

Beta-Carotene Effervescent Tablets (7 mg)

Formulation

Lucarotin® dry powder 10% CWD (BASF), 70 g; Ludipress, 113 g; citric acid, anhydrous, 200 g; sodium bicarbonate, 120 g; sodium carbonate, 12 g; sodium cyclamate, 20 g; aspartame, 15 g; orange flavor, 20 g; polyethylene glycol 6000, powder, 30 g.

Manufacturing Directions

Pass all components through o 0.8-mm sieve, mix, and press with medium or high compression force at maximum 30% of relative atmospheric humidity.

Beta-Carotene Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
7.00 mg	1	Beta-carotene; use Lucarotin CWD (dry powder, 10%) (BASF)	70.00
113.00 mg	2	Ludipress	113.00
200.00 mg	3	Anhydrous citric acid	200.00
120.00 mg	4	Sodium bicarbonate	120.00
12.00 mg	5	Sodium carbonate	12.00
20.00 mg	6	Sodium cyclamate	20.00
15.00 mg	7	Aspartame	15.00
20.00 mg	8	Orange flavor	20.00
30.00 mg	9	PEG-6000 (powder)	30.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve. Mix.
2. Press with medium or high compression force at maximum RH 30%.
3. Use 12-mm biplanar punches for 602-mg tablets.

Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
15.00	1	Beta-carotene (dry powder, 10% with excess)	160.00
240.00	2	Ludipress	240.00
175.00	3	Dicalcium phosphate, granulated with 5% Kollidon 30	175.00
6.00	4	Kollidon CL	6.00
2.00	5	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium compression force.
2. Compress 400 mg in 12-mm biplanar punches.

Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Beta-carotene (dry powder, 10%)	150.00
175.00	2	Dicalcium phosphate, granulated with 5% Kollidon 30	175.00
100.00	3	Avicel PH101	100.00
5.00	4	Kollidon CL	5.00
2.50	5	Aerosil 200	2.50
20.00	6	Talc	20.00
2.50	7	Calcium arachinate	2.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with a medium compression force.
2. Compress 502 mg in 12-mm biplanar punches.

Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
20.00	1	Beta-carotene (dry powder, 10%)	220.00
250.00	2	Avicel PH101	250.00
20.00	3	Kollidon CL	20.00
2.00	4	Aerosil 200	2.00

Manufacturing Directions

1. Mix all components and press with a low compression force.
2. Compress 518 mg in 12-mm biplanar punches.

Beta-Carotene, Vitamin C, and Vitamin E Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Beta-carotene (dry powder, 10%)	100.00
250.00	2	Ascorbic acid (crystalline) (BASF)	250.00
280.00	3	Sodium ascorbate (crystalline)	280.00
500.00	4	Vitamin E acetate (dry powder, SD 50)	500.00
600.00	5	Sorbitol (crystalline)	600.00
500.00	6	Ludipress	500.00
350.00	7	Fructose	350.00
50.00	8	PEG-6000 (powder)	50.00

Manufacturing Directions

1. Mix all components, pass through a sieve, and press with high compression force.
2. Each 20-mm biplanar tablet has an average weight of 2.6 g.

Beta-Carotene, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
12.00	1	Beta-carotene (dry powder, 10% with excess)	125.00
125.00	2	Ascorbic acid (crystalline) (BASF)	125.00
141.00	3	Sodium ascorbate (crystalline) (BASF)	141.00
250.00	4	Vitamin E acetate (dry powder, SD 50)	250.00
119.00	5	Ludipress or sorbitol (crystalline)	119.00
5.00	6	PEG-6000 (powder)	5.00
15.00	7	Orange flavor (FDO)	15.00
10.00	8	Sodium cyclamate	10.00

Manufacturing Directions

1. Mix all components. Pass through a sieve.
2. Press with medium compression force.
3. Compress 790 mg into 12-mm biplanar tablets.

Beta-Carotene, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
6.00	1	Beta-carotene; use Betavit (dry powder, 10% with excess) (BASF)	65.00
100.00	2	Ascorbic acid (powder) (BASF)	100.00
60.00	3	Vitamin E acetate (dry powder, 50%)	60.00
369.00	4	Ludipress	369.00
6.00	5	Magnesium stearate	6.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve. Mix.
2. Press with medium or high compression force.
3. Compress 599 mg into 12-mm biplanar tablets.

Beta-Carotene, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
6.00	1	Beta-carotene; use Betavit (dry powder, 10% with excess) (BASF)	65.00
100.00	2	Ascorbic acid (powder) (BASF)	100.00
60.00	3	Vitamin E acetate (dry powder, 50%)	60.00
233.00	4	Sorbitol (crystalline) (Merck)	233.00
30.00	5	Kollidon VA 64	30.00
8.00	6	Kollidon CL	8.00
4.00	7	Magnesium stearate	4.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve. Mix.
2. Press with medium or high compression force.
3. Compress 502 mg into12-mm biplanar tablets.

Beta-Carotene, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
7.00	1	Beta-carotene; use Betavit (dry powder, 10% with excess) (BASF)	75.00
60.00	2	Ascorbic acid (powder) (BASF)	60.00
50.00	3	Vitamin E acetate (dry powder, 50%)	50.00
240.00	4	Sorbitol (crystalline)	240.00
30.00	5	Kollidon CL	30.00
5.00	6	Magnesium stearate	5.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve. Mix.
2. Press with low compression force.
3. A colorant pigment should be added to obtain a homogeneous appearance of tablets.
4. Use 12-mm biplanar punches for 497-mg tablets.

Betamethasone and Neomycin Gel Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
1.30	1	Betamethasone valerate	0.13
6.50	2	Neomycin sulfate	0.65
150.00	3	Lutrol E 400	15.00
100.00	4	Miglyol® 812	10.00
200.00	5	Lutrol F 127	20.00
QS	6	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve betamethasone valerate in a mixture of Lutrol E 400 and Miglyol 812.
2. Dissolve Lutrol F 127 and neomycin sulfate in water at 5°C to 10°C.
3. Mix both solutions.
4. Maintain cool temperature until the air bubbles disappear. A milky white, soft gel cream is obtained.

Betamethasone Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
70.00	1	Cetylstearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
12.00	4	Liquid paraffin	12.00
2.00	5	Paraben(s)	2.00
697.00	6	Water	697.00
80.00	7	Propylene glycol	80.00
1.00	8	Betamethasone	1.00

Manufacturing Directions

1. Heat the mixture of items 1 to 5 and item 6 separately to approximately 80°C.
2. Add together with rigorous stirring.
3. Heat items 7 and 8 until the active ingredient is dissolved.
4. Mix with above mixture and continue to stir to cool to room temperature to produce white cream.

Betamethasone Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
1.00	1	Betamethasone valerate	1.00
100.00	2	Ethanol (96%)	100.00
200.00	3	Propylene glycol	200.00
220.00	4	Lutrol F 127	220.00
QS	5	Water QS	470.00

Manufacturing Directions

1. Prepare a solution of items 1 to 3 at room temperature and a solution of items 4 and 5 at approximately 6°C (or >70°C).
2. Mix both solutions.
3. Maintain the temperature until the air bubbles disappear.
4. A certain amount of propylene glycol could be substituted by water. The obtained gel is clear and colorless.

Betamethasone Valerate Cream

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.10	1	Betamethasone valerate (34% excess)	1.34
2.00	2	Poloxyl 20 cetostearyl ether (Cetomacrogol 1000)	20.00
8.00	3	Cetostearyl alcohol	80.00
0.10	4	Methyl paraben	1.00
0.034	5	Propyl paraben	0.34
0.10	6	Chlorocresol	1.00
6.00	7	Mineral oil (liquid paraffin)	60.00
0.29	8	Monobasic sodium phosphate	2.90
17.80	9	Petrolatum (soft white paraffin)	178.00
66.00	10	Purified water	660.00

Manufacturing Directions

1. Heat item 10 to 90°C in mixer.
2. Dissolve items 4 and 5 (parabens) to a clear solution by stirring.
3. Dissolve 3 g of item 2 in the parabens solution while stirring.
4. Dissolve items 6 and 8 in the parabens solution while stirring.

5. Set the mixer at a temperature of 65°C to 70°C and speed at 8 rpm. Use manual mode.
6. Load 17 g of items 2, 3, and 9 and 45 g of item 7 in a fat-melting vessel.
7. Heat to 70°C to 75°C while stirring. Maintain temperature at 65°C to 75°C.
8. Mix item 1 in 10 g of item 7 in a stainless steel container.
9. Homogenize for 10 minutes to make a smooth slurry.
10. Check the temperature of the aqueous phase in the mixer (should be 65–70°C).
11. Check the temperature of the fatty phase in the fat-melting vessel (should be 65–70°C).
12. Set the mixer speed 8 rpm and vacuum at 0.4 to 0.6 bar.
13. Transfer the fatty phase to the aqueous phase in mixer vessel through filter under vacuum, while mixing.
14. Start the homogenizer at high speed. Homogenize for 10 minutes.
15. Check and record the pH of cream (limit 4.5–5.2 at 30°C).
16. Cool the temperature to 50°C while mixing. Release the vacuum.
17. Take out 400 g of the cream into the stainless steel vessel and set aside.
18. Add slurry from earlier step to the remaining cream base in mixer.
19. Rinse the container of slurry using 5 g of item 7 and transfer the rinsing to the mixer.
20. Homogenize for 10 minutes at high speed (mixer speed 8 rpm).
21. Load 400 g cream from step above to the mixer.
22. Set the mixer in manual mode at 8 rpm and a vacuum of 0.4 to 0.6 bar.
23. Homogenize at high speed with recirculation, temperature 25°C. Homogenize for 10 minutes with recirculation, stop the homogenizer, and continue mixing to produce a white, homogeneous cream of pH 4.5 to 5.2 at 30°C.

Betamethasone Valerate Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
0.10	1	Betamethasone, use betamethasone valerate	1.30
84.87	2	Petrolatum (soft white paraffin)	848.70
15.00	3	Mineral oil (liquid paraffin)	150.00

Manufacturing Directions

1. Melt item 2 in a fat-melting vessel at 75°C while mixing (do not overheat item 2). Maintain temperature of the molten mass in the melting vessel at 60°C to 65°C.
2. Start the steam on the mixer vessel and set the temperature at 60°C.
3. Transfer 160 g of the molten mass at 60°C to the mixer vessel.
4. Retain the rest of the quantity in the fat-melting vessel.
5. Start mixing in the mixer vessel at medium speed with a vacuum between 0.4 and 0.6 bar until obtaining actual temperature of 40°C to 45°C. Maintain the temperature of mixer vessel at 40°C to 45°C.
6. Add item 1 in 80 g of item 3 and homogenize for 3 minutes using a homogenizer.
7. Keep the slurry aside.
8. Rinse the homogenizer and container with 70 g of item 3.
9. Transfer item 1 slurry from step above and the rinsing from previous step to the mixer vessel.
10. Start mixing under a vacuum of 0.4 to 0.6 bar for 15 minutes.
11. The temperature should be maintained at 40°C to 45°C.
12. Slowly transfer the rest of the quantity of molten mass (temperature 60°C) into mixer vessel. Continue mixing for 5 minutes after each addition.
13. At the end of addition, mix an additional 10 minutes under a vacuum of 0.4 to 0.6 bar.
14. Homogenize for 5 minutes at high speed under a vacuum of 0.4 to 0.6 bar.
15. Cool the ointment to 30°C to 35°C with stirring under a vacuum of 0.4 to 0.6 bar.

Bisacodyl Delayed-Release Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
05.00	1	Bisacodyl	5.00
20.00	2	Cellulose (microcrystalline) (Avicel PH102)	20.00
45.27	3	Lactose (spray dried)[a]	45.27
04.00	4	Maize starch (dried)[b]	4.00
00.73	5	Magnesium stearate	0.73

[a]Particle size distribution: minimum: 98%, 250 μm, 30% to 60%, 100 μm; maximum: 15%, 45 μm.
[b]LOD NMT 4.5%, when dried at 120°C for 4 hours.

Manufacturing Directions

Handle bisacodyl carefully; it can cause itching if it comes into contact with skin. Overmixing of lubricants reduces the hardness. Check the temperature and RH of the room before beginning processing. Limit RH to 50% to 60% and temperature to 27°C to 30°C.

1. Mix items 1 and 2 in a stainless steel drum for 2 to 3 minutes.
2. Pass the mixed powder through a 500-μm sieve, using sifter.
3. Collect in stainless steel drum.
4. Pass item 3 through a 500-μm sieve, using sifter.
5. Collect in stainless steel drum.
6. Load the sieved material into the drum mixer and mix for 5 minutes.
7. Mix items 4 and 5 in a polyethylene bag for 1 minute.
8. Pass the mix through a 250-μm sieve.
9. Collect in a polyethylene bag.
10. Add 3 to 5 g powder to it and mix for 1 minute.
11. Add this mixture and mix for 1 minute in a drum blender.
12. Check the moisture content (limit: 1.0–1.5%).
13. Compress the granules using a rotary tableting machine; 6-mm biconvex tablets have an average weight of 750 mg and hardness of 4 to 5 kp.
14. Apply enteric coating.

Bisacodyl Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
5.00	1	Bisacodyl (micronized) (2% excess)[a]	5.10
447.50	2	Hard fat (Witepsol E 76)	447.50
447.50	3	Hard fat (Witepsol W 45)	447.50

[a]100% particles should be less than 70 μm; fill weight is 1800 mg per suppository.

Manufacturing Directions

The molten suppository mass must be kept stirred throughout the storage period and during manufacturing and filling to avoid sedimentation of the active drug. The active ingredient causes skin irritation, which vanishes after some time without aftereffects. Avoid dust formation during processing. In particular, protect eyes and mucous membranes.

1. Load items 2 and 3 into the fat-melting vessel and heat to 50°C±3°C.
2. Transfer the molten mass to a mixer through a 0.8-mm sieve.
3. Set the temperature at 40°C±2°C.
4. Load item 1 to the mixer containing molten mass. Carefully mix the powder with the molten mass.
5. Set the mixer at a temperature of 40°C±2°C and speed of 10 rpm (manual mode) and mix for 20 minutes.
6. Set the mixer at a temperature of 40°C±2°C, speed of 10 rpm (manual mode), and vacuum of 0.6 bar.
7. Homogenize at low speed while mixing for 10 minutes. Homogenize at high speed while mixing for 3 minutes.
8. Continue mixing of the mass under vacuum in mixer.
9. Heat the storage vessel and set the temperature at 40°C±2°C.
10. Transfer the molten mass from the mixer to the storage vessel.
11. Hold the mass at 40°C±2°C. Continuously mixing at low speed.
12. Fill weight is 900 mg per suppository. Use a fill weight of 1.8 g for 10-mg suppositories.

Bismuth Carbonate Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
266.66	1	Light kaolin	266.66
8.30	2	Pectin	8.30
6.70	3	Bismuth carbonate	6.70
9.40	4	Cellulose (microcrystalline; Avicel™ RC-591)	9.40
1.40	5	Methyl paraben	1.40
0.20	6	Saccharin sodium	0.20
0.40	7	Aspartame	0.40
40.00 mL	8	Sorbitol	40.00 mL
5.00 mL	9	Ethanol	5.00 mL
QS	10	Deionized water	QS to 1 L

Manufacturing Directions

1. Dissolve item 2 in hot water.
2. Disperse item 1 in 75 mL of item 10 at room temperature.
3. With constant agitation, add item 3 and continue stirring.
4. Mix and cool to room temperature.
5. Disperse item 4 in item 10 and add it to the batch.
6. Dissolve item 2 in item 1 dispersion and add to the batch.
7. Dissolve items 6 and 7 in water and add to the batch.
8. Add flavor, color, and water to volume.
9. Pass through homogenizer or colloid mill if necessary.

Bismuth Subsalicylate and Calcium Carbonate Tablet

Formulation

Bismuth subsalicylate, 262.5 mg; microcrystalline cellulose NF, 213.3 mg; calcium carbonate, 67.5 mg; mannitol, 67.5 mg; sodium starch glycolate, 40.5 mg; polyvinyl pyrrolidone, 13.5 mg; magnesium stearate, 5.4 mg; polysorbate 80, 3.4 mg; silica, 0.7 mg; dye, 0.7 mg; total, 675.0 mg.

Manufacturing Directions

1. The ingredients are added to a mixer or granulator in the following order: part of microcrystalline cellulose, calcium carbonate, part of sodium starch glycolate, Polysorbate 80, dye, and bismuth subsalicylate.
2. After the addition of the bismuth subsalicylate and mixing at high shear, the mixture is dried at 86°C to less than 2% moisture.
3. Additional powders (microcrystalline cellulose, sodium starch glycolate, mannitol, and polyvinyl pyrrolidone) are added and granules are formed by spraying water (approximately 10% by weight of the composition) onto the mixture under high shear.
4. After additional drying to less than 3% moisture, silica (glidant) and magnesium stearate (lubricant) are added and mixed for approximately 1 minute.
5. Caplets are then formed on a rotary tablet press.

Bismuth Subsalicylate Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
15.00	1	Magnesium aluminum silicate (Magnabrite K)	15.00
1.50	2	Methyl cellulose	1.50
910.00	3	Deionized water	910.00
0.50	4	Saccharin sodium	0.50
30.00	5	Bismuth subsalicylate	30.00
4.00	6	Salicylic acid	4.00
10.00	7	Sodium salicylate	10.00
29.00	8	Ethanol	29.00
QS	9	Preservatives	QS
QS	10	Colorings	QS

Manufacturing Directions

1. Dry blend items 1 and 2 and slowly add them to item 3, agitating until smooth.
2. Add items 4 to 7 to this dispersion, gradually mixing well each time.
3. Finally, add items 8 to 10 to smooth mix.

Bismuth Subsalicylate Swallow Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
262.50	1	Bismuth subsalicylate	262.50
213.30	2	Microcrystalline cellulose	213.30
67.50	3	Calcium carbonate	67.50
67.50	4	Mannitol	67.50
40.50	5	Sodium starch glycolate	40.50
13.50	6	Polyvinylpyrrolidone (PVP)	13.50
5.40	7	Magnesium stearate	5.40
3.40	8	Polysorbate 80	3.40
0.70	9	Silica	0.70
0.70	10	Dye	0.70

Manufacturing Directions

1. Mix the above ingredients in a mixer in the following order: part of microcrystalline cellulose, calcium carbonate, part of sodium starch glycolate, Polysorbate 80, dye, and bismuth subsalicylate.
2. After the addition of bismuth subsalicylate and mixing at high shear, the mixture is dried at 86°C to less than 2% moisture.
3. Additional powders (microcrystalline cellulose, sodium starch glycolate, mannitol, and PVP) are added and granules are formed by spraying water (approximately 10% by weight of the composition) onto the mixture under high shear.
4. After additional drying to less than 3% moisture, silica (glidant) and magnesium stearate (lubricant) are added and mixed for approximately 1 minute.
5. Caplets are then formed on a rotary tablet press.

Bleaching and Antimicrobial Dentifrice

Manufacturing Directions

1. Weight percentage: hydrogen peroxide (50%), 10.00; carbamide peroxide, 14.00; sodium fluoride, 0.38; Pecogel S-2120 (VP/dimethicolylacrylate is an inclusion complex polymer to retard the solubility of emulsified bleaching actives. It is obtained from Phoenix Chemical, Inc.), 0.50; hydroxyethyl cellulose, 0.50; triethanolamine, 0.30.
2. Water, purified, 10.00; glycerin, 10.75; tetrafluoroethylene (Teflon), 50.58; sodium lauryl sulfate, 1.25; sodium saccharine, 0.18; sodium citrate, 0.20; citric acid, 0.20; triclosan, 0.06; flavor, 1.10.

Bran–Sucrose–Gelatin–Calcium Carbonate Tablet

Manufacturing Directions

1. Gelatin–sucrose syrup is prepared by placing the following ingredients in a mixing kettle equipped with a heater and agitator. distilled water, 24,000 g; gelatin, 3000 g; sucrose granular, 31,995 g.
2. The mixture is heated up to approximately 65.5°C with agitation until solution is affected and the gelatin–sucrose syrup then slowly stirred and held at a temperature of approximately 65.5°C until needed.
3. Wheat bran is comminuted in a Schutz-O'Neill Airswept Pulverizer to provide a particle size whereby a minimum of 94% passes through a U.S. standard No. 20-mesh screen and a maximum of 60% passes through a U.S. standard No. 80-mesh screen. [The required amount of bran for the batch is calculated by the formula: 44250 g × 100/(100% moisture in bran)].
4. After pulverizing, the bran is transferred to a heavy-duty double-sigma arm mixer and mixed with 1500 g of calcium carbonate and the previously prepared gelatin–sucrose syrup added rapidly thereto with stirring.
5. When the bran appears to be damp, the mixture is stirred for a 30-minute period and then stopped.
6. Powdered sucrose (16,600 g) is added and the mixture agitated for an additional 2 to 5 minutes.
7. The wet mix is then discharged through an Ambrette screw extruder and the extrudate spread on drying trays and dried in an oven at 107.2°C to 3% moisture content.
8. The dried extrudate is granulated employing a Fitz mill (2A plate) and then pressed into 1-g tablets by a conventional tableting machine.

Bran Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Bran wheat (milled <1 mm)	250.00
200.00	2	Ludipress	200.00
5.00	3	Kollidon 30	5.00
4.00	4	Aerosil 200	4.00
4.00	5	Magnesium stearate	4.00

Manufacturing Directions

1. Mix all components, pass through a sieve, and press with medium compression force.
2. If the bran is not milled, the hardness of the tablet is higher but the content uniformity is less.
3. Compress 477-mg tablets using 12-mm punches.

Breast Care Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Polysorbate 60	20.00
70.00	2	Cetyl alcohol	70.00
60.00	3	Mineral oil (70 cS)	60.00
40.00	4	Glyceryl stearate	40.00
QS	5	Deionized water	QS
QS	6	Preservative	QS

Manufacturing Directions

1. Heat oil and water phases separately at 65°C to 70°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Fill at 20°C.
5. Only food-grade materials should be used.

Bromhexine Hydrochloride Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
4.00	1	Bromhexine HCl	0.80
1000.00	2	Glycerin (glycerol)	200.00
10.00	3	Benzoic acid	2.00
1.70	4	All fruits flavor	0.34
5.00	5	Tartaric acid	1.00
151.58	6	Alcohol (ethanol, 95%)	30.31
2857.00	7	Sorbitol (70% solution)	571.40
10.00	8	Sodium carboxymethyl cellulose (sodium CMC)	2.00
0.72	9	Sodium hydroxide pellets	0.14
QS	10	Purified water	QS to 1 L

Manufacturing Directions

1. Add 250 g of item 10 to the manufacturing vessel and heat to 65°C to 70°C.
2. Add 20 g of item 2 in a separate stainless steel container and mix item 8 using an Ekato stirrer, carefully avoiding lump formation.
3. Transfer the slurry to the manufacturing vessel and continue mixing to make a clear mucilage. Avoid air entrapment.
4. Cool to 30°C while mixing at slow speed. Transfer the mucilage to container.
5. Load 100 g of item 2 to the manufacturing vessel.
6. Add item 6 in a separate stainless steel container and dissolve item 3 using stirrer.
7. Add 60 g of item 2 to the container while mixing at slow speed.
8. Add and dissolve item 1 to the container while mixing at slow speed. Avoid splashing of the solution. Be sure bromhexine is dissolved completely.
9. Add item 4 to the container and mix well.
10. Transfer the solution to the manufacturing vessel while mixing at high speed.
11. Rinse the container with 20 g of item 2 and transfer the rinsing to the manufacturing vessel while mixing.
12. Rinse the container with 20 g of item 10 and transfer the rinsing to the manufacturing vessel while mixing.
13. Add 15 g of item 10 in a separate stainless steel container.
14. Dissolve item 5 using a stirrer and transfer it to the manufacturing vessel while mixing. Check for clarity of the solution in the manufacturing vessel. The solution must be clear without any undissolved particles of the drug.
15. Add item 7 to the manufacturing vessel while mixing at high speed.
16. Transfer the cooled mucilage of item 8 to the manufacturing vessel used above while mixing at slow speed.
17. Check and record the pH of the solution (limit: 3.3–3.6).
18. Dissolve item 9 in 5 g of cooled item 10 (30°C) in a separate stainless steel container.
19. Adjust the pH of the syrup in the manufacturing vessel using the sodium hydroxide solution.
20. Add sodium hydroxide solution, small portions at a time. Mix well and check the pH after every addition. Adjust the pH to 3.5 (limit: 3.3–3.6).
21. Bring the volume up to 1 L with item 10 and finally mix for 15 to 20 minutes at high speed.
22. Check and record the pH (limit: 3.3–3.6).
23. Filter the syrup at 1.5 bar.
24. Recirculate.

Bromhexine Hydrochloride Syrup (Alcohol Free)

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
4.00	1	Bromhexine HCl	0.80
1000.00	2	Glycerin (glycerol)	200.00
12.00	3	Sodium benzoate	2.40
1.70	4	All fruit flavors	0.34
17.00	5	Tartaric acid	3.40
2250.00	6	Sorbitol (70% solution)	450.00
10.00	7	Sodium carboxymethyl cellulose (sodium CMC)	2.00
QS	8	Purified water	QS to 1 L

Manufacturing Directions

1. Add 240 g of item 8 (25°C) to the manufacturing vessel.
2. Add item 5 and mix for 20 minutes at high speed.
3. Load 180 g of item 2 into the manufacturing vessel and mix for 3 minutes.
4. Add item 1 to the manufacturing vessel and mix for 30 minutes at high speed.
5. Add 20 g of item 2 in a suitable vessel and levigate item 7 using stirrer, carefully avoiding lump formation.
6. Add 40 g of item 8 (70°C) to the stainless steel container while mixing to make a clear mucilage. Mix for 15 minutes. Avoid air entrapment.
7. Cool down to 25°C to 30°C while mixing at slow speed.
8. Transfer the mucilage to the manufacturing vessel.
9. Rinse the vessel with 10 g of item 8 and transfer to the manufacturing vessel.
10. Mix at slow speed for 20 minutes.
11. Transfer item 6 to the manufacturing vessel while mixing. Mix at low speed for 5 minutes.
12. Add 20 g of item 8 (25°C) in a separate stainless steel container and dissolve item 3 using an Ekato stirrer until a clear solution is obtained.
13. Transfer this solution to the manufacturing vessel and mix at low speed for 3 minutes.
14. Add item 4 to the manufacturing vessel and mix at low speed for 3 minutes.
15. Record the pH of the solution (limit: 3.3–3.7). Adjust the pH of the solution with a 10% solution of sodium hydroxide, if required.
16. Make the volume up to 1 L with item 8 (25°C) and finally mix for 15 to 20 minutes at high speed.
17. Filter the syrup at 1.5 bar.
18. Recirculate.

Bromhexine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
8.00	1	Bromhexine HCl	8.00
78.00	2	Lactose monohydrate	78.00
30.40	3	Cornstarch	30.40
3.00	4	Gelatin (powder)	3.00
QS	5	Purified water	12.00
0.60	6	Magnesium stearate	0.60

Manufacturing Directions

The binding solution is susceptible to microbiological growth; hence, prepare the solution directly before the granulation process. Protect bromhexine HCl from light.

1. Make slurry in a separate container by dissolving item 4 in hot item 5 (70–80°C).
2. Mix for 10 minutes using stirrer at medium speed.
3. Pass items 1, 2, and 3 through a 630-μm sieve using a sifter.
4. Charge the sieved material into the mixer.
5. Mix, using mixer and chopper, for 5 minutes at high speed. Add binding solution to the dry powders in the mixer while mixing at low speed.
6. After the addition is complete, mix for an additional 4 minutes at low speed or until a satisfactory mass is obtained.
7. Spread the wet granules onto the trays.
8. Load the trolleys into the drying oven.
9. Dry the granules at 60°C for 10 hours.
10. Turn the granules after 4 hours of drying in order to obtain uniform drying.
11. Transfer the dried granules in stainless steel drums.
12. Check moisture content (limit: NMT 2%).
13. Pass the dried granules first through a 1.5-mm and then a 1.0-mm sieve using a granulator. Collect in stainless steel drums.
14. Load the granules into the blender.
15. Pass item 6 through a 250-μm sieve using a sifter and add to the granules in blender. Blend for 2 minutes.
16. Compress the granules using a rotary tableting machine.
17. Use a 7-mm flat, beveled-edge punch to compress 1.2 g per tablet at a hardness of NLT 3 kp.

Burn Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
120.00	1	Glyceryl stearate SE (Monthybase)	120.00
80.00	2	Myristate octyldodecyl (MOD)	80.00
20.00	3	Apricot kernel oil PEG-6 esters (Labrafil M 1944 CS)	20.00
0.50	4	Sodium methyl paraben	0.50
0.50	5	Sodium propyl paraben	0.50
0.50	6	Sorbic acid	0.50
767.50	7	Deionized water	767.50
10.00	8	Avocado oil	10.00
1.00	9	Fragrance	1.00

Manufacturing Directions

1. Mix and heat items 1 to 7 to 75°C.
2. Cool slowly with stirring.
3. At 30°C, add item 8 and then item 9.

Burn Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
15.00	1	Magnesium aluminum silicate (Veegum®)	15.00
568.00	2	Deionized water	568.00
30.00	3	Propylene glycol	30.00
2.00	4	Dimethicone emulsion	2.00
100.00	5	Mineral oil, light	100.00
170.00	6	Acetylated lanolin alcohol	170.00
50.00	7	Benzocaine, USP	50.00
30.00	8	C18–C36 acid	30.00
120.00	9	Glyceryl stearate and PEG-100 stearate	120.00
5.00	10	Polysorbate 60	5.00
QS	11	Preservatives	QS

Manufacturing Directions

1. Slowly add item 1 to water, agitating with extensive shear force until smooth.
2. Add items 3 and 4 and heat to 75°C to 80°C.
3. Mix and heat items 5 to 11, keeping item 7 suspended to 75°C to 80°C. Mix the two parts while cooling. Pour and fill at 40°C.

Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
150.00	1	Caffeine powder	150.00
36.00	2	Cellulose (microcrystalline) (Avicel PH102)	36.00
46.00	3	Anhydrous lactose	46.00
48.50	4	Di-Pac granular	48.50
3.00	5	Croscarmellose sodium (Ac-Di-Sol SD-711)	3.00
1.50	6	Fumed silica	1.50
0.75	7	Stearic acid	0.75
0.75	8	Magnesium stearate	0.75
1.20	9	Flavor	1.20

Manufacturing Directions

1. Screen items 1, 7, and 8 separately through a 40-mesh sieve.
2. Blend items 1 to 6 and 9 in a V-blender and mix for 3 minutes.
3. Add item 8 to the blender and mix for another 5 minutes.
4. Compress, using 7 kg pressure and 3/8-in flat, beveled-edge punches to produce tablets with an average weight of 311 mg.

Calamine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
80.00	1	Polawax GP200	80.00
10.00	2	Polysorbate 60	10.00
50.00	3	Caprylic/Capric triglyceride	50.00
QS	4	Deionized water	QS to 1 kg
100.00	5	Witch hazel distillate	100.00
50.00	6	Glycerin	50.00
20.00	7	Zinc oxide	20.00
20.00	8	Calamine	20.00
QS	9	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 65°C to 70°C.
2. Add water phase to oil phase while stirring.
3. Add zinc oxide and calamine under high shear.
4. Stir to cool.

Calamine Cream

Bill of Materials <Items 5 & 6 are not mentioned in the text>			
Scale (mg/g)	Item	Material Name	Quantity/kg (g)
20.00	1	Cellulose (microcrystalline) (Avicel RC-591)	20.00
100.00	2	Glycerin	100.00
1.80	3	Methyl paraben	1.80
0.20	4	Propyl paraben	0.20
100.00	5	Glyceryl stearate and PEG-100 stearate	100.00
25.00	6	Cetyl alcohol	25.00
50.00	7	Zinc oxide	50.00
50.00	8	Calamine	50.00
653.00	9	Distilled water	653.00

Manufacturing Directions

1. Mix item 2 with item 9 and heat to 75°C.
2. Add items 3 and 4. Mix until dissolved using a shearing mixer.
3. Maintain temperature at 75°C and gradually add item 1. Continue mixing at 75°C for 15 minutes or until item 1 is homogeneously dispersed. Mix well.
4. When temperature drops to 60°C to 65°C, gradually add items 7 and 8. Mix well until powders are homogeneously dispersed.
5. Pass through homogenizer, if necessary. Adjust theoretical weight with warm distilled water and continue mixing until the cream congeals.

Calamine Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
78.30	1	Calamine	78.30
78.30	2	Zinc oxide	78.30
19.60	3	Glycerin	19.60
230.80	4	Deionized water	230.80
558.00	5	Calcium hydroxide solution	558.00
34.40	6	Purified bentonite (Polargel, NF)	34.40
0.60	7	Carboxymethyl cellulose	0.60

Manufacturing Directions

1. Prepare a saturated solution of item 5 by putting 3 g of item 5 in 1000 mL of purified water. Mix vigorously for 1 hour.
2. Decant the clear, supernatant liquid for use in the formula.
3. Add the balance of water.
4. Add items 6 and 7 to this solution with rapid mixing. Continue mixing for 15 minutes.
5. In a separate vessel, blend items 1 and 2.
6. Add item 3 and mix until uniform.
7. Begin adding the aqueous solution with mixing until it is blended into a lotion.

Calcium and Vitamin D Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Anhydrous calcium phosphate (dibasic)	500.00
133 IU	2	Vitamin D (as vitamin D_3) (3.33 μg/tablet)	3.33 mg
15.00	3	Starch (pregelatinized, NF)	15.00
55.00	4	Cellulose (microcrystalline, NF)	55.00
6.00	5	Magnesium stearate, NF	6.00
5.00	6	Talc (powder), USP	5.00
12.00	7	Wax (hydrogenated vegetable oil) (Sterotex K)	12.00
15.50	8	Sodium starch glycolate, NF	15.50

Manufacturing Directions

1. Charge one-half of dibasic calcium phosphate through a mesh screen into a blender.
2. Premix by hand the pregelatinized starch with vitamin D_3 beadlets in a suitable container and sift through a mesh screen into the blender.
3. Charge the microcrystalline cellulose and the remaining calcium phosphate through a mesh screen into the blender.
4. Mix for 20 minutes.
5. Discharge approximately one-third of the granulation into polyethylene-lined drums.
6. Mix the magnesium stearate, talc, hydrogenated vegetable oil wax, and sodium starch glycolate.
7. Mill through a No. 40 mesh screen into the blender.
8. Return granulation from step above to the blender. Blend together.
9. Compress.

Calcium Chewable Tablets (200 mg Ca)

Formulation

Calcium gluconate (Merck), 845.0 g; calcium citrate (Merck), 500.0 g; Ludipress LCE [1], 297.5 g; citric acid anhydrous, fine granular, 100.0 g; polyethylene glycol 6000, powder, 80.0 g; orange flavor (Dragoco), 30.0 g; Aerosil 200, 17.0 g; aspartame, potassium (Searle), 5.0 g.

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with high compression force at 2417 mg.

Calcium Glycerophosphate Tablets (200 mg)

Formulation

Calcium glycerophosphate, 200.0 g; Ludipress, 297.5 g; magnesium stearate, 2.5 g; Aerosil 200, QS.

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with high compression force at 470 mg.

Calcium Carbonate Chewable Tablet

Manufacturing Directions

1. Granulated calcium carbonate (93.3% calcium carbonate, 6.3% glucose, and 0.4% gelatin), 42.87%; magnesium stearate, 2.50%; colored speckles, 0.75%; flavorants, 0.78%; MPD (31-menthoxy propane 1,2-diol), 0.07%; WS-3 (*N*-ethyl-*P*-menthane-3-carboxamide), 0.05%; aspartame, 0.198%; sodium saccharin, 0.102%; mannitol, QS.
2. The above ingredients are dry blended in a mixer until homogeneous and then direct compressed in a tableting machine to approximately 8.5 Strong Cobb units hardness to produce chewable antacid tablets each weighing 1.25 g (500 mg calcium carbonate per tablet).
3. These tablets may also be prepared by utilizing granulated calcium carbonate which is a 50/50 coblend of calcium carbonate/mannitol.

Calcium Carbonate and Glycine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
400.00	1	Calcium carbonate (precipitated)	400.00
200.00	2	Glycine (aminoacetic acid)	200.00
QS	3	Starch	QS
6.50	4	Mineral oil (light)	6.50
QS	5	Purified water	QS

Manufacturing Directions

1. Add starch to a planetary mixer and add 10 times the quantity of purified water.
2. Heat to boil with constant stirring until a thick, translucent white paste is formed. Use this paste in granulation.
3. Charge calcium carbonate and glycine in a sigma-blade or a planetary mixer and mix for 10 minutes.
4. Granulate this powder with the starch paste until a suitable mass is obtained.
5. Force the wet mass through a No.12 mesh screen onto dryer trays.
6. Dry in an air-forced oven at 54.4°C to 60°C or in a fluid-bed dryer.
7. Pass the dried granules through a No.12 mesh screen, then through a No.18 mesh screen.
8. Pass the granules through a 30-mesh screen, remove the portion passing through the screen, and regranulate.
9. Charge the particles retained on 30-mesh screen in a tumble mixer, add mineral oil, and mix for 8 minutes.
10. Compress 640-mg tablets using 7/16-in punches.

Calcium Carbonate and Vitamin D Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
600.00	1	Calcium (elemental), use calcium carbonate (90%) for direct compression	1665.00
0.235	2	Vitamin D_3 (200 IU), use vitamin D_3 beadlets	0.282
4.16	3	Magnesium stearate	4.16
83.25	4	Sodium starch glycolate	83.25

Manufacturing Directions

1. Make a premix of vitamin D_3 successively in three portions of calcium carbonate (total amount equivalent to approximately 3% of total calcium carbonate), using the geometric dilution.
2. Mix for 10 minutes each time (total: 30 minutes).
3. Add the premix to the sodium starch glycolate. Mix for 10 minutes.
4. Set the blend aside, protected from light, until the next step.
5. Pass the magnesium stearate through a 420-μm aperture screen, if required, and blend it with another portion of calcium carbonate (approximately 10% of total calcium carbonate).
6. Mix for 5 minutes. Set aside.
7. Add the blended material to the balance of the calcium carbonate. Mix for 10 minutes.
8. Add the premix to blend from above. Mix for 5 minutes.
9. Compress on specially shaped 0.8100-in × 0.3700-in ovaloid bisected punches with a monogram on one side.
10. Theoretical weight of 10 tablets = 17.527 g.
11. Coat using one of the HPMC formulae (see appendix).

Calcium Carbonate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Calcium carbonate (precipitated)	500.00
65.00	2	Kollidon 30	65.00
97.00	3	Water	97.00
32.00	4	Kollidon CL	32.00
53.00	5	Ludipress	53.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with the water (item 3).
2. Pass through a 0.8-mm sieve, mix the dry granules with items 4 and 5, and press with low compression force.
3. Fill 656 mg in 12-mm planar punches.

Calcium D-Pantothenate Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
600.00	1	Calcium D-pantothenate (BASF)	610.00
150.00	2	Sorbitol (crystalline)	150.00
140.00	3	Avicel PH101	140.00
30.00	4	Kollidon CL	30.00
50.00	5	PEG-6000 (powder)	50.00
QS	6	Flavors	QS

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with low compression force.
2. Compress 987-mg tablets in 12-mm biplanar punches.

Note: Kollidon CL may be omitted and the tablet weight adjusted.

Calcium D-Pantothenate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
100.00	1	Calcium D-pantothenate (BASF)	100.00
150.00	2	Ludipress	150.00
10.00	3	Kollidon®	10.00
3.00	4	Magnesium stearate	3.00

Manufacturing Directions

1. Mix all components. Pass through a 0.8-mm sieve.
2. Press into 252-mg tablets using medium compression force and biplanar 8-mm punches.

Calcium D-Pantothenate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
280.00	1	Calcium D-pantothenate (BASF)	285.00
50.00	2	Avicel PH101	50.00
150.00	3	Dibasic calcium phosphate	150.00
20.00	4	Kollidon CL	20.00
3.00	5	Stearic acid	3.00
3.00	6	Magnesium stearate	3.00

Manufacturing Directions

1. Mix all components. Pass through a 0.8-mm sieve.
2. Press into 518-mg tablets using medium compression force and 12-mm biplanar punches.

Calcium Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
634.00	1	Calcium lactate	634.00
610.00	2	Calcium gluconate	610.00
185.21	3	Calcium carbonate	185.21
400.00	4	Sodium bicarbonate	400.00
468.25	5	Tartaric acid	468.25
46.25	6	Povidone (Kollidon 30)	46.25
11.75	7	Povidone (Kollidon 30)	11.75
QS	8	Isopropyl or ethyl alcohol (96%)	QS
97.50	9	Crospovidone (Kollidon CL)	97.50
46.25	10	PEG-6000	46.25
QS	11	Flavor	QS

Manufacturing Directions

1. Granulate items 1 to 6 in a solution of items 7 and 8.
2. Dry, sieve, and mix well with items 9 to 11.
3. Compress at low pressure to form 2.5-g tablets, 20 mm in diameter.

Calcium Gluconate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
350.00	1	Calcium gluconate (powder)	360.00
117.00	2	Lactose monohydrate	117.00
11.00	3	Kollidon 30	11.00
QS	4	Isopropanol	90.00
25.00	5	Kollidon CL	25.00
2.00	6	Magnesium stearate	2.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with item 4.
2. Dry, pass through a 0.8-mm sieve, and mix with items 5 and 6.
3. Press into 500-mg tablets using high compression force and 12-mm biplanar punches.

Calcium Glycerophosphate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Calcium glycerophosphate	500.00
117.50	2	Cornstarch	117.50
15.00	3	Kollidon 90 F	15.00
60.00	4	Water	60.00
15.00	5	Kollidon CL	15.00
2.50	6	Magnesium stearate	2.50

Manufacturing Directions

1. Granulate items 1 to 3 with item 4, dry, sieve, and mix with items 5 and 6.
2. Press into 650-mg tablets using medium to high compression force and 12-mm biplanar punches.

Calcium Glycerophosphate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Calcium glycerophosphate	200.00
297.50	2	Ludipress	297.50
2.50	3	Magnesium stearate	2.50
QS	4	Aerosil 200	QS

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve and mix.
2. Press into 470-mg tablets using high compression force and 12-mm biplanar punches.

Calcium Iodide and Ascorbic Acid Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
311.60	1	Glucose liquid (corn syrup)	311.60
53.90	2	Glycerin (96%)	53.90
30.00	3	Anhydrous calcium iodide, use calcium iodide solution 27% w/w	111.11
1.00	4	Ascorbic acid (white powder)	1.00
485.30	5	Sucrose (granulated sugar)	485.30
0.80	6	Saccharin sodium (powder)[a]	0.80
8.00	7	Sodium cyclamate (XIII powder)	8.00
1.31	8	Honey artificial flavor, AU-73	1.31
0.33	9	Floral mint artificial flavor	0.33
51.53	10	Alcohol (ethanol, 190 proof)	51.53
0.60	11	Isoproterenol sulfate (powder)	0.60
0.05	12	FD&C yellow dye No. 5	0.05
0.25	13	Caramel (acid proof)	0.25
QS	14	Water purified	~344.0 mL

[a]Use 1.2 g of saccharin to replace cyclamate; adjust balance with sucrose.

Manufacturing Directions

Isoproterenol is toxic; wear a dust mask and avoid contact. The product is sensitive to oxidation. Manufacture under N_2 protection and protect product from light and heat; all water must be boiled, cooled, and gassed with nitrogen.

1. Load glucose and glycerin into a suitable mixing tank.
2. Add 187 mL purified water to tank with mixing.
3. Begin bubbling N_2 protection for the balance of the process.

4. Add and dissolve saccharin sodium and sodium cyclamate, if used, with mixing.
5. Add calcium iodide to the tank with good mixing.
6. Add and dissolve ascorbic acid and sugar.
7. Dissolve the flavors in alcohol and add with mixing to the main batch.
8. Dissolve isoproterenol in 10 to 13 mL of water and add, with mixing, to the main batch.
9. Dissolve dye in 3.5 mL purified water and add solution to tank with mixing. (*Note*: Dye may be deleted.) Add caramel with mixing to main batch.
10. Move N_2 source from the bottom to the top of the tank.
11. Turn off mixer.
12. Allow to stand overnight under N_2 protection to let entrapped gases escape.
13. QS to 1 L. Mix for 1 hour.
14. Filter and circulate product through a suitable filter press until sparkling clear.

Calcium Phosphate Tablets for Cats and Dogs (Direct Compression)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
400.00	1	Dicalcium phosphate	400.00
100.00	2	Wheaten flour	100.00
1.00	3	Citric acid crystalline	1.00
272.00	4	Lactose monohydrate	272.00
QS	5	Flavors	QS
20.00	6	Kollidon 90 F	20.00
4.00	7	Magnesium stearate	4.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve. Mix.
2. Press with medium to high compression force (20 kN).
3. Compress into 800-mg tablets using 12-mm biplanar punches.

Calcium Phosphate Tablets for Cats and Dogs

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
400.00	1	Dicalcium phosphate	400.00
100.00	2	Wheaten flour	100.00
1.00	3	Citric acid crystalline	1.00
262.00	4	Lactose monohydrate	262.00
QS	5	Flavors	QS
30.00	6	Kollidon 30 F	30.00
150.00	7	Water	150.00 mL
4.00	8	Magnesium stearate	4.00

Manufacturing Directions

1. Granulate items 1 to 6 in item 7, dry, add item 8, and pass through a 0.8-mm sieve.
2. Compress 800-mg tablets using 12-mm biplanar punches.

Carbamide Peroxide Chewing Gum

Formulation

Gum base, 26.25 g; calcium carbonate, 3.75 g; sorbitol, 28.05 g; mannitol, 7.50 g; maltitol, 21.62 g; glycerin, 1.00 g; flavorant, 3.15 g; gum arabic, 1.16 g; titanium dioxide, 0.17 g; wax candellia, 0.03 g; sodium stearate/sodium palmitate, 50% each, 3.00 g; tripolyphosphate sweetener, 0.82 g; Imwitor 370, 1.00 g; carbamide peroxide, 3.00 g.

Manufacturing Directions

1. The gum base is heated to sufficiently soften the base without adversely affecting the physical and chemical make-up of the base.
2. The molten gum base and the filler are then added to a mixing kettle.
3. The sugar alcohols, glycerin, flavor, high-intensity sweetener, and stain-removing agent carbamide peroxide added last with mixing to obtain a homogenous mixture.
4. The mixture is then discharged from the mixing kettle and rolled and scored into a desired piece size by conventional techniques.

Carbamide Peroxide and Hydrogen Peroxide Bleaching Oral Dentifrice

Manufacturing Directions

1. Gel composition as weight percent contains sodium fluoride, 0.32 [0.14 (w/v) fluoride ion]; Carbopol 974 P-NF, 1.25; sorbitol (70% solution), 10.00; glycerin, 10.00; carbamide peroxide, 14.00; sodium lauryl sulfate, 1.50; sodium saccharine, 0.20; flavor, 1.25; FD&C yellow No. 5, 0.15; FD&C red No. 40, 0.05; water purified, 29.60.
2. Paste composition in weight percent contains sodium fluoride, 0.32; hydrogen peroxide (50% solution), 10.00; Carbopol 943, 0.51; sorbitol (70% solution), 5.18; glycerin, 5.18; sodium lauryl sulfate, 1.50; sodium saccharine, 0.20; flavor, 1.25; polytetrafluoroethylene (Teflon), 52.00; water, purified, 29.86.
3. Both phases (steps 1 and 2) are neutralized to a pH of approximately 5.5 and 6.5 with freshly prepared 10% sodium hydroxide and the stripe composition to the main composition is approximately 15:100.
4. The above hydrogen peroxide/carbamide peroxide blend composition is effective and stable when used topically for bleaching tooth surfaces.
5. When extruded from the tube container, the gel composition will be in the form of one or more stripes enclosed in the periphery of the toothpaste surrounded by the paste composition.
6. The gel and the paste composition must be sufficiently of heavy viscosities to prevent migration (bleeding) of the colored gel into the white paste composition.

Carbinoxamine Maleate, Phenylpropanolamine, and Acetaminophen Sustained-Release Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
5.00	1	Carbinoxamine maleate	5.00
75.00	2	Phenylpropanolamine hydrochloride	75.00
50.00	3	Acetaminophen	50.00
143.35	4	Sucrose and maize starch microgranules	143.35
6.34	5	Polyvidone (PVP)	6.34
0.01	6	Dye	0.01
0.075	7	Dye	0.075
0.025	8	Dye	0.025
23.99	9	Talc	23.99

Manufacturing Directions

This product requires separate preparation of microgranules for each active ingredient. This preparation requires a coating pan equipped with air suction and hot air heating system, mixer, automatic airless pump with a spray gun, vibrating sieve, and capsule-filling machine with triple-feed microgranular system.

1. Place the neutral microgranules in the coating pan. Prepare a 20% solution of PVP.
2. Maintain the temperature of microgranules at 20°C±2°C.
3. Using the pump, apply the solution of PVP, then project the active ingredient onto the microgranules with a plastic scoop until they are dry.
4. Repeat these operations until all the active ingredients have been incorporated.
5. Sieve the microgranules with a 1.11-mm sieve.
6. Dry the microgranules at 30°C±5°C for 3 hours.
7. Prepare a 40% solution of shellac in alcohol and the required quantity of talc.
8. Apply the shellac solution, maintaining a microgranule temperature of 20°C±2°C and add the talc simultaneously.
9. Sieve the microgranules through a 1.18-mm sieve.
10. Dry the microgranules at 18°C to 23°C for 8 hours. Store until used.
11. Test for dissolution and rework if necessary.

Carbonyl Iron, Copper Sulfate, and Manganese Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
24.00	1	Carbonyl iron (BASF)	24.00
0.16	2	Copper sulfate	0.16
3.50	3	Manganese sulfate	3.50
100.00	4	Ludipress	100.00
2.00	5	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve. Mix.
2. Press into131-mg tablets using medium compression force and 8-mm biplanar punches.

Carnitine and Coenzyme Q Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1.00	1	Coenzyme Q 10	1.00
1.00	2	Lutrol E 400	1.00
4.00	3	Cremophor RH 40	4.00
QS	4	Preservative	QS
QS	5	Water	QS to 1 L
40.00	6	Carnitine	40.00

Manufacturing Directions

1. Heat the mixture of items 1 to 5 to 60°C. Stir well.
2. Cool to room temperature and add and dissolve item 6.

Cetrimide Antiseptic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Cetearyl alcohol and cetrimonium bromide	50.00
75.00	2	White petroleum jelly	75.00
60.00	3	Mineral oil (70 cS)	60.00
QS	4	Deionized water	QS to1 kg
QS	5	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 60°C to 65°C.
2. Add the water phase to the oil phase while stirring.
3. Stir to cool.

Cetirizine Hydrochloride Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
15.00	1	Cetirizine hydrochloride	15.00
3.00	2	PVP	3.00
1.50	3	Silicon dioxide	1.50
135.00	4	Lactose	135.00
1.50	5	Glyceryl behenate	1.50
QS	6	Water	QS

Manufacturing Directions

1. Cetirizine and lactose are placed in a fluidized-bed apparatus.
2. An aqueous PVP solution (in 85 g of water) is sprayed to get granules.
3. The granules thus obtained are subsequently dried and passed through a sieve (1-mm mesh) and glyceryl behenate is weighed, added, and blended in a drum mixer.
4. The resulting mixture is pressed into 156-mg tablets.
5. These tablet cores are then coated with the following formulation: ethyl cellulose, 10; hydroxypropyl cellulose, 10; stearic acid, 2; alcohol, 188 g.
6. Ethocel, povidone, and stearic acid are first dissolved in denatured alcohol (188 g).
7. The coating solution is then sprayed onto the tablet cores in a coating pan.

Cetylpyridinium Lozenges (2.5 mg)

Formulation

Cetylpyridinium chloride (Merck), 2.5 g; Ludipress LCE [1], 370.0 g; polyethylene glycol 6000, powder, 20.0 g; menthol, crystalline, 6.0 g; aspartame, potassium (Searle), 1.5 g.

Manufacturing Directions

1. Mix all components. Pass through a 0.8-mm sieve.
2. Press with low compression force at 402 mg.

Charcoal Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Activated charcoal	250.00
150.00	2	Bolus alba (Merck)	150.00
28.00	3	Kollidon 25	28.00
38.00	4	Acacia gum	38.00
QS	5	Water + isopropanol (10 + 3)	575.00 mL
15.00	6	Cremophor EL	15.00
QS	7	Isopropanol	300.00 mL

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with item 5 and pass through a 1-mm sieve.
2. Dry until a relative powder humidity of 90% is reached.
3. Add solution of items 6 and 7 and pass again through a 0.8-mm sieve.
4. Dry the granules and press into 481-mg tablets using low compression force and 12-mm planar punches.
5. Dry the obtained tablets.

Chlophedianol, Ipecac, Ephedrine, Ammonium Chloride, Carbinoxamine, and Balsam Tolu Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
0.001 mL	1	Ipecac fluid extract	1.00 mL
5.00	2	Chlophedianol hydrochloride	5.00
1.32	3	Ephedrine hydrochloride (powder)	1.32
8.80	4	Ammonium chloride (reagent-grade granules)	8.80
0.80	5	Carbinoxamine maleate	0.80
0.90	6	Methyl paraben	0.90
0.10	7	Propyl paraben	0.10
6.25	8	Balsam of Tolu (eq. aqueous extract)	6.25
2.66	9	Saccharin sodium (dihydrate powder)	2.66
319.22	10	Sucrose (granulated sugar)	319.22
238.33	11	Glucose liquid (corn syrup)	238.33
83.93	12	Sorbitol solution (calculate as 70% sorbitol crystals)	83.93
40.00	13	Alcohol	40.00
166.67	14	FD&C red dye (Amaranth E123)	166.67 mg
0.80	15	Raspberry flavor	0.80
100.00	16	Propylene glycol	100.00
QS	17	HyFlo filter aid	0.50
QS	18	Water purified	~450.00 mL

Manufacturing Directions

1. Charge balsam of tolu and 25 mL of water in a steam bath.
2. Raise the temperature, stirring continuously in order to mix water with the balsam.
3. Boil for half an hour and allow to decant while cooling.
4. Discard extracted balsam of tolu.
5. Filter the supernatant liquid through filter paper and store apart.
6. Charge 150 mL water in a jacketed mixing tank and heat to boiling.
7. Add and dissolve parabens with mixing.
8. Add and dissolve sugar with constant mixing.
9. Heat to 70°C to 75°C.
10. Once sugar is dissolved, add glucose, sorbitol, and saccharin sodium. Mix well until dissolved.
11. Dissolve ammonium chloride in 28 mL water.
12. Add to mixing tank.
13. Add extract balsam of tolu from first step with mixing. Mix well and cool to 25°C to 30°C.
14. Add and dissolve ephedrine and carbinoxamine in 20 mL water and add to mixing tank. Mix well.
15. Add and dissolve chlophedianol in 50 g of propylene glycol and add to mixing tank.
16. Add balance of propylene glycol to mixing tank.
17. Add and dissolve ipecac fluid extract and raspberry flavor in alcohol.
18. Add to mixing tank.
19. Dissolve dye in 5 mL water and add to tank with continuous mixing.
20. Rinse container with 5 mL of water and add rinsing.
21. Adjust to volume with purified water.
22. Add HyFlo filter aid to syrup and mix well.
23. Recirculate through filter press or equivalent until sparkling clear.

Chlorhexidine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Chlorhexidine diacetate	20.00
300.00	2	1,2-Propylene glycol (pharma)	300.00
220.00	3	Lutrol F 127	220.00
460.00	4	Water	460.00

Manufacturing Directions

1. Dissolve chlorhexidine diacetate in propylene glycol at >70°C.
2. Stir well and slowly add Lutrol F 127 and water.
3. Maintain the temperature until the air bubbles escape.
4. A clear, colorless gel is obtained.

Chlorhexidine Lozenges

Bill of Materials			
Scale (mg/lozenge)	Item	Material Name	Qty/1000 lozenges (g)
5.00	1	Chlorhexidine	5.00
150.00	2	Sorbitol (crystalline)	150.00
5.00	3	Kollidon VA 64	5.00
5.00	4	Menthol (crystalline)	5.00
5.00	5	Eucalyptol (crystalline)	5.00
1.00	6	Aspartame, potassium	1.00
0.10	7	Saccharin sodium	0.10
2.00	8	Aerosil 200	2.00
1.00	9	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium compression force.
2. Compress into 175-mg lozenge using 8-mm biplanar punches.

Chlorpheniramine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
4.00	1	Chlorpheniramine maleate	4.00
75.00	2	Starch 1500	75.00
65.62	3	Microcrystalline cellulose (50 μm)	65.62
2.96	4	Stearic acid	2.96
1.11	5	Fumed silica	1.11
0.37	6	Magnesium stearate	0.37

Manufacturing Directions

1. Blend half of the Starch 1500 with the fumed silica and chlorpheniramine for 5 minutes.
2. Pass this mixture through a 40-mesh screen and return to blender.
3. Add the remaining Starch 1500 to the material in step 1 and blend for 5 additional minutes.
4. Add the microcrystalline cellulose and stearic acid to the material from step 2 and blend for an additional 10 minutes.
5. Add the magnesium stearate to the material from step 3 and blend for an additional 5 minutes.

Chlorpheniramine Maleate Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
2.00	1	Chlorpheniramine maleate	0.40
3000.00	2	Sucrose	600.00
4.50	3	Methyl paraben	0.90
1.50	4	Propyl paraben	0.30
1.00	5	Citric acid (monohydrate)	0.20
2.40	6	Sodium citrate	0.48
2.00	7	Green banana flavor	0.40
–	8	Purified water	QS to 1 L

Manufacturing Directions

1. Add 500 g of purified water to the manufacturing vessel and heat to 95°C to 98°C.
2. Add items 3 and 4 while mixing to dissolve at high speed.
3. Mix for 5 minutes.
4. Add item 2 while mixing at slow speed.
5. Maintain a temperature of 95°C to 98°C.
6. Mix for 1 hour at high speed.
7. Cool down to 30°C while mixing at slow speed.
8. Dissolve items 5 and 6 in 20 g of cooled purified water (25°C).
9. Transfer the solution to the manufacturing vessel while mixing at high speed.
10. Mix for 2 minutes.
11. Add 8 g of cold purified water (25–30°C) in a separate container and dissolve item 1 by using stirrer.
12. Mix for 10 minutes and transfer to the manufacturing vessel.
13. Rinse the container with 2 g of cooled purified water (25°C) and transfer the rinsings to the manufacturing vessel while mixing at high speed.
14. Add item 7 to the manufacturing vessel while mixing.
15. Mix for 10 minutes at high speed.
16. Bring the volume up to 1 L with purified water and finally mix for 15 to 20 minutes at high speed.
17. Check and record the pH (limit: 5.0–5.2 at 25°C).
18. If required, adjust pH with 10% citric acid or 10% sodium citrate solution.
19. Filter the syrup at 1.5 bar.
20. Bubble the syrup with nitrogen gas.

Chlorpheniramine and Pseudoephedrine Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
3.35	1	Chlorpheniramine maleate	3.35
100.00	2	Pseudoephedrine hydrochloride	100.00
396.65	3	Cab-o-Sil M5	396.65
200.00	4	Water	200.00

Manufacturing Directions

1. Chlorpheniramine maleate and pseudoephedrine hydrochloride are mixed in the water until thoroughly dissolved.
2. Cab-o-Sil M5 (silicon dioxide) is poured into a planetary mixer to which the dissolved drug solution is added and mixed at slow speed.
3. This is continued for 5 minutes until the solution and Cab-o-Sil are completely mixed.
4. The mixture is dried in a forced hot air oven for 5 hours to an LOD of less than 2%.
5. Magnesium stearate is then added as a lubricant and tartaric acid is added as an acidulent.
6. The excipients are then thoroughly mixed and the entire composition is compressed into 1-g tablets, each one possessing a potency of 4 mg chlorpheniramine maleate and 120 mg pseudoephedrine hydrochloride.

Chlorpheniramine, Pseudoephedrine, and Dextromethorphan Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
8.00	1	Chlorpheniramine maleate	8.00
120.00	2	Pseudoephedrine hydrochloride	120.00
60.00	3	Dextromethorphan Hydrobromide	60.00
812.00	4	Cab-o-Sil M5	812.00
200.00	5	Water	200.00

Manufacturing Directions

1. Chlorpheniramine maleate, dextromethorphan HBr, and pseudoephedrine hydrochloride are mixed in the water until thoroughly dissolved.
2. Cab-o-Sil M5 (silicone dioxide) is poured into a planetary mixer to which the dissolved drug solution is added and mixed at slow speed.
3. This is continued for 5 minutes until the solution and Cab-o-Sil are completely mixed.
4. The entire composition is dried in a forced hot air oven for 7 hours at 50°C.
5. The composition is dried to an LOD of 1.25%.
6. The dried material is then screened through a No. 30 U.S. standard mesh screen.
7. The excipients are added as mentioned before and the blend is compressed into 1-g tablets, each one possessing a potency of 4 mg chlorpheniramine maleate and 60 mg pseudoephedrine hydrochloride and 30 mg dextromethorphan HBr.

Chymotrypsin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
27.00	1	Chymotrypsin	27.50
71.50	2	Ludipress	71.50
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components. Pass through a 0.8-mm screen.
2. Press with low compression force.
3. Compress into 100-mg tablets using 8-mm biplanar punches.

Cimetidine Tablets (200 mg)

Formulation

Cimetidine, 200 g; Ludipress, 295 g; magnesium stearate, 5 g.

Manufacturing Directions

1. Pass the mixture through a 0.8-mm screen.
2. Press with low compression force at 510 mg at low humidity 30%.

Cimetidine Chewable Tablets

Manufacturing Directions

1. Cimetidine premix granules: cimetidine, 200 mg; Eudragit E100, 20 mg; antacid (Al/Mg) granules sorbitol, direct compression grade, 590 mg; lactose, direct compression grade spray dried, 325 mg; lactose crystalline, 325 mg; dried aluminium hydroxide gel, 250 mg; magnesium hydroxide, 200 mg; croscarmellose sodium type A, 30 mg; magnesium stearate, 15 mg; total, 1735 mg.
2. Tableting mix for compression: cimetidine, 220 mg; premix granules antacid (Al/Mg), 1735 mg; granules microcrystalline cellulose (Avicel PH102), 200 mg; aspartame, 10 mg; aniseed, 20 mg; butterscotch, 20 mg; magnesium stearate, 15.0; total, 2220 mg.
3. A 40% (w/w) solution of the Eudragit E100 in methylene chloride is added with mixing to the cimetidine and blended until granules are formed.
4. The resulting granules are dried and then sieved through a 16-mesh screen.
5. Aluminium hydroxide, magnesium hydroxide, and other ingredients for the antacid granules are sieved through a 12-mesh (1.4 mm) screen and mixed together.
6. The resulting mix is compressed on a rotary tablet press and the resulting compacts are milled using a 12-mesh screen.
7. Cimetidine granules, antacid granules, and extragranular excipients are put into a cone blender and mixed thoroughly.
8. The resulting mix is discharged from the blender and compressed on a suitable rotary tablet press fitted with the appropriate punches.

Citrate Effervescent Powder

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/kg (g)
0.50	1	Oil lemon terpeneless	0.50
10.00	2	Lemon flavor (natural microseal)	10.00
QS	3	Alcohol dehydrated (absolute, doubly rectified)	6.50
440.33	4	Sodium bicarbonate	440.33
0.35	5	Saccharin sodium	0.35
157.50	6	Anhydrous sodium citrate	157.50
178.82	7	Anhydrous citric acid (powder)	178.82
222.50	8	Acid tartaric	222.50

Manufacturing Directions

1. All processing should be done in controlled humidity at a maximum RH of 40% at 25°C.
2. Sodium citrate and citric acid are anhydrous.
3. Dissolve lemon oil in dehydrated alcohol with stirring in a suitable container (delete this step if using powdered lemon flavor).
4. Sift sodium bicarbonate, if necessary, through a 595-μm screen.
5. Charge into a suitable mixer and mix for 10 minutes.
6. Very slowly add solution from first step to the mixer while mixing. Continue mixing for at least 10 minutes and up to a total of 30 minutes, depending on equipment.
7. Screen the massed granulation mixture through a 595-μm screen and divide approximately in half.
8. Premix saccharin sodium into sodium citrate (and lemon powder, if used) and sift through a 595-μm screen or mill fitted with a 595-μm screen (knives forward, medium speed).
9. Sift both citric acid and tartaric acid separately through a 595-μm screen or mill separately using a comminuting mill with a 595-μm aperture (knives forward, medium speed).
10. Load materials into a suitable blender, preferably in the following order: milled tartaric acid, milled citric acid, half of granulation mixture, milled saccharin sodium, sodium citrate, and remaining granulation mixture.
11. Blend for 20 minutes and pack into double plastic bags inside fiber drums.
12. Provide silica gel protection to maintain low humidity in drums.
13. If blended material is lumpy, pass through a 1.2-mm screen before bagging.

Crospovidone Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
1000.00	1	Crospovidone (micronized)	1000.00
150.00	2	Citric acid	150.00
25.00	3	Aerosil 200	25.00
100.00	4	Sucrose (crystalline)	100.00
1.00	5	Saccharin sodium	1.00
QS	6	Water	QS
5.00	7	Magnesium stearate	5.00
125.00	8	Sodium bicarbonate	125.00
65.00	9	Flavor mixture	65.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with item 6, dry, and pass through a sieve.
2. Mix the dry granules with items 7 to 9 and press with medium compression force.
3. The dosage may be increased to 2000 mg crospovidone by increasing the tablet weight to 3200 mg.
4. Compress 1590-mg tablets using 20-mm diameter biplanar punches.

Crospovidone Oral Suspension (2000 mg/10 mL)

Formulation

Kollidon CL-M [1], 20.0 g; sorbitol, crystalline [10], 10.0 g; Kollidon 90F [1], 2.0 g; preservatives, QS; flavor, QS; water, 100 mL.

Manufacturing Directions

Dissolve sorbitol, Kollidon 90F, preservatives and flavors in the water. Add Kollidon CL-M and homogenize by shaking.

Crospovidone Water-Dispersible Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
1000.00	1	Crospovidone M (BASF)	1000.00
50.00	2	Aerosil 200	50.00
250.00	3	Sucrose (crystalline)	250.00
5.00	4	Saccharin sodium	5.00
2.00–3.00	5	Flavors	2.00–3.00
380.00	6	Water	380.00
5.00	7	Magnesium stearate	5.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with item 6, dry, and pass through a sieve.
2. Mix the dry granules with item 7 and press with low compression force.
3. The dosage may be increased to 2000 mg crospovidone by increasing the tablet weight to 2600 mg.
4. Compress 1280-mg tablets using 20-mm biplanar punches.

Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50.00 μg	1	Cyanocobalamin; use gelatin-coated cyanocobalamin (0.1%)	50.00
150.00	2	Ludipress	150.00
1.50	3	Magnesium stearate	1.50
2.00	4	Sicovit Quinoline lake, yellow	2.00
3.00	5	Sicovit Yellow lake, orange	3.00

Manufacturing Directions

1. Prepare a premix of item 1 and 2 and add to items 3 to 5.
2. Pass through a 0.5-mm sieve and press with low compression force.
3. Compress into 209-mg tablets using 8-mm biplanar punches.

Dexpanthenol Gel Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Dexpanthenol (BASF)	50.00
100.00	2	Liquid paraffin	100.00
150.00	3	Lutrol E 400	150.00
180.00	4	Lutrol F 127	180.00
QS	5	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve dexpanthenol and Lutrol E 400 in water, add liquid paraffin, and stir, heating to 60°C to 70°C.
2. Slowly add Lutrol F 127 and stir until dissolved.
3. Cool to room temperature, stirring continuously until the air bubbles disappear.

Dextromethorphan, Pseudoephedrine, and Chlorpheniramine Maleate Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
2.00	1	Dextromethorphan hydrobromide	2.00
4.00	2	D-Pseudoephedrine hydrochloride	4.00
0.40	3	Chlorpheniramine maleate	0.40
25.00	4	Sorbitol syrup	25.00
0.20	5	Saccharin sodium	0.20
3.00	6	Hydroxyethyl cellulose (Natrosol®)	3.00
2.50	7	Sodium benzoate	2.50
1.05	8	Banana flavor	1.05
1.10	9	Custard flavor	1.10
1.20	10	Trisodium citrate dihydrate (powder)	1.20
QS	11	Deionized water	QS to 1 L

Manufacturing Directions

1. In a suitable stainless steel vessel, combine sorbitol syrup, hydroxyethyl cellulose, and deionized water. Mix well.
2. Add sodium benzoate and stir again for 5 minutes.
3. After obtaining a clear solution, stir the hydroxyethyl cellulose suspension, rinse the container with deionized water, and transfer the rinsings to the vessel.
4. Heat the vessel to 40°C to 50°C and stir the mix for 1 hour.
5. After 1 hour, a clear gel without lumps is obtained.
6. Dilute the gel with sorbitol syrup and cool to 30°C.
7. In a separate vessel, add deionized water and heat while stirring to 50°C.
8. After reaching this temperature, dissolve, in this order: dextromethorphan hydrobromide, chlorpheniramine maleate, and pseudoephedrine hydrochloride and saccharin sodium.
9. Cool the solution to 25°C.
10. In a suitable stainless steel container, add deionized water and while stirring dissolve trisodium citrate under 0.6 bar vacuum and high speed.
11. Transfer the active substance solution to the syrup vehicle.
12. Rinse the vessel twice with deionized water.
13. Add while stirring (low) the custard and banana flavors.
14. Mix for 10 minutes.
15. Then, while stirring, add the solution from step above. Keep stirring for 15 minutes at moderate speed.
16. Stop stirring and check pH (limit: 5.9–6.2). Adjust with 10% trisodium citrate solution. After each addition, where necessary, stir for 5 minutes before recording pH again.
17. Finally, make up the volume with deionized water and stir once more for 15 minutes under vacuum (0.6 bar) at moderate speed.
18. Stop stirring and remove vacuum. Check final volume once more.
19. Filter the clear syrup under compressed air pressure, first through a filter of 330-µm and then through a 20-µm filter of propylene type.

Dihydroxyaluminum Sodium Carbonate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
31.00	1	Dihydroxyaluminum sodium carbonate (Giulini A 265)	31.00
61.50	2	Sugar	61.50
2.00	3	Magnesium stearate	2.00
15.00	4	Starch	15.00
QS	5	Flavor, sweetener	0.50

Manufacturing Directions

Blend to mix and compress 110 mg in 6-mm punch.

Dimenhydrinate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50.00	1	Dimenhydrinate	50.00
245.00	2	Ludipress	245.00
5.00	3	Magnesium stearate	5.00

Manufacturing Directions

1. Mix all components, sieve, and press with low compression force.
2. Compress into 300-mg tablets using 8-mm biplanar punches.

Dimenhydrinate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50.00	1	Dimenhydrinate	50.00
50.00	2	Cellulose (microcrystalline) (Avicel PH101)	50.00
125.00	3	Lactose	125.00
2.29	4	Croscarmellose sodium (Ac-Di-Sol, SD-711)	2.29
1.00	5	Fumed silicon dioxide	1.00
0.50	6	Stearic acid	0.50
0.50	7	Magnesium stearate	0.50

Manufacturing Directions

1. Screen items 1, 5, and 6 separately through a 40-mesh sieve.
2. Blend items 1, 2, 4, and 5 in a V-blender for 3 minutes.
3. Add item 3 in the blender and mix for 17 minutes.
4. Add item 6 and blend for 3 minutes.
5. Add item 7 to the blender and mix for 5 minutes.
6. Compress using 3/8-in flat, beveled-edge punches to a hardness of 6 kp and average tablet weight of 228 mg.

Dimenhydrinate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Dimenhydrinate	100.00
40.00	2	Lactose monohydrate	40.00
40.00	3	Cornstarch	40.00
6.00	4	Kollidon 90 F	6.00
30.00	5	Isopropanol	30.00
14.00	6	Kollidon CL	14.00
16.00	7	Talc	16.00
2.00	8	Aerosil 200	2.00
2.00	9	Calcium arachinate	2.00

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with item 5, dry, pass through an 0.8-mm sieve, mix with items 6 to 9, and press with low compression force.
2. Compress into 210-mg tablets using 9-mm biconvex punches.

Dimenhydrinate Tablets (50 mg), DC

Formulation

Dimenhydrinate, 50.0 g; Aerosil 200, 4.0 g; Ludipress, 140.0 g; Kollidon CL, 2.0 g; magnesium stearate, 1.5 g.

Manufacturing Directions

1. Mix dimenhydrinate with Aerosil 200, add the other components, sieve.
2. Press with low compression force at 202 mg.

Diphenhydramine and Pseudoephedrine Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
	1	Diphenhydramine hydrochloride	25.00
	2	Pseudoephedrine hydrochloride	60.00
	3	Cab-o-Sil	415.00
	4	Water	200.00

1. Diphenhydramine hydrochloride and pseudoephedrine hydrochloride are mixed in the water until thoroughly dissolved.
2. Cab-o-Sil M5 (silicon dioxide) is poured into a planetary mixer to which the dissolved drug solution is added and mixed at slow speed.
3. This is continued for 5 minutes until the solution and Cab-o-Sil are completely mixed.
4. The entire composition is dried in a forced hot air oven for 7 hours at 50°C.
5. The composition is dried to LOD 1%.
6. The dried material is then screened through a No. 30 U.S. standard mesh screen and compressed to give average weight of 1 g containing 50 mg diphenhydramine hydrochloride and 120 mg pseudoephedrine hydrochloride.

Diphenhydramine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
25.00	1	Diphenhydramine hydrochloride	25.00
150.00	2	Calcium phosphate (dibasic)	150.00
20.00	3	Starch (StaRX 1500)	20.00
QS	4	PVP	QS
QS	5	Alcohol, USP	QS
75.00	6	Stearic acid (fine powder)	75.00
25.00	7	Cellulose (microcrystalline)	25.00
QS	8	Purified water, USP	QS

Manufacturing Directions

1. In a planetary mixer, charge diphenhydramine hydrochloride, calcium phosphate dibasic, and starch.
2. Mix for 5 to 10 minutes.
3. In a separate mixer, charge PVP, alcohol, and water in the ratio 1:50:40.
4. Moisten this mixture with solution from the previous step to granulate.
5. Record the volume used.
6. Pass the wet mass through a No. 14 mesh screen on dryer trays.
7. Dry the granulation at 48.8°C to 54.4°C or use a fluid-bed dryer.
8. Pass the dried granules through a No. 20 mesh screen.
9. Charge dried granules to twin-shell blender and add stearic acid (previously passed through No. 30 mesh screen) and microcrystalline cellulose.
10. Mix for 5 to 7 minutes.
11. Compress to 300-mg tablets using a rotary press with 5/16-in standard concave punches.

Econazole Nitrate and Benzoyl Peroxide Antiacne Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
200.00	1	PEG-6 and PEG-32 and glyceryl stearate (Tefose 63)	200.00
30.00	2	Mineral oil	30.00
30.00	3	Apricot kernel oil PEG-6 esters (Labrafil® M 1944)	30.00
0.50	4	Sorbic acid	0.50
0.50	5	Sodium methyl paraben	0.50
724.00	6	Deionized water	724.00
5.00	7	Benzoyl peroxide	5.00
10.00	8	Econazole nitrate	10.00

Manufacturing Directions

1. Mix and heat items 1 to 6 together and bring temperature to 75°C.
2. Allow to cool while stirring.
3. Add items 7 and 8 at 30°C and mix well until uniform.

Econazole Nitrate and Benzoyl Peroxide Antiacne Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PEG-6 stearate, cetech-20, and steareth-20 (Tefose® 2000)	50.00
30.00	2	Mineral oil	30.00
20.00	3	Cetyl alcohol	20.00
0.70	4	Sodium methyl paraben	0.70
0.30	5	Sorbic acid	0.30
884.00	6	Deionized water	884.00
5.00	7	Benzoyl peroxide	5.00
10.00	8	Econazole nitrate	10.00

Manufacturing Directions

1. Mix and heat items 1 to 3 together and bring temperature to 75°C.
2. Allow to cool while stirring.
3. Mix items 4 to 6 and add to above while stirring.
4. Cool with stirring.
5. Add items 7 and 8 at 30°C while stirring.

Eucalyptol Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
80.00	1	Eucalyptol	80.00
40.00	2	Cremophor RH 40	40.00
QS	3	Preservative	QS
QS	4	Water	QS to 1 L

Manufacturing Directions

Mix eucalyptol and cremophor at 65°C, stir well, and slowly add the warm solution of item 3 to produce a clear or slightly opalescent, colorless liquid.

Eucalyptol Solution (8%)

Formulation

1. Eucalyptol, 8.0 g; Cremophor RH 40 [1], 4.0 g.
2. Preservative, QS; Water, 100 mL.

Manufacturing Directions

Mix eucalyptol and Cremophor at 65°C, stir well, and add slowly the warm solution II.

Eucalyptus and Mint Emulsion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
427.50	1	Distilled water	427.50
375.00	2	Eucalyptamint	375.00
70.00	3	Sodium stearoyl lactylate (Pationic® SSL)	70.00
35.00	4	PEG-20 hydrogenated lanolin (Supersat ANS4)	35.00
17.50	5	Ritasynt IP	17.50
80.00	6	Cetearyl alcohol, polysorbate 60, PEG-15 stearate, and steareth-20 (Ritachol 1000)	80.00

Manufacturing Directions

1. Heat item 1 to 71°C.
2. Combine rest of the ingredients in another container and heat to 71°C.
3. Slowly add water at 71°C and mix for 1 hour.
4. Cool the mixture to 35°C to 45°C and fill.

Eucalyptus and Mint Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
160.00	1	Menthol	160.00
40.00	2	Eucalyptus	40.00
800.00	3	Anhydrous lanolin, USP	800.00

Manufacturing Directions

1. Mix lanolin until melted (approximately at 50°C), add remaining ingredients, and mix for 1 hour.
2. Fill hot.

Ferrous Fumarate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Ferrous fumarate	200.00
295.00	2	Ludipress	295.00
5.00	3	Magnesium stearate	5.00

Manufacturing Directions

1. Mix all components. Pass through a 0.8-mm sieve.
2. Press with low compression force.
3. Compress into 509-mg tablets using 12-mm biplanar punches.

Ferrous Sulfate, Manganese Sulfate, and Copper Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
65.00	1	Anhydrous ferrous sulfate	65.00
3.50	2	Manganese sulfate	3.50
0.16	3	Copper sulfate	0.16
70.00	4	Ludipress	70.00
10.00	5	Kollidon 30	10.00
2.00	6	Magnesium stearate	2.00
3.00	7	Aerosil 200	3.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with high compression force.
2. Compress into 149-mg tablets using 8-mm biplanar punches.

Ferrous Sulfate Oral Solution

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Quantity/L (g)
75.00	1	Ferrous sulfate[a]	125.00
294.00	2	Sucrose	490.00
147.00	3	Maltitol solution (Lycasin® 80/55)	245.00
0.30	4	Citric acid (monohydrate)	0.50
0.90	5	Citric acid (monohydrate)	1.50
0.06	6	FD&C yellow dye No. 6 (sunset yellow FCF)	1.00
3.12	7	Guarana flavor 12144-33	5.20
0.33	8	Potassium sorbate	0.55
0.30	9	Saccharin sodium	0.50
–	10	Purified water	QS to 1 L

[a]Equivalent to 15 mg iron (Fe).

Manufacturing Directions

1. Bubble nitrogen throughout the process.
2. Check and record pH of the purified water (limit: 5.0–6.5).
3. Collect 166.67 g of purified water in mixer.
4. Heat to 90°C to 95°C for 10 minutes.
5. Add item 8. Stir to dissolve to a clear solution.
6. Add item 2. Stir to dissolve to a clear solution.
7. Add item 3. Stir for 10 minutes and cool to 30°C to 35°C.
8. Dissolve item 4 in 10 g of purified water (30–35°C) and add to first step.
9. Dissolve item 9 in 10 g of purified water (30–35°C) and add to first step.
10. Dissolve item 5 in 273.33 g of purified water (30–35°C).
11. Then add item 1 to the clear solution and dissolve slowly without aeration.
12. Add to mixer.
13. Dissolve item 6 in 10 g of purified water (25–30°C) and add to first step.
14. Add item 7 to first step.
15. Mix at low speed for 10 minutes.
16. Bring volume up to 1 L with purified water.
17. Check and record pH (target: 2.20, limit: 1.95–5.15).
18. Filter the drops with recirculation.
19. Transfer the filtered drops to a storage vessel under an N_2 blanket.
20. Use the nitrogen blanket in the tank throughout the storage and filling period.

Ferrous Sulfate Oral Syrup

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
200.00	1	Ferrous sulfate[a]	40.00
3350.00	2	Sucrose	670.00
750.00	3	Maltitol solution (Lycasin® 80/55)	150.00
4.16	4	Citric acid (monohydrate)	833.20
8.33	5	Citric acid (monohydrate)	1.66
0.50	6	Color	0.10
15.50	7	Flavor	3.10
–	8	Purified water	QS to 1 L

[a]Equivalent to 40 mg elemental iron.

Manufacturing Directions

1. Bubble nitrogen throughout the process.
2. Heat 300 g of purified water to 95°C.
3. Add item 2 while stirring at low speed.
4. Dissolve to clear solution by stirring at 95°C.
5. Add item 3.
6. Stir at low speed and cool to 25°C to 30°C.
7. Dissolve item 4 in 17 g of item 8 and add to the first step.
8. Dissolve item 5 in 180 g of purified water in a separate stainless steel container.
9. Then add item 1 to the clear solution and dissolve slowly without aeration.
10. Add to first step.
11. Dissolve item 6 in 16 g of purified water and add to the first step.
12. Add item 7 to the first step.
13. Mix at low speed for 10 minutes.
14. Bring volume up to 1 L with purified water.
15. Check and record pH (limit: 2–5).
16. Filter the syrup at 1.5 bar.
17. Recirculate approximately 100 to 150 mL of syrup.
18. Use a nitrogen blanket in the tank throughout the storage period.

Ferrous Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Anhydrous ferrous sulfate	203.00
185.00	2	Ludipress	185.00
15.00	3	Kollidon VA 64	15.00
4.00	4	Magnesium stearate	4.00
4.00	5	Talc	4.00
3.00	6	Aerosil 200	3.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press to tablets with medium compression force.
2. Compress into 413-mg tablets using 8-mm biplanar punches.

Fir Needle Oil Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
30.00	1	Fir needle oil (Frey & Lau)	30.00
50.00	2	Camphora	50.00
60.00	3	Cremophor RH 40	60.00
403.00	4	Ethanol (96%)	403.00
457.00	5	Water	457.00

Manufacturing Directions

1. Mix the active ingredients with Cremophor RH 40 and heat to 50°C to 60°C.
2. Add the ethanol to the well-stirred solution, then slowly add the warm water to produce a clear or slightly opalescent liquid.
3. The amount of Cremophor RH 40 required depends on the type of fir needle oil.

Folic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
5.00	1	Folic acid[a]	5.24
12.00	2	Maize starch (dried)[b]	12.00
5.26	3	Cellulose (microcrystalline) (Avicel PH102)	5.26
20.00	4	Cellulose (microcrystalline) (Avicel PH102)	20.00
1.50	5	Colloidal silicon dioxide (Aerosil 200)	1.50
66.00	6	Lactose (spray-dried)[c]	66.00
2.50	7	Talc (fine powder)	2.50
2.50	8	Stearic acid (fine powder)	2.50

[a]Extra folic acid is added (0.08 mg/tablet) to compensate water (water NMT 8.0%).
[b]LOD: NMT 4.5% when dried at 120°C for 4 hours.
[c]Meets the USP NF, except particle size distribution, as follows: minimum 98%, 250 μm; 30% to 60%, 100 μm; maximum 15%, 45 μm.

Manufacturing Directions

1. Folic acid must be protected from exposure to direct light.
2. Sift items 1, 2, and 3 through a Fitz mill (impact forward, high speed) and collect in a stainless steel drum.
3. Load the material into a blender and mix for 3 minutes.
4. Sift items 4 to 8 through a 500-μm sieve using a sifter and collect in a stainless steel drum.
5. Load this sieved material into a blender.
6. Mix for 5 minutes.
7. Unload the lubricated powder into a stainless steel drum. Check for small lumps or globules in the powder mix.
8. If required, pass the entire mass through a 500-μm sieve using a sifter and mix for 1 minute in a blender.
9. Compress into 1.15-g tablets (hardness: 3–7 kp) using 7-mm round flat punches.
10. For 1-mg tablets, compensate with lactose and compress as above.

Folic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
5.00	1	Folic acid	5.00
195.00	2	Ludipress	195.00
1.50	3	Magnesium stearate	1.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press into tablets using medium compression force.

   If the content uniformity does not meet the requirements, prepare a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation.
2. Compress into 213-mg tablets using 8-mm biplanar punches.

Foot Bath

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
200.00	1	Polysorbate 20	200.00
2.50	2	Menthol	2.50
10.00	3	Alpha-bisabolol	10.00
20.00	4	Disodium undecylenamido MEA-sulfosuccinate	20.00
20.00	5	Perfume (menthol compatible)	20.00
QS	6	Deionized water	QS to 1 L
QS	7	Preservative, color	QS

Manufacturing Directions

1. Predissolve menthol, alpha-bisabolol, and perfume in Polysorbate 20.
2. Add mixture to the water phase while stirring.
3. Stir until homogeneous and then fill.

Foot Freshener Cream

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
30.00	1	Alcohol and ceteareth-20 (Cosmowax® EM5483)	30.00
30.00	2	Isopropyl myristate (Crodamol® IPM)	30.00
5.00	3	Cetyl esters (Crodamol® SS)	5.00
20.00	4	Oleyl alcohol	20.00
5.00	5	Propylene glycol	5.00
5.00	6	Carbopol 980	5.00
QS	7	Deionized water	QS to 1 L
300.00	8	Ethanol (DEB100)	300.00
2.00	9	Triclosan (Irgasan® DP300)	2.00
0.50	10	Menthol	0.50
4.00	11	Triethanolamine 99 (to give pH 6–7)	~4.00

Manufacturing Directions

1. Preblend ethanol, irgasan, and menthol and warm to 50°C.
2. Heat water and oil phases separately to 70°C.
3. Add the water phase to the oil phase while stirring.
4. Stir to cool, adding the preblend at 60°C. Adjust pH.

Foot Mousse

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
300.00	1	Ethanol (DEB100)	300.00
1.00	2	Menthol	1.00
QS	3	Deionized water	QS
20.00	4	Undecyleneamide DEA and diethanolamine	20.00
5.00	5	Cetrimonium bromide	5.00
10.00	6	PEG-75 and water	10.00
QS	7	Perfume, preservative, color	QS

Manufacturing Directions

1. Dissolve menthol in ethanol.
2. Add remaining ingredients.
3. Pack into mechanical mousse applicator, such as the Kunststoff AG Supermatic foamer system, Airspray International BV jet foamers, or Calmar foamers.

Garlic Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
95.00	1	Calcium phosphate, dibasic	95.00
94.00	2	Lactose monohydrate	94.00
9.00	3	Kollidon 30	9.00
25.00	4	Water	25.00
100.00	5	Dried garlic powder	100.00
2.00	6	Magnesium stearate	2.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 3 and 4, pass through a 0.8-mm sieve, add items 5 and 6, and press with low compression force.
2. Compress 312 mg using 9-mm biconvex punches.

Garlic Extract + Thyme Extract + Vitamin C (300 mg+25 mg+100 mg)

Formulation

Garlic extract, granulated (Aflopa), 300 g; thyme extract, 25 mg; powder (Aflopa), 25 g; ascorbic acid, crystalline (BASF), 100 g; Kollidon CL, 14 g; Ludipress, 268 g; magnesium stearate, 7 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve and press to tablets with medium compression force at 714 mg.

Ginkgo Extract Tablets (40 mg)

Formulation

Ginkgo biloba extract, dry powder, 240 g; Aerosil (Biogen) 200, 1 g; Kollidon CL, 4 g; Ludipress, 203 g; magnesium stearate, 2 g.

Manufacturing Directions

Mix the ginkgo extract with Aerosil 200, add the other components, pass through a 0.8-mm sieve, and press to tablets with low compression force at 254 mg.

Glycerin Suppositories

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
1800.00	1	Glycerin (glycerol)	1800.00
0178.00	2	Sodium stearate	178.00
0099.00	3	Purified water	99.00

Manufacturing Directions

1. The suppository mass is manufactured at a temperature of 120°C.
2. Care must be taken to see that molten suppository mass does not accidentally spill on the person.
3. The inside of the vessel should not be touched with the bare hand as it is at a temperature of 120°C.
4. Sodium stearate powder is light and fluffy; avoid inhaling the dust.
5. Load item 1 into the mixer and heat to 120°C±2°C while stirring at low speed.
6. Load item 2 into the mixer containing item 1.
7. Mix until complete solubilization is achieved.
8. Cool to 105°C±2°C.
9. Add item 3 slowly to the mixer containing the mass while stirring.
10. Mix for 20 minutes.
11. Immediately transfer the hot mass to the heated storage vessel or heated vessel of a Sarong SAAS suppository-filling machine.
12. Check the temperature; it should be 105°C±2°C.
13. Fill weight: 2077 mg per suppository.

Glycerin Suppositories for Children

Bill of Materials			
Scale (mg/suppository)	Item	Material Name	Qty/1000 Suppositories (g)
900.00	1	Glycerin (glycerol) (0.06% excess)	900.50
089.00	2	Sodium stearate	89.00
049.50	3	Purified water	49.50

Manufacturing Directions

1. Fill weight: 1039 mg per suppository.
2. See manufacturing directions for glycerin suppositories.

Glycol Foam (Nonaqueous)

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Polawax A31	4.00
710.00	2	Propylene glycol	71.00
150.00	3	Ethanol DEB100	15.00

Manufacturing Directions

1. Dissolve Polawax in propylene glycol/ethanol.
2. Pack into containers and pressurize.
3. Ethanol may be omitted if desired.
4. In aerosol pack, 90% concentrate and 10% propellant 12/114 may be used.
5. Propylene glycol is a suitable vehicle for glycol-soluble medicaments.
6. The above formulation provides a mousse for such a system.

Guaifenesin Pseudoephedrine, Carbinoxamine, and Chlophedianol Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
20.00	1	Guaifenesin	20.00
400.00	2	Sucrose	400.00
240.00	3	Glucose liquid	240.00
120.00	4	Sorbitol solution	120.00
3.00	5	Saccharin sodium	3.00
2.50	6	Sodium benzoate (powder)	2.50
30.00	7	Pseudoephedrine hydrochloride	30.00
1.00	8	Carbinoxamine maleate	1.00
6.60	9	Chlophedianol hydrochloride	6.60
105.00	10	Dye red E123 (Amaranth)	0.105
3.75	11	Dye blue FD&C No. 1	3.75 mg
QS	12	Acid, hydrochloric	QS
50.00	13	Menthol crystals	50.00 mg
2.75	14	Flavors	2.75
65.00	15	Orange oil terpeneless	65.00 mg
5.66	16	Alcohol (190 proof)	5.66
GS	17	HyFlo filter aid	0.526
QS	18	Purified water	~420.00

Manufacturing Directions

1. Charge 260 mL purified water into a suitable tank.
2. Begin heating water to 70°C to 80°C while adding guaifenesin and sucrose with stirring.
3. Continue stirring to dissolve ingredients.
4. Remove heat. Add glucose liquid and sorbitol to solution from step above with stirring.
5. Add saccharin sodium, sodium benzoate, pseudoephedrine hydrochloride, carbinoxamine maleate, and chlophedianol hydrochloride to solution from preceding step.
6. Stir well to dissolve all ingredients.
7. Dissolve dye red E123 and dye blue FD&C No. 1 in 10 mL warm purified water.
8. Add dye solution to solution from preceding step with stirring.
9. Cool solution to 30°C to 35°C.
10. QS to 975 mL using purified water. Mix well.
11. Adjust to pH 4.25 (range: 4.0–4.5) with hydrochloric acid (approximately 0.65 g/L of drops).
12. Stir well after each addition of acid.
13. Dissolve menthol, flavors, and orange oil in alcohol. Add mixture to solution from previous step with good stirring.
14. Stir the solution slowly for 2 hours.
15. Allow to stand overnight to cool and remove entrapped air.
16. QS to 1 L with purified water. Stir well.
17. Add HyFlo filter aid to solution and mix well.
18. Recirculate through filter press or equivalent until sparkling clean.

Guaifenesin Tablets

Manufacturing Directions

1. Inner tablet: guaifenesin, 175.0 mg; microcrystalline cellulose, 35.1 mg; crospovidone, 35.0 mg; PVP, 7.3 mg; talc, 2.3 mg; zinc stearate, 2.3 mg; total, 257 mg.
2. Outer tablet: guaifenesin, 425.0 mg; hydroxypropylmethylcellulose K4M, 139.9 mg; stearic acid, 30.0 mg; zinc stearate, 5.4 mg; total, 600.3 mg.
3. The inner tablet is made by oscillating guaifenesin and half of the PVP through a 30-mesh screen.
4. The blend is then transferred to a pharmaceutical grade blender and mixed until it is of uniform consistency.
5. It is then granulated with PVP that had been previously dissolved in a sufficient amount of purified water to make a solution of approximately 8% to 12% of PVP.
6. This mixture is discharged and dried in a forced air oven at 40°C until the water content is less than 1%.
7. The dried granulation is then oscillated through a 12-mesh screen and returned to the blender.
8. The remaining PVP, microcrystalline cellulose, and talc are added to this dried granulation and mixed until it is of uniform consistency.
9. Finally, zinc stearate is added and the mixture is mixed until it is of uniform consistency.
10. This mixture is then compressed into inner tablets using a standard tableting press.
11. The outer tablet is made by first passing guaifenesin through an oscillator equipped with a 30-mesh screen.
12. After this step, guaifenesin is transferred to a blender and hydroxypropylmethylcellulose K4M and stearic acid are added to it. It is mixed until uniform.
13. Zinc stearate is added and the mixture is blended until uniform.
14. The mixture of ingredients that comprise the outer tablet is compressed around the already formed inner tablet on a standard compression coating tablet press.

Guaifenesin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g) Percent (w/w)
69.77	1	Guaifenesin USP	69.77
16.00	2	Starch 1500	16.00
9.48	3	Microcrystalline cellulose NF	9.48
4.00	4	Starch 1500	4.00
0.50	5	Stearic acid NF	0.50
0.25	6	Magnesium stearate	0.25
100.00	7	Total	100.00

Manufacturing Directions

1. Granulation: Items 1 and 2 are preblended for 2 minutes prior to granulating with water to appropriate moisture.
2. Wet mass for 3 minutes.
3. Size the granulation.
4. Lubricant is passed through a 60-mesh screen prior to blending.
5. Colloidal silicon dioxide is passed through a 30-mesh screen along with the MCC.
6. All the ingredients, except the lubricant, are blended for 10 minutes.

Hemorrhoid Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Lanolin alcohol (Ivarlan 3310)	20.00
448.00	2	Petrolatum	448.00
450.00	3	Petrolatum amber	450.00
30.00	4	Shark liver oil	30.00
10.00	5	Live yeast cell derivative (Biodyne's TRF)	10.00
10.00	6	Deionized water	10.00
20.90	7	Lanolin	20.90
1.00	8	Thyme oil	1.00
0.10	9	Phenyl mercuric nitrate	0.10

Manufacturing Directions

1. Mix and heat items 1 to 4 to 70°C. Cool to 50°C and hold.
2. Separately combine items 5 to 7 and heat to 40°C and mix until homogenous dispersion is achieved. With rapid mixing, add this mixture to previous mixture. Mix again and cool to 40°C. Add items 8 and 9.
3. Continue mixing while cooling to 35°C.

Herbal Hemorrhoid Tablet

Manufacturing Directions

1. Initially genera *Glycyrrhizae radix*, *Rhei rhizoma*, *Ephedrae herba*, *Moutan radicis cortex*, *Menthae herba*, *Pinelliae rhizoma*, *Pasoniae radix*, *Acontii tuber*, *Corni fructus*, gypsum, *Ginseng radix*, and *Pelladendri radix*, respectively, are washed with water to remove sand, clay, dust, and the like.
2. These natural substances are cleaned and dried to a moisture content of approximately 5%.
3. 168 g of *G. radix*, 104 g of *R. rhizoma*, 104 g of *E. herba*, 168 g of *M. radicis cortex*, 104 g of *M. herba*, 168 g of *P. rhizoma*, 56 g of *P. radix*, 56 g of *A. tuber*, 56 g of *C. fructus*, 168 g of *G. radix*, and 104 g of *P. radix* are cut into a particle size of approximately 1 cm and mixed together.
4. To the mixture mentioned above are added, 104 g of *Testudinis carapax*, 56 g of *Natrii sulfas*, 168 g of gypsum, 56 g of cinnabaris, and 256 g of talcum.
5. Thereafter, this mixture is placed in an extractor having an aromatic vapor collector.
6. 12 L of water are added to approximately 2 kg of the mixture in the extractor.
7. The mixture in the extractor is heated up to approximately 80°C for 1 hour and then extracted.
8. The aqueous mixture is filtered first in a centrifugal separator and then is filtered again in a microfilter.
9. The aromatic vapor distilled from the aqueous mixture is condensed and added as an aromatic liquid to the filtrate.
10. The filtrate is evaporated through an automatic vacuum evaporator to a moisture content of approximately 30% to produce an extract, which is useful as an antihemorrhoidal composition in extract form.
11. At this time, the concentrated liquid is dried through a dry sprayer to produce a granulated formulation, a tablet formulation, a pill formulation, an ointment formulation, or the like, for use as an antihemorrhoid medicine.

Horsetail Extract Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
450.00	1	Horsetail extract (powder)	456.00
14.00	2	Kollidon VA 64	14.00
5.00	3	Lutrol F 68	5.00
QS	4	Isopropanol	~120.00
14.00 g	5	Kollidon CL	14.00
QS	6	Magnesium stearate	QS

Manufacturing Directions

1. Granulate the extract (item 1) with solution of items 2 to 4, dry, pass through a 0.8-mm sieve, mix with items 5 and 6, and press with high compression force.
2. Compress 489 mg using 12-mm biplanar punches.

Hydrocortisone Aqueous Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	Hydrocortisone acetate	10.00
100.00	2	Lutrol E 400	100.00
50.00	3	Cremophor RH 40	50.00
5.00	4	Carbopol 940 (Goodrich)	5.00
495.00	5	Water	495.00
QS	6	Preservative	QS
260.00	7	Water	260.00
8.00	8	Triethanolamine	8.00
—	9	Water	7.20

Manufacturing Directions

1. Heat item 6 in item 7 to 80°C, prepare a solution of items 3 and 4 in item 5, and add to above solution of preservative.
2. Add and suspend item and mix.
3. Prepare a solution of item 8 in item 9 and add to the above solution at 70°C and cool to form gel.

Hydrocortisone Aqueous Gel

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Hydrocortisone acetate	1.00/1.00
150.00	2	Cremophor A 25	–15.00
20.00	3	Cremophor RH 40	5.00/20.00
QS	4	Preservative	QS
640.00	5	Water	26.00/64.00

Manufacturing Directions

1. Suspend item 1 in a mixture of items 2 and 3 at 70°C.
2. Prepare solution of item 4 by heating item 5 to 70°C and add it slowly to the hot item 4.
3. Continue to stir until the gel is cool to form clear, colorless gels.

Hydrocortisone Cream

Bill of Materials			
Scale (g /100 g)	Item	Material Name	Qty/kg (g)
1.00	1	Hydrocortisone, micronized (3% excess)	10.30
6.00	2	Propylene glycol	60.00
0.10	3	Chlorocresol	1.00
5.00	4	Mineral oil (liquid paraffin)	50.00
2.00	5	Poloxyl 20 cetostearyl ether (Cetomacrogol 1000)	20.00
8.00	6	Cetostearyl alcohol	80.00
18.00	7	Petrolatum (white soft paraffin)	180.00
0.29	8	Monobasic sodium phosphate	2.90
0.035	9	Propyl paraben	0.35
0.10	10	Methyl paraben	1.00
59.60	11	Purified water	596.00

Manufacturing Directions

1. Load 10 g of item 5 and items 4, 6, and 7 in fat-melting vessel.
2. Heat to 70°C to 75°C while stirring.
3. Cool down the temperature to 65°C.
4. Maintain temperature at 65°C to 70°C.
5. Heat item 11 to 90°C in mixer.
6. Dissolve items 9 and 10 to a clear solution by stirring.
7. Cool down the temperature to 65°C.
8. Maintain temperature to 65°C to 70°C.
9. Add 10 g of item 5 and items 3 and 8 to the parabens solution to dissolve.
10. Mix for 15 minutes.
11. Maintain temperature at 65°C to 70°C.
12. Transfer oil phase to the aqueous phase in mixer vessel through mesh under vacuum while stirring at manual mode (10 rpm) at a temperature of 60°C.
13. Homogenize at high speed.
14. Maintain temperature of 60°C.
15. Vacuum at 0.4 bar for 10 minutes.
16. Cool temperature to 45°C.
17. Mix item 1 in 48 g of item 2 in a separate container at 45°C using homogenizer to make slurry.
18. Add to the dispersed phase while mixing at 10 rpm and keep temperature at 45°C.
19. Rinse the container with 12 g of item 2 and add to the dispersed phase.
20. Mix and homogenize under vacuum at 0.4 bar for 10 minutes, low speed (10 rpm), at a temperature of 45°C.
21. Cool the temperature to 30°C while mixing at 10 rpm in automode under a vacuum of 0.4 bar.

Hydrocortisone Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
70.00	1	Cetylstearyl alcohol	70.00
15.00	2	Cremophor A 6	15.00
15.00	3	Cremophor A 25	15.00
120.00	4	Liquid paraffin	120.00
2.00	5	Paraben	2.00
688.00	6	Water	688.00
80.00	7	Propylene glycol	80.00
10.00	8	Hydrocortisone	10.00

Manufacturing Directions

1. Heat the mixture of items 1 to 5 and the water separately to approximately 80°C.
2. Add the water to the obtained solution of items 1 to 5 with rigorous stirring.
3. Heat items 7 to 8 until the active ingredient is dissolved, mix with above, and continue to stir while cooling to room temperature to produce a white cream.

Hydrocortisone Ethanolic Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Hydrocortisone acetate	5.00
60.00	2	Cremophor RH 40	60.00
9.00	3	Triethanolamine	9.00
76.00	4	Water	76.00
600.00	5	Ethanol, 96%	600.00
5.00	6	Carbopol 940 (Goodrich)	5.00
245.00	7	Water	245.00

Manufacturing Directions

Prepare solution of items 6 and 7 and mix slowly with solution of items 1 to 5 to produce a clear, colorless gel.

Hydrocortisone Ointment

Bill of Materials			
Scale g /100 g	Item	Material Name	Qty/kg (g)
1.00	1	Hydrocortisone, micronized (6% excess)	10.60
91.50	2	Petrolatum (white soft paraffin)	915.00
7.00	3	Mineral oil (liquid paraffin)	70.00
0.50	4	Sorbitain sesquioleate (Arlacel 83)	5.00

Manufacturing Directions

1. Melt items 2 and 4 at 75°C in fat-melting vessel.
2. Start heating mixer vessel to 75°C.
3. Transfer molten items from first step to mixer through stainless steel mesh under vacuum at 0.4 to 0.6 bar.
4. Start mixer at 10 rpm in manual mode.
5. Cool down to 50°C.
6. Disperse item 1 in 60 g of item 3 using a spatula in a water bath at 60°C.
7. Homogenize for 6 minutes using homogenizer.
8. Add this to mixer while mixing.
9. Rinse the homogenizer and container with 10 g of item 3 and transfer the rinsings to the mixer.
10. Homogenize the dispersion under vacuum at 0.4 to 0.6 bar while stirring at 10 rpm in homogenizer at high speed for 10 minutes.
11. Cool the temperature to 30°C, using a mixer speed 10 rpm and vacuum of 0.4 to 0.6 bar in automode.
12. Transfer the ointment to stainless steel container.

Hydrogen Peroxide Bleaching Dentifrice Paste

Manufacturing Directions

1. Add to 50 g purified water, 1.5 g of emulsifier Carbopol 934/PVP in 75:25 ratio and dissolve with gradual stirring.
2. To the mixture, 20 mL of hydrogen peroxide (50%) are added and mixed for additional 5 to 10 minutes.
3. The acid composition is then adjusted between pH 5.5 and 6.5 with 10% NaOH.
4. The composition thickens to a gel and set aside.
5. In a separate vessel, 210 g of methyl methacrylate crosspolymer GMX-0610 obtained from Perspere Corp is added.
6. In another separate vessel, continuous phase of the invention is prepared comprising the following ingredients: weight%, sodium fluoride, 1.05; propylene glycol, 24.10; sodium lauryl sulfate, 5.04; water, 43.40; vinyl pyrrolidone/acrylic acid*, 1.02; hydroxyethyl cellulose, 2.01; glycerin, 18.85; sodium saccharine, 0.47; flavor, 2.76; sodium benzoate, 0.55; benzoic acid, 0.06; sodium EDTA, 0.14; sodium hydroxide (10% solution), 0.55; *dry blend copolymer containing 25% vinyl pyrrolidone and 75% carbopol.
7. The vinyl pyrrolidone in the mixture delays the solubility of the emulsion further than carbopol alone.
8. After the bleaching composition (step 1) has been prepared to desired consistency, 50 g of this composition is added to 50 g of the water insoluble abrasive suspension (step 2) and the intimate mixture of the two immiscible phases are dispersed in each other and then, with the aid of the colloidal mill, agitated until extremely fine homogeneous dispersion is obtained.
9. 100 g of the dispersion so obtained is then added to 50 g of the continuous phase (step 3) and the two phases mixed in a colloidal mill and the resultant composition comprised the discontinuous phases (step 1) dispersed homogenously throughout the continuous phase (step 2) and (step 3) of the present invention.
10. The final formulation is expressed as weight in percentage as follows: water, purified, 15.75; methyl methacrylate crosspolymer GMX-0610, 53.71; hydrogen peroxide,

10.00; Carbopol 934, 0.37; hydroxyethyl cellulose, 0.73; sodium fluoride, 0.38 (0.17% F ions); sodium lauryl sulfate, 1.83; propylene glycol, 8.75; glycerin, 6.84; sodium saccharine, 0.17; sodium benzoate, 0.20; benzoic acid, 0.02; sodium EDTA, 0.05; flavor, 1.00; sodium hydroxide (10%), QS (pH 6.5), 0.20.

11. Carbopol in this composition sufficiently retards the dissolution of the emulsed hydrogen peroxide to allow the abrasive agent methyl methacrylate crosspolymer GMX-0610 to remove the dental plaque and pellicles from the enamel surface and thus allow the bleaching active hydrogen peroxide to diffuse through the plaque-free enamel with ease.

Ibuprofen Fast Dissolve Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Ibuprofen coated	121.90
	2	Citric acid	11.00
	3	Magnasweet 135	3.90
	4	Aspartame	6.50
	5	Cherry flavor	7.80
	6	Croscarmellose sodium	39.00
	7	Silicon dioxide	1.95
	8	Magnesium stearate	3.25
	9	Fast-dissolving granulation (see below)	457.90

Manufacturing Directions

1. Fast-dissolving granulation is made by combining 400 g of melted PEG-900 with fructose powder (100 g) in a planetary mixer (low shear mixer) and mixed until the granules formed.
2. The granulations are allowed to cool, then are screened.
3. Ingredients are screened, then mixed in a V-blender.
4. Tablets are compressed (653.7 mg) at 600 lb (approximately 2.7 kN).
5. The tablets have hardness of 0.2 to 0.5 kp and disintegrate in less than 15 seconds.

Ibuprofen-Coated Fast-Crumbling Granule Tablet

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
200.00	1	Ibuprofen	200.00
16.00	2	Sodium croscarmellose (AGG)	16.00
27.50	3	Aspartame	27.50
12.20	4	Precipitated silica	12.20
35.00	5	Ethyl cellulose	35.00
8.00	6	Hypermellose	8.00
1.33	7	Sodium (AGM) croscarmellose	1.33
	8	Pharmacoat 606	

Manufacturing Directions

1. A suspension is obtained by mixing ethyl cellulose, 80% precipitated silica, and 30% aspartame in ethyl alcohol, until a homogeneous suspension is obtained.
2. The powder mixture consisting of ibuprofen, item 7, 70% aspartame and 20% precipitated silica is then fluidized.
3. The granulation is then started by spraying the mixture for approximately 15 to 20 minutes at a spraying rate of 25 g/min and a suspension atomization pressure of 0.8 bar.
4. The actual coating is then performed by spraying the remainder of the mixture over approximately 1 hour 30 minutes at a spraying rate of 15 to 20 g/min and a suspension atomization pressure of 1.5 bar.
5. 15% of the mixture is sprayed during the granulation step, the remainder to 100% being sprayed during the coating step.
6. The granules obtained are then formulated as fast-crumbling multiparticulate tablets, the composition of which is as follows: coated granules, 300 mg; mannitol, 344 mg; sodium croscarmellose, 21 mg; precipitated silica, 7 mg; aspartame, 20 mg; mint flavoring, 4 mg; magnesium stearate, 4 mg.

Ibuprofen Pediatric Suspension

Bill of Materials			
Scale (mg/5mL)	Item	Material Name	Qty/L (g)
100.00	1	Ibuprofen, low-density[a]	20.00
3000.00	2	Sucrose	600.00
10.00	3	Sodium benzoate	2.00
5.00	4	Saccharin sodium	1.00
5.00	5	Edetate disodium (sodium EDTA)	1.00
500.00	6	Glycerin (glycerol)	100.00
500.00	7	Sorbitol (70% solution)	100.00
10.00	8	Xanthan gum (Keltrol-F)	2.00
20.00	9	Microcrystalline cellulose (Avicel RC-591)	4.00
5.00	10	Polysorbate 80 (Tween 80)	1.00
8.50	11	Citric acid	1.70
1.35	12	FD&C red No. 40	0.27
7.50	13	Mixed fruits flavor	1.50
5.00	14	Strawberry flavor	1.00
QS	15	Purified water	QS to 1 L

[a]Meets USP criteria with the following additional requirements: 100% particle size less than 50 μm and tapped density of 0.3 to 0.4 g/mL.

Manufacturing Directions

1. Heat 302 g of item 15 to 90°C and dissolve item 2 while mixing in mixer.
2. Cool to approximately 50°C.
3. Add items 3, 4, 5, 7, and 11 to mixer while mixing and dissolve.
4. Filter the syrup through Seitz Supra 2600 filters in clean stainless steel tank.
5. In a clean stainless steel vessel, dissolve item 10 in 35 g of item 15 (40°C).
6. Add item 1 slowly while mixing with stirrer.
7. Mix for 30 minutes to make uniform dispersion. *Caution*: Avoid excessive foaming.
8. Disperse items 8 and 9 in item 6 in a clean and dry stainless steel container using stirrer.
9. Add 75 g of hot item 15 (70–90°C) at once while mixing.
10. Mix for 20 minutes to make a homogeneous smooth mucilage.
11. Add approximately 500 g syrup, ibuprofen dispersion, and mucilage to the mixer.
12. Rinse the containers of ibuprofen dispersion and mucilage with 50 g of item 15 (40°C).
13. Add the rinsings to the mixer.
14. Set the mixer: temperature, 25°C, speed, 18 rpm; and manual mode vacuum, 0.5 bar.
15. Mix for 3 minutes at low homogenizer speed.
16. Mix for 2 minutes at high homogenizer speed. Check the suspension for uniformity of dispersion.
17. Homogenize for additional 3 minutes at high speed, if required.
18. Add the balance of the syrup (approximately 507.6 g) from previous step to the mixer.
19. In a separate container, dissolve item 12 in 6 g of cooled item 15 (40°C) and transfer to the mixer.
20. Add items 13 and 14 to the mixer.
21. Set the mixer: temperature, 25°C; speed, 18 rpm; manual mode vacuum, 0.5 bar.
22. Mix for 15 minutes.
23. Mix for 5 minutes at homogenizer low speed.
24. Mix for 5 minutes at high homogenizer speed.
25. Check the suspension for uniformity.
26. Adjust the final volume to 1 L by using purified water.

Ibuprofen Chewable Tablets

Manufacturing Directions

1. PVAP and PVP-K90, equivalent to a 2:1 weight ratio, are dissolved in minimum volumes of an aqueous ammonium hydroxide solution (28% v/v) and water, respectively, and then mixed.
2. To the resulting mixture, ibuprofen, equal to the amount of PVAP used, is dissolved and then 0.1N HCl solution is added dropwise until the pH of the solution is 1.
3. The white solid precipitate is filtered, washed with water, and then vacuum dried.
4. The entrapped granules containing 39.06% ibuprofen are used in the preparation of tablets.
5. Appropriate amounts of the granules and the cherry vehicle, corresponding to 200 mg of ibuprofen per 668 mg of tablet, are accurately weighed and then mixed and tablets compressed.

Ibuprofen Sustained-Release Bilayer Tablets

Manufacturing Directions

1. Immediate-Release Layer Composition
    1. Part I: Ibuprofen USP, 160.0 mg; microcrystalline cellulose NF, 32.0 mg (Avicel PH 101); starch NF, 32.0 mg; pregelatinized starch NF (Starch 1500), 16.0 mg; sodium starch glycolate NF, 6.4 mg.

2. Part II: Hydroxypropylmethylcellulose 2910 USP (Methocel E-5), 1.6 mg; purified water USP, QS.
3. Part III: Sodium starch glycolate NF, 1.6 mg; (Explotab) colloidal silicon dioxide NF, 0.8 mg; total, 250.4 mg.
4. Weigh the components of part I and preblend them in a high shear mixer (Fielder: impeller speed of approximately 118 rpm for 3 minutes).
5. Prepare the granulating agent (part II) by dissolving the hydroxypropylmethylcellulose 2910 USP into the purified water USP (a ratio of 3.2 g of hydroxypropylmethylcellulose to 200 g water).
6. Deliver the granulating agent to the powders of part I in the high shear mixer.
7. Granulate the mixture for 20 minutes (Fielder: impeller speed of approximately 118 rpm).
8. Remove the completed wet granulation from the high shear mixer and load into the product bowl of a fluid-bed apparatus (e.g., Aeromatic or Glatt).
9. With an inlet air temperature of approximately 60°C, dry the granulation to a moisture level of 0.5% to 1.1% as determined by LOD (e.g., Computrac). The wet granulation can also be dried on trays in drying ovens.
10. Sieve the dried granulation (e.g., Glatt Quick Sieve: Stator No. 3, Screen No. 1, 5 mm, 1000 rpm). Other machines such as a Fitzpatrick Communition Mill can be used.
11. Blend the sieved and dried granulation with the powders of part III using a suitable mixer such as a twin-shell, ribbon, or planetary mixer.

2. Sustained-Release Layer
   1. Povidone USP (Plasdone K 29/32), 14.7 mg; alcohol USP and purified water USP (QS); 1:1 mixture.
   2. Part III: pregelatinized starch NF (Starch 1500 LM), 8.0 mg; microcrystalline cellulose NF (Avicel PH101), 7.3 mg; magnesium stearate NF, 5.0 mg; colloidal silicon dioxide NF (Cab-O-Sil), 5.0 mg. total, 523.3 mg; total tablet weight, 773.7 mg.
   3. Weigh the components of part I and preblend them in a high shear mixer (Fielder: impeller speed of approximately 250 rpm for 1 minute).
   4. Prepare the granulating agent (part II) by dissolving Povidone USP in a 1:1 mixture of alcohol USP and purified water USP (a ratio of 12.25 g of povidone to 100 g of alcohol/water).
   5. Spray the granulating agent at a rate of 600 mL/min onto part I in the high shear mixer.
   6. Granulate the mixture for 1 minute after the addition of part II (Fielder: impeller speed of approximately 250 rpm).
   7. Remove the completed wet granulation from the high shear mixer and load it into the product bowl of a fluid-bed apparatus (e.g. Aeromatic or Glatt).
   8. With an inlet air temperature of approximately 60°C, dry the granulation to a moisture level of 0.3% to 0.8% as determined by LOD (e.g., Computrac).
   9. The wet granulation can also be dried on trays in drying ovens.
   10. Sieve the dried granulation (Fitzpatrick Communition Mill, Model D6: medium speed, knives forward, 0.093 screen). Other machines such as Glatt Quick Sieve can also be used.
   11. Blend the sieved and dried granulation with the powders of part III using a suitable mixer such as a twin-shell, ribbon, or planetary mixer.
3. Compression of Tablets or Caplets
   1. Load the granulation of the immediate-release layer into one hopper and the granulation of the sustained-release layer into the second hopper of a bilayer tableting machine (e.g., Stokes Versapress).
   2. Compress tablets using 0.749 × 0.281 × 0.060 extra deep concave capsule-shaped tooling. (Tablet tooling of other shapes such as oval or round can also be used.)
   3. The sustained-release layer has a target weight of 523.3 mg, and the immediate-release layer has a target weight of 250.4 mg. Ideal tablet hardness immediately after compression is 11 to 12 kp.

Ibuprofen Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Ibuprofen	200.00
88.00	2	Maize starch	88.00
30.00	3	Maize starch	30.00
12.80	4	Maize starch (dried)[a]	12.80
1.60	5	Stearic acid (fine powder)	1.60
–	6	Purified water	144.00

[a]LOD: NMT 4.5% when dried at 120°C for 4 hours.

Manufacturing Directions

1. Pass item 3 through a 250-μm sieve using a sifter.
2. Prepare a slurry of item 3 with 10.67 g of cold item 6 (25–30°C) in a stainless steel container.
3. Pour the slurry into a vessel containing 37.33 g of hot item 6 (70–90°C).
4. Heat to 80°C to 90°C and mix until mixture swells and becomes translucent.
5. Cool to 50°C.
6. Check weight (theoretical weight, 58.00 g). If required, adjust with hot purified water. Record the quantity of extra water added.
7. Pass items 1 and 2 through sifter using 250-μm sieve.
8. Load it into a mixer (if required, grind item 1 through a 1-mm sieve).
9. Mix the powder for 15 minutes at high speed.
10. Add binding solution to the dry powder in the mixer and mix for 15 minutes at high speed. Check for satisfactory wet mass.
11. Pass the wet mass through a Fitz mill using sieve 24207, knives forward, medium speed.
12. Collect and spread the granules onto the trays, one-third the thickness of the tray.
13. Load the trolleys into the oven and dry the granules at 55°C for 36 hours.
14. After 12 hours of drying, stir the granules in the trays and change the position of the trays for uniform drying.
15. Check the moisture of the dried granules. The limit NMT is 2.5%. Dry further if required to obtain moisture content of 2.5%.
16. Check the weight of dried granules (theoretical weight = 318.00 g).
17. Pass the dried granules through a 1.5-mm sieve using a granulator. Collect in a stainless steel drum and add it to the blender.
18. Pass items 4 and 5 through a 250-μm sieve using a sifter.
19. Add the sieved material to the granules in a blender and mix for 5 minutes.
20. Compress 330 mg in 10-mm convex punches at 4 to 9 kp.
21. Coat the tablets using one of the PVP coating solutions provided in the appendix or use the sugar-coating formulation given below.

Bill of Materials: Sugar Coating			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
7.06	1	Sandrac varnish (WMR)	7.06
3.33	2	Povidone (PVP K-25)	3.33
1.86	3	Povidone (PVP K-25)	1.86
175.85	4	Sucrose	175.85
0.16	5	Titanium dioxide	0.16
1.20	6	Polishing emulsion	1.20
1.33	7	Talc (fine powder)	1.33
–	8	Purified water	87.10

22. Load the tablets into the pan.
23. Start the tablets rolling with the exhaust on and air supply off.
24. Pour the item 1 solution onto the rolling tablets and allow the tablets to roll, using hand agitation if required, permitting the solution to spread well over the tablet bed.
25. Permit the tablets to roll until tack develops, at which point item 7 should be quickly sprinkled over the tablets.
26. Allow to roll freely for 2 minutes at 45°C.
27. Do not roll too long, as the seal may be worn from the tablet edges.
28. After two minutes of rolling, jog the tablets every 1 minute over a period of 15 minutes with exhaust and drying air on at 45°C.
29. Continue jogging for a further 15 minutes. Jog every 3 minutes with exhaust and drying air temperature on at 45°C.
30. Dissolve 2.40 g of item 2 in 28.80 g of item 8.
31. Apply a half quantity of it to the tablets over 5 minutes. Allow to dry and apply the remainder over a 15-minute period.

32. Heat 11.52 g of item 8 to boiling, dissolve 26.88 g of item 4, and cool down to 25°C.
33. Check weight (theoretical weight, 38.40 g). If less, adjust weight to 38.40 g with purified water.
34. Apply sugar coat over a 30-minute period.
35. Dry the tablets in the coating pan at 30°C, jogging every 1 hour for 6 hours.
36. Heat 72 g of item 8 in mixer to boiling.
37. Dissolve 168 g of item 4 and then cool to 25°C.
38. Filter the syrup through a 180-μm stainless steel sieve.
39. Dissolve item 3 in 3.68 g of item 8.
40. Dissolve 4.53 g of item 4 in item 6.
41. Disperse item 5 in approximately 10.67 g of sugar syrup from the previous step and homogenize.
42. Mix these steps with sugar syrup. Check for evenness of the dispersion.
43. Apply sugar coating.

Bill of Materials: Polishing Coat			
	Item	Material Name	Qty/kg (g)
	1	Beeswax, bleached (white beeswax)	28.75
	2	Polyethylene glycol (PEG-6000)	70.00
	3	Carnauba wax	57.50
	4	Talc (fine powder)	125.00
	5	Ethanol, 95%	718.75

44. Melt items 1, 2, and 3 in a steam-heated vessel by gentle heating to 70°C or in a stainless steel container on a hotplate heater.
45. Add item 4 to the vessel or stainless steel container and stir manually.
46. Add item 5 to the vessel or stainless steel container and stir manually.
47. Pass the mixture through a homogenizer.
48. Store the polishing emulsion in a closed container at room temperature.
49. Apply gloss solution.
50. Add item 6 without air to the tablet bed carefully to get a uniform distribution while rolling.
51. After 5 minutes of distribution, turn on the cold air and roll further until a shine appears.
52. Once the desired polish appears, stop rolling the pan.
53. Dry the tablets in the pan at 30°C for 30 minutes. Final tablet weight should be 480 mg.

Inosin Tablets

Bill of Materials			
Scale (g/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Inosin (Ribaxin, Russia)	200.00
51.00	2	Lactose monohydrate	51.00
6.00	3	Kollidon 90 F	6.00
QS	4	Isopropanol	60.00 mL
10.00	5	Kollidon CL	10.00
3.00	6	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with the solvent mixture of items 4.
2. Dry and pass through a 0.8-mm sieve, add items 5 and 6, and press with low compression force.
3. Compress 270 mg in 9-mm biconvex punches.

Insect Bite Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
180.00	1	Trilaneth-4 phosphate, glyceryl stearate, and PEG-2 stearate	180.00
20.00	2	Hydrogenated palm/kernel oil PEG-6 esters	20.00
80.00	3	Mineral oil	80.00
0.30	4	Sodium methyl paraben	0.30
0.70	5	Sorbic acid	0.70
646.70	6	Deionized water	646.70
10.00	7	Benzocaine	10.00
10.00	8	Butamben	10.00
2.00	9	Menthol	2.00
0.30	10	Resorcinol	0.30
50.00	11	Ethoxydiglycol	50.00

Manufacturing Directions

1. Dissolve items 7 to 10 in item 11.
2. Mix and heat items 1 to 6 to 75°C.
3. Allow to cool slowly with constant stirring.
4. At 35°C, add this to previous mixture.
5. Homogenize if necessary.

Iron (Polymer-Coated Particle) Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Elemental iron, use ferrous sulfate polymer-coated particles (233 mg iron per gram ferrous sulfate)	450.60
200.00	2	Cellulose microcrystalline	200.00
254.40	3	Lactose monohydrate	254.40
36.00	4	Sodium starch glycolate	36.00
9.00	5	Magnesium stearate	9.00

Note: Factor in potency of ferrous sulfate polymer-coated particles.
Adjust with item 3. Item 1 is prepared by first granulating ferrous sulfate using alcohol and water, drying, and sieving particles over 1200 μm in size. Regranulate smaller particles. Apply enteric (HPMC) coating to the granules in a fluid-bed dryer.

Manufacturing Directions

1. Charge a suitable mixer/blender with microcrystalline cellulose and disperse the ferrous sulfate polymer-coated powder.
2. To this mix, add about half the lactose (item 3) and blend for 5 minutes.
3. Pass the sodium starch glycolate through a 500-μm sieve, followed by about half of the remaining lactose.
4. Add to the mix.
5. Blend for further 5 minutes.
6. Pass the magnesium stearate (item 5) through a 500-μm sieve, followed by the remaining lactose.
7. Add to the previous mix.
8. Blend for further 5 minutes.
9. Compress 950 mg per tablet at 8 to 14 kpi using 8-mm × 16-mm punches. Do not rework tablets.
10. Coat the tablets using a HPMC coating solution (see appendix).

Iron Infant Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.18	1	Propyl paraben	0.18
0.022	2	Methyl paraben	0.02
1000.00	3	Sorbitol solution	1.00 kg
4.00	4	Citric acid (hydrous powder)	4.00
125.00	5	Iron sulfate	125.00
0.106	6	Sodium metabisulfite	0.10
0.50	7	Guarana flavor (artificial)	0.50
20.00	8	Alcohol (ethanol)	900.14
0.14	9	Dye	0.14
QS	10	Sodium hydroxide	QS
QS	11	Citric acid (powder)	QS
QS	12	Purified water	QS to 1 L
QS	13	HyFlo filter aid	1.00
QS	14	Liquid nitrogen	QS
QS	15	Carbon dioxide gas	QS

Manufacturing Directions

The product is susceptible to oxidation. No effort should be spared to protect it from atmospheric air. Maintain carbon dioxide (CO_2) or nitrogen atmosphere where indicated. The product must be manufactured and held in a glass-lined or stainless steel tank. Product waiting to be filled should either be in a closed tank with a CO_2 atmosphere or in an open tank covered with polyethylene sheeting taped tightly with a constant slow stream of CO_2 gas flowing into the tank headspace. Avoid vortex formation throughout processing.

1. Charge 144 mL of purified water into a mixing tank.
2. Heat to 95°C to 100°C and add parabens with strong agitation.
3. Add sorbitol solution and citric acid (item 4) while mixing.
4. Bring solution to 90°C while mixing.
5. Cool the solution while mixing to 60°C to 65°C and hold at this temperature with CO_2 or nitrogen gas bubbling into it.
6. CO_2 gas protection is continued for the remainder of the manufacturing process.
7. Add ferrous sulfate and dissolve while mixing, holding at 60°C to 65°C.
8. Cool to 25°C with mixing.
9. Add sodium metabisulfite and dissolve while mixing.
10. Avoid vortex formation.
11. Dissolve dye in 2 mL of freshly boiled purified water and add to the tank. Mix.
12. Dissolve the guarana flavor in alcohol, add to the tank, and mix.
13. Check pH (range: 1.8–2.2). Adjust if necessary, with a solution of 10% sodium hydroxide or a solution of 10% citric acid.
14. Make up to volume with freshly boiled purified water and mix.
15. Readjust to volume if necessary with freshly boiled purified water and mix.
16. Add HyFlo filter aid and mix. Filter through press until clear.
17. Bubble CO_2 or nitrogen gas into the clear filtrate for 5 minutes, then seal tank and hold product under CO_2 or nitrogen protection.

Iron Polystyrene and Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
125.00	1	Glycerin	125.00
1.40	2	Methyl paraben	1.40
0.16	3	Propyl paraben	0.16
79.61	4	Sorbitol; use sorbitol solution	364.33
3.30	5	Xanthan gum	3.30
10.00	6	Sucrose (granulated)	100.00
0.20	7	Saccharin (insoluble)	2.00
105.00	8	Elemental iron; use iron polystyrene sulfonate	530.31
50.00	9	Ascorbic acid, USP (35% excess)	61.95
0.10	10	Flavor	1.00 mL
0.10	11	Flavor (artificial guarana)	1.00 mL
QS	12	Sodium hydroxide	12.1.0
QS	13	Dye	2.00
9.50	14	Distilled purified water	~95.00 mL
10.00	15	Sorbitol solution	~10.00

Manufacturing Directions

1. Add glycerin (item 1) to the tank.
2. Commence heating with agitation.
3. Add and disperse parabens.
4. Continue heating to 70°C to 80°C and mix until solution is complete.
5. Force cool to 30°C, then add and disperse xanthan gum (item 5).
6. Add sorbitol solution (item 4) and 80 mL of purified water (item 14) and heat with mixing to 60°C to 70°C until the xanthan gum is fully dissolved.
7. Add and disperse saccharin and sugar (items 6 and 7).
8. Mix at 60°C to 70°C until dispersion is complete.
9. Force cool to 25°C to 30°C with continuous mixing.
10. Commence N_2 gas protection and maintain for the remainder of the manufacturing process.
11. Add and disperse ascorbic acid.
12. Continue mixing for 30 minutes at 25°C to 30°C.
13. *Note*: Use suitable SS high-powered stirrer.
14. Mix the iron polystyrene sulfonate milled slurry in the original epoxy-lined drums under N_2 gas protection until uniform.
15. Add the slurry to the main batch and mix for 30 minutes at 25°C to 30°C.
16. (*Note*: Avoid scraping the epoxy lining of the steel drum while mixing and use a plastic or rubber scraper to assist in complete transfer of the mixed slurry.) Add and disperse the flavors. Mix well.
17. Check and record pH. Adjust pH using a 20% sodium hydroxide solution (1 g in 5 mL water) to a value of 3 (range: 2.8–3.2).
18. Dissolve the dye in 5 to 7 mL of water at 40°C to 45°C by stirring for 10 minutes.
19. Add this solution to the main batch through a 420-μm screen with mixing.
20. Rinse container with 2 to 3 mL water at 40°C to 45°C and add to bulk through a 420-μm screen.
21. Continue to mix under vacuum until mixture is uniform.
22. Pass the suspension through the colloid mill at a gap setting of 100 to 150 μm.
23. Adjust the flow rate such that the temperature rise of the suspension does not exceed 10°C.
24. Collect the milled suspension in a stainless steel jacketed tank with vacuum.
25. Mix at 25°C to 30°C under vacuum until a uniform suspension is achieved.
26. Flush the bulk suspension with nitrogen and seal.
27. Hold at 25°C to 30°C.

Kaolin–Pectin Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
147.60	1	Sodium methyl paraben	4.92
6.72	2	Sodium propyl paraben	224.00
36.00	3	Magnesium aluminum silicate type IA	1.20
5832.00	4	Kaolin (powder)	194.40
130.00	5	Pectin	4.33
120.00	6	Sodium CMC (premium, low-viscosity)	4.00
210.00	7	Cyclamate calcium	7.00
21.00	8	Saccharin calcium (powder)	0.70
15.375	9	Flavor	0.51
1.234	10	Flavor	41.13
QS	11	Distilled purified water (approx.)	QS
QS	12	Citric acid (anhydrous powder)	QS

Manufacturing Directions

1. Charge 600 mL of water into a suitable jacketed mixing tank.
2. Add the methyl paraben and propyl paraben to the tank and heat to 90°C to 95°C.
3. Cool to 70°C, add the magnesium aluminum silicate, and mix for 30 minutes or until evenly dispersed.
4. Hold temperature at 70°C.
5. Add kaolin with constant mixing at 70°C until evenly dispersed.
6. Add pectin and mix for 2 hours, maintaining a temperature of 70°C.
7. Add the premium, low-viscosity sodium CMC and mix for at least 30 minutes maintaining a temperature of 70°C.
8. Cool to 60°C and hold at this temperature.
9. Add, in order, the cyclamate calcium and saccharin calcium and mix thoroughly for 20 minutes.
10. While mixing, cool to room temperature and allow to stand overnight to hydrate.
11. After overnight standing (minimum 12 hours), mix for 30 minutes.
12. Add flavors while mixing.
13. Check and record pH (range: 4.5–7.5). If pH is more than 7.5, adjust with a 60% solution of citric acid to the desired pH.
14. Add water to 1 L and mix thoroughly for 3 hours.
15. Strain product through muslin cloth into holding tanks and cover.

Kaolin–Pectin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
QS	1	Distilled purified water	300 mL
50.00	2	Cornstarch	50.00
50.00	3	Povidone (K-29–32)	50.00
QS	4	Distilled purified water	0.50 L
630.00	5	Hydrated aluminum–magnesium silicate	630.00
100.00	6	Kaolin (powder)	100.00
50.00	7	Pectin	50.00
80.00	8	Cornstarch	80.00
80.00	9	Sodium lauryl sulfate	7.00
10.00	10	Magnesium stearate	10.00

Manufacturing Directions

1. Heat purified water (item 1) to 75°C to 80°C and add cornstarch (item 2) with continuous stirring until a translucent paste is formed. Use this paste within 1 hour.
2. Dissolve povidone in purified water (item 4) in a separate container. Ensure that dissolution is complete.
3. Charge the following into a suitable planetary mixer: hydrated aluminum–magnesium silicate, kaolin, and pectin.
4. Mix for 5 minutes.
5. Add freshly prepared starch paste from the first step and the povidone solution to the powder blend from the third step. Mix until a mass of suitable consistency is obtained.
6. Add extra-purified water, if needed.
7. Spread the wet mass on paper-lined trays and dry in the oven at 50°C for 2 hours.
8. Pass the semidried mass through a 4.8-mm (4-mesh) screen by hand or by using a suitable granulator and load the granule mass onto paper-lined trays.
9. Dry in the oven at 50°C until the moisture content is between 10% and 15%.
10. Pass the dried granules through a 1-mm (18-mesh) screen on a comminuting mill at medium speed, knives forward, into clean, tared, polyethylene-lined drums. Seal and weigh.
11. Transfer the dried granules to a suitable blender.
12. Screen the following items through a 595-μm (30-mesh) screen and add to the blender: cornstarch (item 8), sodium lauryl sulfate, and magnesium stearate.
13. Blend for 5 to 10 minutes.
14. Compress on a suitable compression machine using 1/2-in round standard concave punches, upper punch with logo, and lower punch with a bisect line.
15. Compress 977 mg at 10 to 18 kpi.
16. Coat using an aqueous Methocel coating and polish as desired.

Keratolytic Cream

Bill of Materials			
Scale (mg/10 g)	Item	Material Name	Qty/kg (g)
150.00	1	Polawax (self-emulsifying wax)	15.00
150.00	2	PPG-2 myristyl ether propionate (Crodamol PMP)	15.00
50.00	3	Sorbitol isostearate	5.00
35.00	4	Safflower oil, super-refined	3.50
20.00	5	Avocado oil, super-refined	2.00
20.00	6	Cetyl palmitate	2.00
50.00	7	Salicylic acid	5.00
1.50	8	Propyl paraben	0.15
1.00	9	Butylated hydroxyl anisole	0.10
487.50	10	Deionized water	48.75
10.00	11	Sodium borate	1.00
3.00	12	Methyl paraben	0.30
2.00	13	Imidazolidinyl urea	0.20
20.00	14	Hydrolyzed collagen + hyaluronic acid (Cromoist HTA)	2.00

Manufacturing Directions

1. Dissolve item 7 in item 2 with mixing and heating to 70°C.
2. Add balance of items 1 to 9 and mix with heat to 80°C. Add items 10 to 13 together separately and heat to 80°C.
3. Add this mixture to the first mixture with mixing and cool to 40°C.
4. Add item 14 with mixing and cool to the desired fill temperature.
5. Adjust pH if necessary to 3 to 4 with 10% triethanolamine solution.

Khellin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
25.00	1	Khellin	25.00
124.00	2	Ludipress	124.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix intensively, and press.
2. Compress 150 mg in 8-mm biplanar punches.

Lidocaine Gel

Bill of Materials			
Scale (mg/10 g)	Item	Material Name	Qty/kg (g)
20.00	1	Lidocaine hydrochloride	2.00
560.00	2	Water	56.00
200.00	3	Propylene glycol (pharma)	20.00
220.00	4	Lutrol F 127	22.00

Manufacturing Directions

1. Prepare solution of items 1 to 3 at room temperature, heat to 70°C or cool to 6°C, and slowly add item 4 to the well. Stir solution until it is dissolved.
2. Maintain the temperature until the air bubbles escape to obtain a clear, colorless gel.

Lidocaine Gel Cream

Bill of Materials			
Scale (mg/10 g)	Item	Material Name	Qty/kg (g)
50.00	1	Lidocaine hydrochloride	5.00
500.00	2	Water	50.00
150.00	3	Propylene glycol (pharma)	15.00
100.00	4	Liquid paraffin	10.00
200.00	5	Lutrol F 127	20.00

Manufacturing Directions

1. Prepare solution of items 1 to 3 at room temperature and mix with item 4.
2. Heat to 70°C or cool to 6°C and slowly add item 5 to the well. Stir solution until it is dissolved.
3. Maintain the temperature until the air bubbles escape.

Lidocaine Ointment

Bill of Materials			
Scale (g/100 g)	Item	Material Name	Qty/kg (g)
5.00	1	Lidocaine base	50.00
28.00	2	PEG-3350	280.00
40.00	3	PEG-400	400.00
25.00	4	Propylene glycol	250.00
2.00	5	Purified water	20.00

Manufacturing Directions

1. Load items 2 and 3 into a fat-melting vessel.
2. Heat to 70°C.
3. Cool to 40°C while stirring at slow speed (10–12 rpm).
4. Maintain the temperature between 40°C and 45°C under continuous stirring.
5. Heat 200 g of item 4 to 40°C to 45°C in a stainless steel container.
6. Dissolve item 1 by stirring with stirrer.
7. Add item 5 under continuous stirring.
8. Maintain the temperature between 40°C and 45°C under continuous stirring.
9. Filter through cloth filter.
10. Transfer the drug solution into a mixer previously set with a temperature of 40°C to 45°C.
11. Rinse the stainless steel container with 50 g of item 4.
12. Add the rinsing into the mixer.
13. Transfer the molten mass from the fat-melting vessel at 40°C through a stainless steel filter to the mixer containing the drug solution while mixing at 10 to 12 rpm.
14. When the transfer is over, start the homogenizer at low speed, with a vacuum of 0.6 bar and stirrer speed of 10 rpm (manual mode).
15. Mix and homogenize for 10 minutes with recirculation.
16. Maintain temperature at 40°C to 45°C.
17. Stop the homogenizer and set the mixer at temperature 25°C and stirrer speed at 10 rpm (manual mode).
18. Cool the cream to 25°C.
19. When the ointment is cooled to 25°C, unload the ointment into a stainless steel container.

Lidocaine, Eugenol, and Menthol Dental Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
55.20	1	Beeswax (white, slabs)	55.20
150.00	2	Anhydrous lanolin (regular)	150.00
723.70	3	Petrolatum (white, regular)	723.70
40.00	4	Lidocaine base	40.00
1.20	5	Saccharin sodium (powder)	1.20
QS	6	Deionized, purified water	3.00 mL
1.00	7	Eugenol	1.00
5.00	8	Menthol (crystals)	5.00
0.80	9	Peppermint oil	0.80
20.16	10	Metaphen ointment base	20.16

Manufacturing Directions

1. Melt beeswax, lanolin, and petrolatum together at 70°C to 80°C and strain into a suitable container.
2. Do not heat above 70°C to 80°C.
3. Mix together.
4. Melt lidocaine base and strain into the container while mixing.
5. Dissolve the sodium saccharin in purified water heated to 70°C.
6. Add to the container while mixing.
7. Cool down to 45°C to 50°C while mixing.
8. Mix the eugenol, menthol, and peppermint oil together and liquefy.
9. Warm gently to 35°C to 40°C, if necessary.
10. Strain into the container while mixing.
11. Gently melt metaphen ointment base and strain into the container while mixing.
12. Mix thoroughly until congealed.

Loperamide Hydrochloride Fast-Melt Tablet

Manufacturing Directions

1. Prepare granules by using loperamide hydrochloride, 5%; sodium bicarbonate, 27%; citric acid anhydrous, 27%; tartaric acid, 3%; microcrystalline cellulose, 15%; anhydrous lactose, 8%; xylitol, 12%; and Crodesta F160, 3%.
2. The above ingredients are dried at elevated temperature in the presence of a desiccant to significantly reduce the moisture content of each material.
3. The ingredients are then blended for 10 minutes and extruded in a hot melt extruder at 70°C to 100°C to soften and melt the thermal binders (sucrose stearate and xylitol) to form granules containing the effervescent ingredients.
4. Granules are passed through a screen and then blended with the following ingredients: LH-EFG (30–80 mesh), 50%; microcrystalline cellulose, 31%; mannitol, 8%; Ac-Di-Sol, 5%; L-HPC LH-11, 2%; aspartame, 3%; redberry flavor, 0.4%; magnesium stearate, 0.5%; Cab-o-Sil M5P, 0.1%, which are mixed for 5 minutes prior to compression.
5. Loperamide FICI tablets are then compressed to a hardness of approximately 1 to 3 kg and tablets disintegrate in purified water in approximately 15 to 35 seconds.

Loratadine and Pseudoephedrine Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
25.00	1	Loratadine	25.00
180.00	2	Pseudoephedrine sulfate	180.00
5.00	3	PVP	5.00
75.00	4	Low-substituted hydroxypropyl cellulose	75.00
75.00	5	Crospovidone	75.00
1.50	6	Colloidal silicon dioxide	1.50
250.00	7	Crystalline sugar seeds	250.00
120.00	8	Purified water	120.00

Manufacturing Directions

1. A binder solution is prepared by dissolving 5 g of PVP in 120 g of water.
2. 25 g of loratadine, 180 g of pseudoephedrine sulfate, 25 g of microcrystalline cellulose, 75 g of low-substituted hydroxypropyl cellulose, 75 g of crospovidone, and 1.5 g of colloidal silicon dioxide are mixed and screened through a 20-mesh sieve to give a mixed powder.
3. The binder solution of step 1 is sprayed onto 250 g of crystalline sugar seeds in a centrifugal granulator, the mixed powder is dusted onto the crystalline sugar seeds in the centrifugal granulator to afford pellets using the rotation panel rate of 140 to 200 rpm, the spraying rate of the binder solution of 2 to 20 mL/min, air spraying pressure of 1 to 2 kg/cm^2, air spraying volume of 5 to -300 L/min, and powder (step 2) spraying rate of 5 to 30 g/min.

Loratadine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Loratadine	10.00
69.93	2	Pregelatinized starch	69.93
69.63	3	Microcrystalline cellulose	69.63
0.37	4	Colloidal silicon dioxide	0.37
0.25	5	Magnesium stearate	0.25

Manufacturing Directions

1. A multistep blending process is used to ensure proper distribution of the active. Initially, half of the Starch 1500 is combined with the drug and colloidal silicon dioxide.
2. This mixture is blended in a twin shell V-blender for 5 minutes.
3. The mixture is then discharged and passed through a 40-mesh screen by hand.
4. This step not only breaks up the silicon dioxide but also helps to distribute the active.
5. The screened mixture is returned to the blender and the remainder of the Starch 1500 is added and blended for an additional 5 minutes.
6. The MCC is then added and blended for 10 minutes.
7. The magnesium stearate is added last and blended for 5 minutes.
8. The magnesium stearate is passed through a 60-mesh screen prior to weighing.
9. Tablets are compressed at 100 mg or proportionally for different strengths.

Loratadine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Loratadine	10.00
67.30	2	Lactose monohydrate	67.30
22.00	3	Maize starch	22.00
10.00	4	Maize starch	10.00
5.00	5	Maize starch, dried	5.00
0.70	6	Magnesium stearate	0.70
QS	7	Purified water	QS

Manufacturing Directions

1. Sift items 1 to 3 through a 630-μm stainless steel sieve, load in mixer, and mix for 5 minutes.
2. In a separate container, prepare binder solution by mixing item 4 using purified water at 30°C to 40°C, heat translucent slurry to 90°C to 95°C, and cool to 45°C to 50°C.
3. Mix the binder solution with the first step and granulate, dry on trays at 55°C for 8 hours, dry to LOD of 2% to 3% (2 hours after beginning drying, crush mixture for uniform drying).
4. Heat additional 1 hour at 55°C if LOD is not within limits.
5. Add magnesium stearate, tumble mix, and compress using 7-mm round punches to 10-tablet weight of 1.15 (within 3%) to achieve thickness of 2.3±0.3 mm and hardness of 4 to 7 kp.

Loratadine Fastab

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Loratadine (micronized)	10.00
180.60	2	Pharmaburst	180.60
2.70	3	Acesulfame K	2.70
2.00	4	Magnesium stearate	2.00
2.00	5	Talc (fine powder)	2.00
2.70	6	Dry anise flavor	2.70

Manufacturing Directions

1. Sift and mix items 1, 2, 3, and 6.
2. Lubricate with magnesium stearate and fine talc powder.
3. Compress 200 mg in 6-mm punches.

Lycopene Tablet Cores (6 mg)

Formulation

LycoVit 10% dry powder, 60 g; Ludipress, 330 g; Kollidon CL, 6 g; magnesium stearate, 4 g.

Manufacturing Directions

1. Mix the LycoVit dry powder with the other components.
2. Sieve through a 0.8-mm screen and press with medium to high compression force at 400 mg.

Magaldrate Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Magaldrate, USP	500.00
400.00	2	Lactose monohydrate	400.00
50.00	3	Orange flavor (FDO)	50.00
20.00	4	Kollidon 90 F	20.00
6.00	5	Banana flavor (FDO)	6.00
6.00	6	Cocoa flavor (FDO)	6.00
1.00	7	Saccharin sodium	1.00
180.00	8	Water	180.00
5.00	9	Aerosil 200	5.00
3.00	10	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with solution of items 4 to 8, pass through a 0.8-mm sieve, dry, mix with items 9 and 10, and press with low compression force.
2. Compress 1 g in 16-mm biplanar punches.

Magaldrate Chewable Tablets (500 mg)

Formulation

1. Magaldrate USP, 500 g; lactose monohydrate [8], 400 g; orange flavor (FDO), 50 g.
2. Kollidon 90 F [1], 20 g; banana flavor (FDO), 6 g; cocos flavor (FDO), 6 g; saccharin sodium, 1 g; water, 180 g.
3. Aerosil 200, 5 g; magnesium stearate, 3 g.

Manufacturing Directions

1. Wet granulation: Granulate mixture I with solution II, pass through a 0.8-mm sieve, dry, mix with III and press with low compression force at 1000 mg.

Magaldrate Chewable Tablets (1000 mg)

Formulation

Magaldrate (Reheis), 1000 g; Ludipress LCE, 930 g; Lutrol E4000F [1], 60 g; aspartame, potassium (Searle), 10 g; peppermint flavor, QS.

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium compression force at 2 g.

Magaldrate Dispersible Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
700.00	1	Magaldrate	700.00
435.00	2	Lactose monohydrate	435.00
10.00	3	Kollidon 90 F	10.00
50.00	4	Kollidon CL	50.00
5.00	5	Magnesium stearate	5.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with low compression force (4–6 kN).
2. Compress 1.2 g in 16-mm biplanar punches.

Magaldrate Instant Powder or Dry Syrup

Bill of Materials			
Scale (mg/Sachet)	Item	Material Name	Qty/1000 Sachets (g)
800.00	1	Magaldrate, USP	800.00
640.00	2	Kollidon CL-M	640.00
200.00	3	Sorbitol (crystalline)	200.00
40.00	4	Orange flavor	40.00
40.00	5	Kollidon 90 F	40.00
4.00	6	Coconut flavor	4.00
4.00	7	Banana flavor	4.00
0.80	8	Saccharine sodium	0.80
QS	9	Water	~280.00 mL

Manufacturing Directions

1. Granulate mixture of items 1to 4 with solution of items 5 to 9 and pass through a 0.8-mm sieve to obtain free-flowing granules.
2. Fill 2 g in sachets or 20 g in a 100-mL flask.
3. Instant granules in sachets: suspend 2 g (= one sachet) in a glass of water (= 800 mg magaldrate).

Magaldrate Suspension

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Magaldrate USP	100.00
80.00	2	Kollidon CL-M	80.00
20.00	3	Kollidon 90 F	20.00
10.00	4	Orange flavor	10.00
0.50	5	Coconut flavor	0.50
0.80	6	Banana flavor	0.80
0.20	7	Saccharine sodium	0.20
QS	8	Preservatives	QS
QS	9	Water	QS to 1 L

Manufacturing Directions

1. Dissolve or suspend all the solids in water under aseptic conditions; pH should be approximately 9.

Magaldrate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
400.00	1	Magaldrate (powder, 100 mesh)	400.00
325.00	2	Sucrose	325.00
60.00	3	Cellulose (microcrystalline) (Avicel PH101)	60.00
30.00	4	Cornstarch	30.00
8.84	5	Guar gum	8.84
0.50	6	Saccharin sodium	0.50
–	7	Purified water	100.00 mL
–	8	Alcohol SD 3A (200 proof)	100.00 mL
QS	9	Flavor	0.60 mL
QS	10	Flavor	1.00 mL
0.06	11	Ethyl vanillin	0.06
8.00	12	Talc	8.00
16.00	13	Magnesium stearate	16.0

Manufacturing Directions

1. Pass granulated sugar (take approximately 10% excess) through 500-µm stainless steel screen on comminuting mill (impact forward, high speed).
2. Screen the milled sugar through 250-µm aperture on sieve shaker.
3. Weigh the required quantity and charge into a suitable mixer.
4. Discard remaining sugar.
5. Screen magaldrate powder (take approximately 5% excess) through 150-µm stainless steel screen on sieve shaker.
6. Weigh the required quantity and add to the blend above.
7. Mix well.
8. Screen, if necessary, microcrystalline cellulose, cornstarch, and guar gum through 500-µm aperture on sieve shaker.
9. Add to the first step and mix well.
10. Dissolve saccharin sodium in water.
11. To this add alcohol and mix well.
12. Add this hydroalcoholic solution to magaldrate blend and knead well.
13. Add more water, if necessary, and QS to mass.
14. Pass wet mass through 2.8-mm aperture on sieve shaker or oscillating granulator and spread uniformly on stainless steel trays.
15. Tray dry granules at 70°C to 75°C.
16. After 3 to 4 hours of drying, screen semidried granules through 1.4-mm aperture on sieve shaker and reload for further drying.
17. (This step helps in drying granules faster and more uniformly.) Dry to LOD of 1% to 1.5%.
18. Screen dry granules through 1-mm aperture on sieve shaker and store in drums doubly lined with polyethylene bags.
19. Charge half of the granulation into a suitable blender.
20. From the balance of the granules, take out the fines (approximately 40 g of fines for a batch of 1000 tablets) through 250-µm aperture on sieve shaker.
21. Retain coarse particles for later use.
22. Mix together the flavors in a suitable vessel.
23. Add and dissolve the ethyl vanillin.
24. Check that the solution is clear before proceeding.
25. Charge a suitable mixer with the fines from above.
26. While mixing, disperse the flavor solution.
27. Add magnesium stearate and talc and mix thoroughly.
28. Pass the blend through a 250-µm aperture on sieve shaker.
29. Add the dispersed flavor blend to the granules.
30. Add remaining granules and blend for 8 to 10 minutes.
31. Discharge blended granules into suitable airtight containers doubly lined with polyethylene bags.
32. Compress on a suitable machine fitted with 14.4-mm diameter round punches with beveled edges.
33. Weight: 8.5 g/10 tablets, thickness: approximately 3.6 to 3.8 mm, hardness: 8 to 10 kPa.

Magaldrate with Simethicone Suspension

Bill of Materials			
Scale (mg/5 mL)	Item	Material Name	Qty/L (g)
QS	1	Distilled purified water	285.00 mL
9.00	2	Methyl paraben	1.80
1.00	3	Propyl paraben	0.20
5.00	4	Benzoic acid	1.00
3.75	5	Saccharin sodium (dihydrate powder)	0.75
400.00	6	Magaldrate (wet cake; 18–20%)	400.00
1.00 g	7	Sorbitol solution (70%)	260.00
12.50	8	Silicon dioxide (colloidal) (international)	2.50
QS	9	Citric acid (hydrous powder)	QS
200.00	10	Dimethyl polysiloxane emulsion (30%)	40.00
0.005 mL	11	Flavor	1.00 mL
1.26 g	12	Glycerin	252.00
25.00 g	13	Potassium citrate monohydrate	5.00
13.30	14	Xanthan gum	2.66

Manufacturing Directions

This product is highly prone to microbial contamination. All equipment coming into contact with the product should be treated with a freshly prepared sodium hypochlorite solution (100 ppm), made with freshly boiled and cooled down water on the day of use. Bottles and caps should also be so treated. Freshly boiled and cooled deionized water should be used for rinsing.

1. Charge 285 mL purified water into a suitable jacketed tank and heat to 90°C to 95°C.
2. Add and dissolve parabens, benzoic acid, saccharin sodium, and potassium citrate.
3. While maintaining temperature at 85°C to 90°C, add, in small quantities, half the quantity of magaldrate cake or powder, if used, and disperse well.
4. (Adjust speed of the agitator and homogenizer to ensure effective mixing and to maintain free mobility of the suspension.) Add sorbitol solution and mix well.
5. Raise the temperature, if necessary, maintaining temperature at 85°C to 90°C.
6. Add in small quantities the remaining half of the magaldrate cake or powder and disperse well.
7. Mix for 1 hour and then remove heat. (Adjust speed of the agitator and homogenizer to maintain the mobility of suspension.) Separately blend colloidal silicon dioxide with xanthan gum and disperse the blend in glycerin, with constant mixing.
8. While maintaining temperature at 85°C to 95°C, add and disperse the suspension from the previous step to the main tank and mix well.
9. Avoid lump formation at any stage.
10. Cool to room temperature.
11. Add dimethyl polysiloxane emulsion and mix well.
12. Add flavor and mix well.
13. Dissolve citric acid in twice the quantity of purified water and adjust pH if necessary.
14. Check and record pH (range: 7.5–8.0). Add purified water to volume and mix well for a minimum of 30 minutes.
15. Filter through a 180-μm aperture nylon cloth and store in a suitable tank.

Magaldrate with Simethicone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
525.00	1	Sucrose, NF	525.00
15.00	2	Lactose monohydrate, NF	15.00
60.00	3	Simethicone, USP	60.00
60.00	4	Cellulose microcrystalline (Avicel PH101), NF	60.00
12.00	5	Silicone dioxide colloidal (International)	12.00
400.00	6	Magaldrate, USP	400.00
40.00	7	Acacia (special grade), NF	40.00
0.05	8	Dye	0.05
–	9	Distilled purified water, USP	100.00 mL
–	10	Alcohol SD 3A (200 proof)	100.00 mL
1.50	11	Flavor	1.50
0.15	12	Ethyl vanillin, NF	0.15
5.00	13	Silicon dioxide (colloidal)	5.00
30.00	14	Starch monohydrate	30.00
10.00	15	Lactose monohydrate	10.00
80.00	16	Talc powder, USP	80.00
5.30	17	Magnesium stearate	5.30

Manufacturing Directions

1. Pass the granulated sucrose (with approximately 10% excess) through a 500-μm aperture stainless steel screen on comminuting mill (impact forward, high speed).
2. Screen the milled sugar through a 250-μm screen on sieve shaker.
3. Weigh the required quantity and charge into a suitable mixer (planetary mixer or dough mixer). Discard the remainder.
4. Screen lactose (item 2) through a 250-μm aperture screen on sieve shaker and add to powdered sugar from step above. Mix well.
5. While mixing vigorously, add and disperse simethicone (add slowly in a fine stream of flow to avoid lump formation). Mix well.
6. Rough blend colloidal silicon dioxide (item 5) and microcrystalline cellulose and add to the simethicone dispersed mass from previous step.
7. Mix initially at low speed for 4 to 5 minutes and thereafter mix vigorously for 5 to 10 minutes.
8. Either screen simethicone dispersed mass through a 1.0-mm aperture on sieve shaker or pass through a comminuting mill using a 1.4-mm aperture screen (impact forward, medium speed).
9. Load into a mass mixer and continue mixing.
10. Screen magaldrate powder (with approximately 7% excess) through a 150-μm aperture screen on sieve shaker and weigh the required quantity.
11. To this quantity add acacia and rough blend.
12. Add this blend in the dough mixer, dispersing in small quantities, and mix well for 30 to 40 minutes until simethicone is well absorbed in the dry blend. Discard remaining magaldrate powder.
13. Dissolve dye in water, then add alcohol and mix well.
14. Wet down mass with colored hydroalcoholic solution and knead well.
15. Add more hydroalcoholic solution, if necessary (water:alcohol, 1:1), to mass.
16. Screen wet mass through a 2.8-mm aperture screen on sieve shaker or oscillating granulator and spread uniformly on trays.
17. Tray dry granules at 71°C to 74°C until LOD is within 1% to 1.5% (test at 105°C for 1 hour).
18. After approximately 3 to 4 hours of drying, screen semidried granules through a 1.4-mm aperture on sieve shaker and reload for further drying.
19. (*Note*: This step helps in drying granules faster and more uniformly and avoids color mottling on final product.) Screen dried granules through a 1.0-mm aperture screen on sieve shaker and store in drums lined with double polyethylene bags. Alternative drying can be done in a fluid-bed dryer.
20. Pass dried granules through a 1-mm aperture screen on sieve shaker.
21. Pass coarse granules through a comminuting mill using a 1.4-mm aperture screen (knives forward, slow speed) and then through 1.0-mm aperture on sieve shaker.
22. Store granules in drums lined with double polyethylene bags.
23. Charge half of the base granulation into a suitable blender.
24. From the balance of the granules take out fines (approximately 50 g of fines for a batch of 1000 tablets) through a 250-μm aperture on sieve shaker and hold in a suitable vessel.
25. Add and dissolve ethyl vanillin in liquid flavor.
26. Check for clarity and only then disperse over dried starch.

27. Rough blend colloidal silicon dioxide (item 13) with lactose monohydrate (item 15), talc, and magnesium stearate and add to the flavored starch.
28. To this mixture, add fines from the second step above and mix well by hand or in a suitable mixer.
29. Screen through a 250-µm aperture on sieve shaker.
30. Add this flavored, dispersed blend to the base granulation (first step) in a blender.
31. Add the remaining bulk granules from the second step to the base granulation and blend well for 8 to 10 minutes. (*Caution*: Do not mix for too long as the granules may crumble to a finer size, which may adversely affect hardness during compression.) Discharge blended granules into suitable airtight containers lined with double polyethylene bags until ready for compressing.
32. Compress on a suitable machine fitted with 14.4-mm diameter round punches with beveled edges. Compress 1244 mg per tablet.

Magnesium Carbonate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
260.00	1	Magnesium carbonate, USP	262.00
238.00	2	Ludipress	238.00
4.00	3	Magnesium stearate	4.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium compression force.
2. Compress 500 mg in 12-mm biplanar punches.

Medicated Foot Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Lanolin	5.00
90.00	2	Stearic acid	90.00
5.00	3	Cetyl alcohol	5.00
40.00	4	Isopropyl palmitate	40.00
10.00	5	Oleyl alcohol	10.00
20.00	6	Mineral oil and lanolin alcohol (liquid base CB3929)	20.00
7.50	7	Oil of wintergreen	7.50
3.00	8	Oil of thyme	3.00
5.00	9	Oil of pine	5.00
5.00	10	Menthol	5.00
5.00	11	Camphor	5.00
QS	12	Deionized water	QS to 1 kg
80.00	13	Glycerin	80.00
18.00	14	Triethanolamine 99%	18.00
QS	15	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately at 65°C to 70°C.
2. Add water phase to oil phase while stirring.
3. Add the triethanolamine dropwise.
4. Stir to cool.

This product can be used as a disinfecting and soothing cream for the feet.

Menthol Mouthwash

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Menthol	10.00
10.00	2	Eucalyptus oil	10.00
40.00	3	Cremophor RH 40	40.00
4.50	4	Saccharin sodium	4.50
2.00	5	Sodium citrate	2.00
5.00	6	Citric acid	5.00
50.00	7	Lutrol F 127	50.00
67.00	8	Ethanol 96%	67.00
QS	9	Sicovit colorant	QS
QS	10	Water	801.00

Manufacturing Directions

1. Mix items 1 to 3 and heat to approximately 60°C.
2. Prepare solution of items 4 to 10, heat it to approximately 60°C, and add it slowly to the well-stirred mixture of items 1 to 3.
3. Clear, colored liquid has a fresh mint taste.

Methyl Salicylate Analgesic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
30.00	1	Tromethamine magnesium aluminum silicate (Veegum® PRO)	30.00
30.00	2	Hydroxypropylcellulose	30.00
350.00	3	Deionized water	350.00
350.00	4	Ethanol	350.00
40.00	5	Cocoyl sarcosine (Vanseal CS)	40.00
25.00	6	Oleath-10	25.00
25.00	7	PEG-25 hydrogenated castor oil	25.00
50.00	8	Isopropyl myristate	50.00
20.00	9	Triethanolamine	20.00
5.00	10	Camphor	5.00
5.00	11	Menthol	5.00
2.00	12	Eucalyptus oil	2.00
65.00	13	Methyl salicylate	65.00
QS	14	Preservatives	QS

Manufacturing Directions

1. Dry blend item 1 and item 2 and slowly add them to items 3 and 4, agitating to ensure homogenous dispersion.
2. Combine items 5 to 9 separately and items 10 to 14 separately, then mix them together.
3. Finally, add this mixture to the first mixture and mix until uniform.

Methyl Salicylate Analgesic Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
15.00	1	Magnesium aluminum silicate (Veegum®)	1.50
547.00	2	Deionized water	54.70
2.00	3	Simethicone emulsion	0.20
30.00	4	Propylene glycol	3.00
150.00	5	Methyl salicylate	15.00
50.00	6	Menthol	5.00
6.00	7	Polysorbate	0.60
50.00	8	C18–C36 acid	5.00
150.00	9	Glyceryl stearate and PEG-100 stearate	15.00
QS	10	Preservatives	QS

Manufacturing Directions

1. Add item 1 to water slowly and mix vigorously to smooth dispersion.
2. Add items 3 and 4, mixing one at a time. Heat to 75°C to 80°C.
3. Separately mix and heat items 5 to 9 to 75°C to 80°C and combine the two parts while mixing.
4. Cool while mixing and add item 10 at 40°C.

Methyl Salicylate Heat Rub Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
25.00	1	PPG-5-cetech-10-phosphate (Crodafos SG)	25.00
40.00	2	Emulsifying wax, NF (Polawax)	40.00
45.00	3	PPG-1 cetyl ether (Procetyl 10)	45.00
10.00	4	Menthol	10.00
10.00	5	Camphor	10.00
75.00	6	Methyl salicylate	75.00
30.00	7	Glycerin	30.00
10.00	8	Gelatin, NF (Crodyne BY-19)	10.00
3.00	9	Diethanolamine	3.00
742.00	10	Deionized water	742.00
10.00	11	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	10.00

Manufacturing Directions

1. Premix items 4, 5, and 6 with item 3.
2. When completely dissolved, add items 1 and 2 and heat to 75°C to 80°C.
3. Dissolve item 8 in water and add items 7 and 9.
4. Heat to 80°C; slowly add this part to previous part using good mechanical mixing.
5. Allow to cool while mixing to 40°C and then add item 11.
6. Cool to 30°C and fill.

Methyl Salicylate and Menthol Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
110.00	1	Methyl salicylate	110.00
50.00	2	Menthol	50.00
200.00	3	Lutrol E 400	200.00
60.00	4	Cremophor RH 40	60.00
70.00	5	Propylene glycol (pharma)	70.00
320.00	6	Lutrol F 127	320.00
QS	7	Water	190.00

Manufacturing Directions

1. Dissolve item 6 in solution of items 1 to 5 and mix with item 7.
2. The clear gel can be diluted with water.
3. Because of the high concentration of the active ingredients and of Lutrol F 127, the consistency of the colorless clear gel is extremely hard.
4. By reducing the concentration of the active ingredients, the amount of Lutrol F 127 can also be reduced and the consistency of the gel will be normal.

Metoclopramide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Anhydrous metoclopramide hydrochloride; use metoclopramide hydrochloride	10.54
7.00	2	Maize starch (dried)	7.00
1.00	3	Silicon dioxide (colloidal)	1.00
0.76	4	Magnesium stearate	0.76
5.00	5	Starch (pregelatinized)	5.00
101.24	6	Lactose	101.24
QS	7	Purified water	~15.00 mL

Manufacturing Directions

1. Dried maize starch must be used for lubrication.
2. Dry the starch at 80°C for 36 hours prior to its use in manufacturing.
3. Check LOD of starch; the LOD must be less than 2%.
4. Pass the lactose, pregelatinized starch, and metoclopramide hydrochloride through a 1.25-mm aperture screen and transfer it to a suitable mass mixer. Mix for 5 minutes.
5. Add the water slowly to the mixer and mix for 30 minutes or until a suitable consistency is obtained. Add extra water, if required.
6. Pass the mass through a 4.8-mm aperture screen or an oscillating granulator (or by hand) and dry in a tray dryer or fluid-bed dryer at 50°C until the moisture content is less than 5.5%.
7. Pass the granules through an 875-μm aperture screen on an oscillating granulator (or comminuting mill at medium speed, knives forward) into tared, polyethylene-lined drums. Seal and weigh.
8. Carry out remaining steps at an RH less than 50% and temperature less than 26°C.
9. Transfer the dried granulation to a suitable blender.
10. Screen the starch (item 2), magnesium stearate, and silicon dioxide through a 250-μm aperture screen on a sieve shaker and add to the blender.
11. Blend for 10 minutes.
12. Discharge the granules into polyethylene-lined drums. Seal and weigh for yield.
13. Compress 1.255 g per 10 tablets in 6.35- or 7.14-mm standard concave punches.

Miconazole Nitrate Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
21.00	1	Miconazole nitrate (5% excess)	21.00
200.0	2	Tefose 63	200.0
30.00	3	Labrafil M[a]	30.00
30.00	4	Mineral oil (liquid paraffin)	30.00
0.05	5	Butylated hydroxyanisole	0.05
2.00	6	Benzoic acid	2.00
720.00	7	Purified water	720.00

[a]Synonyms: Labrafil M 1944 CS, oleoyl macrogolglycerides, apricot kernel oil PEG-6 complex.

Manufacturing Directions

1. Melt items 2, 3, and 4 (fatty phase) in fat-melting vessel.
2. Heat to 65°C to 70°C.
3. Disperse items 1 and 5 in the fatty phase while mixing at high speed for 20 minutes.
4. Add item 7 to the mixer and heat to 80°C to 90°C.
5. Dissolve item 6 and cool down to 65°C to 70°C.
6. Transfer the fatty phase to the mixer with vacuum at 0.2 to 0.3 bar.
7. Start cooling down while mixing at 10 rpm and homogenize at high speed for 20 minutes, then cool down to 25°C to 28°C while mixing at a vacuum of 0.2 to 0.3 bar (65–45°C) or 0.5 to 0.7 bar (45–25°C).

Mineral and Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
6.65	1	Hypophosphorous acid	6.65
16.47	2	Calcium hypophosphite	16.47
31.68	3	Calcium lactate (powder)	31.68
1.00	4	Methyl paraben	1.00
0.20	5	Propyl paraben	0.20
1.00	6	Benzoic acid	1.00
150.00	7	Sucrose (granular)	150.00
5.20	8	Ferrous gluconate	5.20
2.00	9	Niacinamide (5% excess)	2.10
0.33	10	Riboflavin-5-phosphate sodium	0.33
1.00	11	D-pantothenyl alcohol (dexpanthenol; 20% excess)	1.20
0.60 μg	12	Vitamin B_{12} (cyanocobalamin) (35% excess)	0.81 mg
0.20	13	Pyridoxine hydrochloride	0.20
0.30	14	Thiamine hydrochloride (regular powder) (55% excess)	0.46
4.782	15	Flavor, raspberry blend	4.78
1.945	16	Flavor, chocolate	1.945
0.64	17	Orange oil (terpeneless, No. 54125)	0.64
0.21	18	Lime oil, distilled	0.21
4.28	19	Alcohol	4.28
2.50	20	Saccharin sodium	2.50
10.00	21	Ascorbic acid (white powder/EP) (45% excess)	14.50
3.00	22	Caramel (acid proof)	3.00
2.00	23	Anhydrous citric acid	2.00
10.0 μg	24	Butylated hydroxyanisole (BHA)	10.0 mg
3.39	25	Corn oil	3.39
0.40	26	Vitamin A palmitate (1.5 million U/g) (40% excess)	0.56
0.08	27	Viosterol in corn oil (syn. oleovitamin D; 1000 mg/g) (40% excess)	0.112
1.5 g	28	Acacia (special grade)	1.50
0.127	29	Sodium lauryl sulfate (acetone-washed)	0.127
171.00	30	Deionized, purified water	~171.00
QS	31	Glucose liquid (corn syrup)	QS to 1 L

Manufacturing Directions

Do not expose this preparation during manufacturing to direct sunlight. Riboflavin is sensitive to light.

1. Add 83.7 mL purified water to a stainless steel jacketed tank.
2. Add calcium hypophosphite, calcium lactate, the parabens, and benzoic acid.
3. Heat mixture to 60°C with agitation.
4. Shut off mixer and wash tank until free of all powders with 25.9 mL purified water.
5. Heat to and maintain a maximum temperature of 100°C until solution is complete. Do not agitate. Avoid loss of water through evaporation. Cover opening of tank.
6. After solution occurs, take sample from bottom of tank and examine for clarity. Solution must be clear.
7. Add hypophosphorous acid (if used) with mixing.
8. Turn off heat, add 222 g glucose, and start agitator. (*Caution*: Use CO_2 cover throughout. Wherever water is used, it should be CO_2-saturated water.) Dissolve ferrous gluconate in 7.4 mL water CO_2-saturated by heating.
9. Add 278 g glucose with mixing. Add and dissolve sugar.
10. Allow solution to cool to 35°C and mix well.
11. To 29.6 mL water, add and dissolve nicotinamide, riboflavin, D-pantothenyl alcohol, vitamin B_{12}, pyridoxine, and thiamine. Mix until solution is complete and add to tank. Dissolve by heat, if necessary.

12. Charge raspberry blend flavor and chocolate flavor into tank. Charge saccharin into tank and mix until dissolved.
13. Charge ascorbic acid into tank. Mix well.
14. Charge caramel into tank and mix well.
15. Dissolve citric acid in 3 mL water and add.
16. Heat corn oil to 50°C to 60°C and add and dissolve BHA. Be sure the BHA is completely dissolved before continuing.
17. Cool to room temperature. While cooling oil mixture, saturate with CO_2 and maintain heavy CO_2 coverage for balance of operation.
18. Set aside a small amount of this mixture as a rinse for the vitamin A and viosterol containers in step above.
19. Add vitamin A palmitate and viosterol to the cool corn oil mixture, rinsing the containers with the oil reserved above.
20. Add the rinse to the bulk. Mix well.
21. Add the acacia to the oil mixture with good mixing.
22. Dissolve sodium lauryl sulfate in 3 mL CO_2-saturated purified water. To avoid excessive foaming, do not bubble CO_2 gas through the water/sodium lauryl sulfate solution.
23. Add the sodium lauryl sulfate solution to the oil mixture and stir to a thick creamy emulsion.
24. Add 7.56 g glucose to the emulsion with mixing.
25. Blend 13.33 mL CO_2-saturated purified water with 77.04 g glucose and add emulsion with stirring.
26. Recycle primary emulsion back into holding tank while setting mill.
27. Homogenize until all oil globules are less than 8 μm in diameter using colloid mill with a fine setting. Do not change mill setting after removing sample unless samples are unacceptable.
28. Add primary emulsion to syrup solution with mixing. Add glucose QS to 965 mL and mix well. Allow to stand overnight to vent entrapped air.
29. Adjust the volume to 1 L using glucose or glucose and CO_2-saturated water.
30. Strain through 149-μm aperture or similar screen into clean reserve tank and recheck volume.

Mint–Menthol Mouthwash

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
20.00	1	Mint oil	20.00
0.40	2	Menthol	0.40
0.90	3	Eucalyptus oil	0.90
10.00	4	Alpha-bisabolol (BASF)	10.00
0.60	5	Thymian oil	0.60
40.00	6	Cremophor RH 40	40.00
4.50	7	Saccharin sodium	4.50
2.00	8	Sodium citrate	2.00
5.00	9	Citric acid	5.00
0.20	10	Sodium fluoride	0.20
50.00	11	Glycerol	50.00
50.00	12	Lutrol F 127	50.00
0.60	13	Salicylic acid	0.60
1.00	14	Benzoic acid	1.00
175.00	15	Sorbitol, crystalline	175.00
216.00	16	Ethanol 96%	216.00
QS	17	Sicovit colorant	QS
QS	18	Water	48.40

Manufacturing Directions

1. Mix items 1 to 6 and heat to approximately 60°C.
2. Prepare solution of items 7 to 18, heat it to approximately 60°C, and add it slowly to the well-stirred mixture of items 1 to 6.
3. Clear, colored liquids have a fresh mint taste.

Mint Oil Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
35.00	1	Peppermint oil	35.00
138.00	2	Cremophor RH 40	138.00
520.00	3	Ethanol 96%	520.00
QS	4	Water	307.00

Manufacturing Directions

1. Mix the peppermint oil with Cremophor RH 40, stir well, and slowly add ethanol and water.
2. Clear, colorless liquid is of low viscosity.

Multivitamin and Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
7.00	1	Beta-carotene; use beta-carotene dry powder (10%, Pharma)	70.00
2.20	2	Thiamine mononitrate	2.20
2.20	3	Riboflavin	2.20
6.50	4	Nicotinamide	6.50
11.50	5	Calcium D-pantothenate	11.50
2.20	6	Pyridoxine hydrochloride	2.20
0.06	7	Cyanocobalamin; use cyanocobalamin dry powder (0.1%)	6.00
85.00	8	Ascorbic acid (powder)	85.00
32.00	9	Vitamin E acetate (dry powder; SD 50)	32.00
210.00	10	Ludipress	210.00
7.00	11	Kollidon® VA 64	7.00
3.00	12	Magnesium stearate	3.00
7.00	13	Orange flavor	7.00
2.50	14	Saccharin sodium	2.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, mix, and press with medium compression force.
2. Compress 448 mg using 12-mm planar punches.

Multivitamin and Calcium Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/100 g (mg)
0.10	1	Vitamin A palmitate	10.00
0.50 μg	2	Vitamin D 40 mio IU/g	0.05
1.00	3	Vitamin E acetate, BASF	100.00
0.02	4	BHT	2.00
45.00	5	Cremophor RH 40	4.50 g
100.00	6	Water	10.00 g
450.00	7	Saccharose	45.00 g
2.00	8	Methyl paraben	200.00
0.80	9	Citric acid	80.00
96.00	10	Glycerol	9.60 g
0.70	11	Calcium gluconate	70.00
250.00	12	Water	25.00 g
0.15	13	Thiamine hydrochloride, BASF	15.00
0.15	14	Riboflavin 5′-phosphate sodium	15.00
0.55	15	Nicotinamide	55.00
0.15	16	Pyridoxine hydrochloride	15.00
3.00	17	Ascorbic acid, crystalline	300.00
1.00	18	Sorbic acid	100.00
50.00	19	Propylene glycol (pharma)	5.00 g

Manufacturing Directions

1. Heat items 1 to 5 and item 6 separately to approximately 60°C and mix slowly, stirring well to obtain a clear solution.
2. Dissolve items 7 to 9 in the hot solution of items 10 to 12 to obtain a clear solution.
3. Mix all the solutions upon cooling and add solutions of items 13 to 19. Adjust the pH value to 4.0 to 4.1.
4. Pass during 10 minutes nitrogen through the solution and fill in bottles under nitrogen cover.

Multivitamin and Carbonyl Iron Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
5000 IU	1	Vitamin A acetate (dry powder; 500,000 IU/g)	10.00
2.20	2	Thiamine mononitrate, BASF	2.20
2.20	3	Riboflavin	2.20
16.50	4	Nicotinamide	16.50
11.50	5	Calcium D-pantothenate	11.50
2.20	6	Pyridoxine hydrochloride	2.20
6.00	7	Cyanocobalamin (dry powder; 0.1%)	6.00
85.00	8	Ascorbic acid (powder)	85.00
31.00	9	Vitamin E acetate (dry powder; SD 50)	31.00
311.00	10	Ludipress	311.00
10.00	11	Carbonyl iron (powder OF)	10.00
3.00	12	Magnesium stearate	3.00
7.20	13	Orange flavor	7.20
2.50	14	Saccharin sodium	2.50

Manufacturing Directions

1. Mix all ingredients, pass through a 0.8-mm sieve, mix, and press with high compression force (20 kN).
2. Compress 500 mg in 12-mm biplanar punches.

Multivitamin and Fluoride Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
1.20	1	Riboflavin; use coated riboflavin (25% excess)	5.28
0.30	2	Folic acid (powder)	0.31
1.00	3	Fluoride; use sodium fluoride (powder)	2.21
19.50	4	Starch (bright yellow 2 LA)	19.50
1.05	5	Pyridoxine; use pyridoxine hydrochloride (6% excess)	4.02
1.05	6	Thiamine HCl; use coated thiamine mononitrate (5% excess)	3.21
13.50	7	Niacin; use nicotinamide	40.20
4.50 μg	8	Vitamin B_{12}; use cyanocobalamin oral powder in starch (10% excess)	5.17
20.00	9	Ascorbic acid; use surface-coated ascorbic acid and sodium	21.00
40.00	10	Sodium ascorbate; use surface-coated sodium ascorbate (5% excess)	47.25
7.49	11	Anhydrous citric acid	7.49
15 IU	12	Vitamin E; use vitamin E (D,L-alpha-tocopheryl) (5% excess)	31.50
400 IU (10 μg)	13	Vitamin D; use vitamin D_3 beadlets (25% excess)	0.65
9.36	14	Flavor	9.36
2500 IU or 0.75 mg	15	Vitamin A; use vitamin A palmitate beadlets (500 mU/g), USP (60% excess)	8.25
500.60	16	Sugar (compressible)	500.60

Manufacturing Directions

Manufacture this product at less than 40% RH and a temperature less than 26.7°C.

1. If lumpy, hand screen riboflavin through an 8-mesh screen and mix with folic acid, sodium fluoride powder, and approximately 3.5 g of bright yellow starch in a suitable blender until the yellow color of premix is uniform.
2. Cross-feed the premixed items, pyridoxine hydrochloride, thiamine mononitrate, nicotinamide, cyanocobalamin oral powder in starch, ascorbic acid, citric acid, and vitamin E through an 846-μm screen on a comminuting mill (knives forward, medium speed).
3. Transfer the powders to a suitable blender.
4. Clear mill with a part of the compressible sugar and transfer to the blender.
5. Charge vitamin D_3 beadlets, sodium ascorbate, flavor, and vitamin A palmitate into the blender.
6. Blend for 10 minutes.
7. Discharge the contents of the blender into polyethylene-lined drums.
8. Pass the remaining compressible sugar through an 846-μm screen on a comminuting mill (knives forward, medium speed).
9. Transfer to the blender.
10. Screen the material from previous step, the magnesium stearate, and the remaining bright yellow starch through an 846-μm screen and transfer to the blender. (*Note*: Mill material not passing through the screen through an 846-μm screen on a comminuting mill at medium speed with knives forward.) Blend for 20 minutes.
11. Discharge blender into polyethylene-lined drums and weigh for yield.
12. Use precompression, if available, to obtain a tablet with adequate friability.
13. Coat as needed (see appendix).

Multivitamin and Mineral Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
6.65	1	Hypophosphorous acid (50% pure)	6.655
16.47	2	Calcium hypophosphite	16.47
31.68	3	Calcium lactate (powder)	31.68
1.00	4	Methyl paraben	1.00
0.20	5	Propyl paraben	200.00 mg
1.00	6	Acid benzoic	1.00
150.00	7	Sucrose	150.00
5.20	8	Ferrous gluconate	5.20
2.00	9	Niacinamide (white powder) (5% excess)	2.10
0.32	10	Riboflavin-5-phosphate sodium	328.77 mg
1.00	11	D-Pantothenyl alcohol (dexpanthenol; 20% excess)	1.20
0.00060	12	Vitamin B_{12} (cyanocobalamin; 35% excess)	810.00 μg
0.20	13	Pyridoxine hydrochloride	200.00 mg
0.30	14	Thiamine hydrochloride (powder, regular) (55% excess)	465.00 mg
4.78	15	Flavor, raspberry blend	4.782
1.94	16	Flavor, chocolate	1.945
0.64	17	Orange oil, terpeneless No. 54125	642.00 mg
0.21	18	Lime oil (distilled)	214.975 mg
4.28	19	Alcohol (ethanol, 190 proof)	4.28
2.50	20	Saccharin sodium	2.50
10.00	21	Acid ascorbic (45% excess)	14.50
3.00	22	Caramel (acid proof)	3.00
2.00	23	Anhydrous citric acid	2.00
0.0010	24	Butylated hydroxyanisole (BHA)	10.0 mg
3.39	25	Corn oil	3.39
0.56	26	Vitamin A palmitate (1.5 million UA/g, 40% excess)	560.00 mg
0.08	27	Viosterol in corn oil (syn. oleovitamin D; 1000 mD/g; D_3 in arachis oil) (40% excess)	112.00 mg
1.50	28	Acacia	1.50
0.12	29	Sodium lauryl sulfate (acetone washed)	127.41 mg
171.00	30	Purified water	~171.00
QS	31	Glucose liquid	QS to 1 L

Manufacturing Directions

Do not expose this preparation during manufacturing to direct sunlight. Riboflavin is sensitive to light.

1. Add 83.7 mL of purified water to a stainless steel jacketed tank.
2. Add calcium hypophosphite, calcium lactate, parabens, and benzoic acid.
3. Heat mixture to 60°C with agitation.
4. Shut off mixer and wash tank free of all powders with 25.9 mL purified water.
5. Heat to and maintain a maximum temperature of 100°C until solution is complete. Do not agitate. Avoid loss of water through evaporation. Cover opening of tank. After solution occurs, take sample from bottom of tank and examine for clarity. Solution must be clear.
6. Add acid hypophosphorous (if used) with mixing.
7. Turn off heat and add 222 g glucose and start agitator. (*Caution*: Use CO_2 cover throughout. Wherever water is used, it should be CO_2-saturated water.) Dissolve ferrous gluconate in 7.4 mL water CO_2 saturated by heating.
8. Add 278 g glucose with mixing. Add and dissolve sugar.
9. Allow solution to cool to 35°C and mix well.
10. To 29.6 mL water, add and dissolve nicotinamide, riboflavin, D-pantothenyl alcohol, vitamin B_{12}, pyridoxine, and thiamine.

11. Mix until solution is complete and add to tank. Dissolve by heat, if necessary.
12. Charge raspberry blend flavor and chocolate flavor into tank.
13. Charge saccharin into tank and mix until dissolved.
14. Charge ascorbic acid into tank and mix well.
15. Charge caramel into tank and mix well.
16. Dissolve citric acid in 3 mL water and add this solution to above.
17. Heat corn oil to 50°C to 60°C and add and dissolve BHA. Be sure the BHA is completely dissolved before continuing.
18. Cool to room temperature. While cooling oil mixture, saturate with CO_2 and maintain heavy CO_2 coverage for balance of operation.
19. Set aside a small amount of this mixture as a rinse for the vitamin A and viosterol containers in previous step.
20. Add vitamin A palmitate and viosterol to the cool corn oil mixture, rinsing the containers with the oil reserved earlier.
21. Add the rinse to the bulk and mix well.
22. Add the acacia to the oil mixture with good mixing.
23. Dissolve sodium lauryl sulfate in 3 mL CO_2-saturated purified water. To avoid excessive foaming, do not bubble CO_2 gas through the water/sodium lauryl sulfate solution.
24. Add the sodium lauryl sulfate solution to the oil mixture and stir to a thick creamy emulsion.
25. Add 7.56 g glucose to the emulsion with mixing.
26. Blend 13.33 mL CO_2-saturated purified water with 77.04 g glucose and add emulsion with stirring.
27. Recycle primary emulsion back into the holding tank while setting mill.
28. Homogenize until all oil globules are less than 8 μm in diameter using colloid mill with a fine setting. After setting mill, sample. Do not change mill setting after removing sample unless samples are unacceptable.
29. Add primary emulsion to syrup solution with mixing. Add glucose QS to 965 mL and mix well.
30. Allow to stand overnight to vent entrapped air. Adjust the volume to 1 L using glucose or glucose and CO_2-saturated water.
31. Strain through 149-μm aperture or similar screen into clean reserve tank and recheck volume.

Multivitamin and Mineral Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
4000 IU/400 IU	1	Vitamin A/vitamin D crystalets (500,000 A/50,000 D/g) (25% excess)	10.00
40.00	2	Vitamin A acetate (powder; 500 MA) (20% excess)	50.00
10.00	3	Thiamine hydrochloride (10% excess)	11.00
5.00	4	Riboflavin	5.00
100.00	5	Nicotinamide niacinamide (white powder)	100.00
200.00	6	Ascorbic acid (white powder) (10% excess)	220.00
20.00	7	Calcium pantothenate (dextro) (30% excess)	26.00
5.00	8	Pyridoxine hydrochloride	5.00
7.33	9	Povidone (K-29–32)[a]	7.33
29.16	10	Anydrous refined alcohol isopropyl	29.16
24.20	11	Talc powder	24.20
6.07	12	Magnesium stearate (impalpable powder)	6.07
4.75	13	Stearic acid (fine powder)	4.75
10.0	14	Iron, use; iron sulfate (dried)	31.26
1.00	15	Copper[a]	1.00
0.15	16	Iodine[a]	0.15
1.00	17	Manganese[a]	1.00
5.00	18	Magnesium[a]	5.00
1.50	19	Zinc[a]	1.50
0.10	20	Cobalt; use cobalt sulfate	0.47
5.00	21	Potassium; use potassium sulfate	11.14
0.20	22	Molybdenum; use sodium molybdate (dihydrate)	0.50
6.00 μg	23	Vitamin B_{12}; use cyanocobalamin (1000 μg/g oral powder in gelatin; 5% excess)	6.30

[a]Provided as mineral mix (includes 3% excess).

Bill of Materials for Mineral Mix			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
13.85	1	Copper sulfate	14.28
0.01175	2	Calcium iodate monohydrate	0.01212
0.1228	3	Manganese sulfate monohydrate	0.1267
0.1480	4	Zinc sulfate (pure dry powder)	0.1526

Manufacturing Directions

1. Mineral mix processing:
   a Grind copper sulfate, calcium iodate, manganese sulfate, and zinc sulfate through Fitz mill screen 0 band (high speed, impact forward).
   b. *Note*: Vitamin A is susceptible to destruction by oxidation and also excessive exposure to actinic light and moisture. Compression of this tablet should be done where RH is less than 40%. Protect granulation with CO_2 if material is not to be compressed soon after granulation.
   c. Hand screen vitamins A and D crystallets and vitamin A acetate through 1.2-mm aperture screen.
   d. Load into mass mixer (screen using 1.2-mm aperture screen, if necessary) thiamine HCl, riboflavin, nicotinamide, ascorbic acid, calcium pantothenate, pyridoxine HCl, and the vitamins A and D mix from above.
   e. Blend for 10 minutes.
   f. Dissolve povidone in alcohol (approximately 26 mL).
   g. Add povidone solution to blended materials and mix for 5 minutes.
   h. Scrape mixer, then add alcohol to mass (approximately 11 mL).
   i. Pass wet mass through a 15.88-mm aperture (or similar), band-fitted to rotary granulator. (*Note*: Wet mass can set hard; therefore, granules should be spread quickly onto trays.) Dry the granulation at 49°C until LOD is less than 1.0%.
   j. Pass the dried granulation through a 1.2-mm aperture screen fitted to an oscillating granulator.
   k. Mill the talc (item 11), magnesium stearate, stearic acid, iron sulfate, mineral mix, cobalt sulfate, potassium sulfate, and sodium molybdate through a 595-μm-aperture screen at high speed, impact forward.
   l. Load half of the granulation into a suitable blender. Add mineral mix and cyanocobalamin oral powder.
   m. Add balance of granulation and blend for 30 minutes.
   n. Compress and coat using a sealing subcoating of PVP (see appendix), followed by HPMC coating solution and clear Methocel gloss.

Multivitamin and Mineral Tablets with Beta-Carotene

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
150.00	1	Beta-carotene (dry powder; 10%)	150.00
2.50	2	Thiamine mononitrate	2.50
2.90	3	Riboflavin	2.90
2.00	4	Pyridoxine hydrochloride	2.00
22.00	5	Nicotinamide	22.00
12.00	6	Calcium D-pantothenate	12.00
110.00	7	Ascorbic acid for direct compression	110.00
550.00	8	Calcium phosphate (dibasic)	550.00
82.00	9	Ferrous fumarate	82.00
166.00	10	Magnesium oxide	166.00
2.50	11	Cupric sulfate	2.50
13.80	12	Manganese sulfate	13.80
57.20	13	Potassium chloride	57.20
37.00	14	Zinc sulfate	37.00
57.00	15	Avicel PH102	57.00
50.00	16	Kollidon CL	50.00
5.70	17	Stearic acid	5.70
5.00	18	Magnesium stearate	5.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with high compression force.
2. Compress 1300 mg per tablet using 16-mm biplanar punches.

Multivitamin, Calcium, and Iron Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
5.00	1	Vitamin A acetate (dry powder)	5.00
2.00	2	Vitamin D (dry powder; 500,000 IU/g)	2.00
1.20	3	Thiamine mononitrate (100,000 IU/g)	1.20
1.80	4	Riboflavin, BASF	1.80
12.00	5	Nicotinamide	12.00
4.00	6	Vitamin E acetate (dry powder, SD 50)	4.00
50.00	7	Ascorbic acid (powder), BASF	50.00
60.00	8	Ferrous fumarate	60.00
200.00	9	Dibasic calcium phosphate granulated with 5% Kollidon 30	200.00
125.00	10	Calcium carbonate	125.00
45.00	11	Avicel PH101	45.00
1.50	12	Aerosil 200	1.50

Manufacturing Directions

1. Mix all components, pass through a sieve, and press to tablets.
2. Compress 500 mg in 11-mm biplanar punches.

Multivitamin + Calcium + Iron Tablets (1 RDA of Vitamins)

Formulation

Vitamin A acetate dry powder, 500,000 IU/g (BASF), 5.0 g; vitamin D dry powder, 100,000 IU/g, 2.0 g; thiamine mononitrate, 1.2 g; riboflavin, 1.8 g; nicotinamide, 12.0 g; vitamin E acetate dry powder SD 50, 4.0 g; ascorbic acid, powder, 50.0 g; ferrous fumarate, 60.0 g; dibasic calcium phosphate [9], 200.0 g; granulated with 5% Kollidon 30; calcium carbonate, 125.0 g; Avicel PH 101, 45.0 g; Aerosil 200, 1.5 g.

Manufacturing Directions

1. Mix all components, pass through a sieve, and press to tablets at 500 mg.

Multivitamin + Carbonyl Iron Tablets (1–2 RDA of Vitamins)

Formulation

Vitamin A acetate dry powder, 500,000 IU/g, 10.0 g; thiamine mononitrate, 2.2 g; riboflavin, 2.2 g; nicotinamide, 16.5 g; calcium D-pantothenate, 11.5 g; pyridoxine hydrochloride, 2.2 g; cyanocobalamin, dry powder 0.1%, 6.0 g; ascorbic acid, powder, 85.0 g; vitamin E acetate dry powder SD 50, 31.0 g; Ludipress, 311.0 g; carbonyl iron powder OF, 10.0 g; magnesium stearate, 3.0 g; orange flavor, 7.2 g; saccharin sodium, 2.5 g.

Manufacturing Directions

1. Mix all ingredients, pass through a 0.8-mm sieve, mix, and press with high compression force (20 kN) at 500 mg.

Multivitamin Chewable Tablets for Children

Formulation

Vitamin A acetate dry powder, 500,000 IU/g, 7.0 g; thiamine mononitrate, 1.2 g; riboflavin, 1.2 g; nicotinamide, 20.0 g; pyridoxine hydrochloride, 1.8 g; cyanocobalamin, 0.1% dry powder, 6.5 g; ascorbic acid, powder, 60.0 g; vitamin D_3 acetate dry powder, 100,000 IU/g, 5.0 g; vitamin E acetate, 31.0 g; dry powder SD 50; sorbitol, crystalline [10], 200.0 g; sucrose, crystalline, 200.0 g; Kollidon VA 64, 20.0 g; Aerosil 200, 1.0 g; orange flavor, dry powder, 30.0 g; raspberry flavor, dry powder, 6.0 g; passion fruit flavor, dry powder, 3.0 g; cyclamate sodium, 2.0 g.

Manufacturing Directions

1. Mix all ingredients, pass through a 0.8-mm sieve, and press with medium to high compression force (20 kN) at 575 mg.

Multivitamin Chewable Tablets for Children

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
3500 IU	1	Vitamin A acetate (dry powder; 500,000 IU/g)	7.00
1.20	2	Thiamine mononitrate	1.20
1.20	3	Riboflavin	1.20
20.00	4	Nicotinamide	20.00
1.80	5	Pyridoxine hydrochloride	1.80
6.50	6	Cyanocobalamin (dry powder; 0.1%), BASF	6.50
60.00	7	Ascorbic acid (powder)	60.00
5.00	8	Vitamin D_3 acetate (dry powder; 100,000 IU/g)	5.00
31.00	9	Vitamin E acetate (dry powder, SD 50)	31.00
200.00	10	Sorbitol (crystalline)	200.00
200.00	11	Sucrose (crystalline)	200.00
20.00	12	Kollidon VA 64	20.00
1.00	13	Aerosil 200	1.00
30.00	14	Orange flavor (dry powder)	30.00
6.00 g	15	Raspberry flavor (dry powder)	6.00
3.00	16	Passion fruit flavor (dry powder)	3.00
2.00	17	Cyclamate sodium	2.00

Manufacturing Directions

1. Mix all ingredients, pass through a 0.8-mm sieve, and press with medium to high compression force (20 kN).
2. Compress 575 mg using 12-mm biplanar punches.

Multivitamin Drops

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
13,600 IU	1	Vitamin A palmitate (1.7 MM IU/g)	8.00
5200 IU	2	Vitamin D_3 (40 MM IU/g)	0.13
5.00	3	Vitamin E acetate	5.00
150.0	4	Cremophor EL (or Cremophor RH 40)	150.00
2.00	5	Parabens (methyl and propyl)	2.00
525.00	6	Water purified	525.00
4.00	7	Thiamine hydrochloride	4.00
2.00	8	Riboflavin 5-phosphate sodium	2.00
2.00	9	Pyridoxine hydrochloride	2.00
2.00	10	Nicotinamide	2.00
0.20	11	Sodium bisulfite	0.20
200.00	12	Propylene glycol	200.00
QS	13	Water purified	10.00
QS	14	Hydrochloric acid	QS

Manufacturing Directions

1. Heat mixture of items 1 to 4 to approximately 60°C, stir strongly, and slowly add solution of items 5 and 6 (60°C).
2. To the obtained clear solution, add solution of items 7 to 13.
3. Adjust the pH with item 14 to approximately 4 and QS to volume.

Multivitamin Effervescent Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/1000 Sachet (g)
2.60	1	Thiamine hydrochloride	0.26
3.00	2	Riboflavin	0.30
11.00	3	Nicotinamide	1.10
2.50	4	Pyridoxine hydrochloride	0.25
15.00	5	Calcium D-pantothenate	1.50
200.00	6	Ascorbic acid (powder)	20.00
500.00	7	Citric acid	50.00
1300.00	8	Sucrose	130.00
800.00	9	Fructose	80.00
200.00	10	Kollidon CL-M	20.00
250.00	11	Flavors	25.00
20.00	12	Cyclamate sodium	2.00
1.00	13	Saccharine sodium	0.10
150.00	14	Kollidon VA 64	15.00
350.00	15	Isopropanol	35.00
5000 IU	16	Vitamin A acetate (dry powder; 325,000 IU/g CWD)	1.50
800 IU	17	Vitamin D_3 (dry powder; 100,000 IU/g CWD)	0.80
21.00	18	Vitamin E acetate (dry powder; 50%)	2.10
0.0660	19	Cyanocobalamin (gelatin-coated; 0.1%)	0.66
400.00	20	Sodium bicarbonate	40.00

Manufacturing Directions

1. Granulate mixture of items 1 to 13 with solution of items 14 and 15.
2. Pass through a 0.8-mm sieve, dry well, and mix with items 16 to 20.
3. Fill 4 g in sachets.

Multivitamin Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
13.00	1	Thiamine mononitrate	13.00
4.00	2	Riboflavin	4.00
11.00	3	Pyridoxine hydrochloride	11.00
66.00	4	Nicotinamide	66.00
17.00	5	Calcium D–pantothenate	17.00
360.00	6	Tartaric acid (powder)	360.00
550.00	7	Sodium bicarbonate	550.00
300.00	8	Sucrose (crystalline)	300.00
300.00	9	Sucrose (powder)	300.00
35.00	10	Kollidon 30	35.00
5.00	11	Kollidon 30	5.00
QS	12	Isopropanol	~80.00
6.00	13	Riboflavin	6.00
550.00	14	Ascorbic acid (powder)	550.00
20.00	15	Cyanocobalamin (dry powder, 0.1%)	20.00
12.00	16	Vitamin A palmitate (250,000 IU/g dry powder CWD)	12.00
60.00	17	Vitamin E acetate (dry powder; 50%)	60.00
80.00	18	PEG-6000 (powder)	80.00
100.00	19	Kollidon CL	100.00

Manufacturing Directions

1. Granulate the mixture of items 1 to 10 with solution of items 11 and 12. Dry at 60°C with vacuum.
2. Mix with items 13 to 19 and press with high compression force at maximum 30% of relative atmospheric humidity.
3. Compress 2.5 g per tablet using 20-mm biplanar punches.

Multivitamin Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
5.50	1	Thiamine mononitrate	5.50
5.50	2	Riboflavin	5.50
6.50	3	Pyridoxine hydrochloride	6.50
60.00	4	Nicotinamide	60.00
30.00	5	Calcium D-pantothenate	30.00
200.00	6	Ascorbic acid (powder)	200.00
0.20	7	Cyanocobalamin (dry powder, 0.1%)	20.00
30.00	8	Vitamin A acetate (dry powder; 325,000 IU/g CWD)	30.00
55.00	9	Vitamin E acetate (dry powder; 50%)	110.00
500.00	10	Citric acid (powder)	500.00
400.00	11	Tartaric acid (powder)	400.00
500.00	12	Sodium bicarbonate	500.00
600.00	13	Ludipress	600.00
70.00	14	PEG-6000 (powder)	70.00
0.50	15	Saccharin sodium	0.50
40.00	16	Cyclamate sodium	40.00
200.00	17	Sucrose, crystalline	200.00
200.00	18	Fructose	200.00
100.00	19	Flavors (Firmenich)	100.00

Manufacturing Directions

1. Mix all components and sieve through a 0.8-mm screen.
2. Press with high compression force at maximum 30% relative atmospheric humidity.
3. Compress 3 g in 20-mm biplanar punches.

Multivitamin Effervescent Tablets I, DC (1–2 RDA of Vitamins)

Formulation

Lucarotene dry powder 10%, 23.0 g; CWD G/Y, dry vitamin E acetate 50% DC, 40.0 g; thiamine mononitrate, 2.0 g; riboflavin C, 2.0 g; nicotinamide, 22.0 g; calcium D-pantothenate, 11.0 g; pyridoxine hydrochloride, 2.0 g; cyanocobalamin 0.1% dry powder, 6.0 g; ascorbic acid, powder, 85.0 g; Ludipress LCE, 477.0 g; sodium bicarbonate, 600.0 g; tartaric acid, 400.0 g; polyethylene glycol 6000, powder, 90.0 g; orange flavor (Dragoco), 60.0 g; aspartame (Searle), 30.0 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, mix, and press with high compression force at a maximum of 30% of relative atmospheric humidity at 1850 mg.

Multivitamin Effervescent Tablets II, DC (3–4 RDA of Vitamins)

Formulation

Thiamine mononitrate, 5.5 g; riboflavin, 5.5 g; pyridoxine hydrochloride, 6.5 g; nicotinamide, 60.0 g; calcium D-pantothenate, 30.0 g; ascorbic acid, powder, 200.0 g; cyanocobalamin 0.1% dry powder, 20.0 g; vitamin A palmitate dry powder, 325,000 IU/g CWD, 30.0 g; vitamin E acetate dry powder 50%, 110.0 g; tartaric acid, powder, 400.0 g; sodium bicarbonate, 500.0 g; Ludipress, 600.0 g; polyethylene glycol 6000, powder, 70.0 g; saccharin sodium, 0.5 g; cyclamate sodium, 40.0 g; sucrose, crystalline, 200.0 g; fructose, 200.0 g; flavors (Firmenich), 100.0 g.

Manufacturing Directions

Mix all components, sieve through a 0.8-mm screen, and press with high compression force at maximum 30% relative atmospheric humidity.

Multivitamin Effervescent Tablets with Beta-Carotene

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
2.00	1	Thiamine mononitrate	2.00
2.00	2	Riboflavin	2.00
2.00	3	Pyridoxine hydrochloride	2.00
22.00	4	Nicotinamide	22.00
11.00	5	Calcium D–pantothenate	11.00
400.00	6	Tartaric acid (powder)	400.00
300.00	7	Lactose monohydrate	300.00
100.00	8	Cornstarch	100.00
3.00	9	Cornstarch	3.00
50.00	10	Water	50.00
23.00	11	Beta-carotene (dry powder; 10% CWD; food grade)	23.00
6.00	12	Cyanocobalamin (powder; 0.1%)	6.00
85.00	13	Ascorbic acid (powder)	85.00
40.00	14	Vitamin E acetate (dry powder; 50%)	40.00
600.00	15	Sodium bicarbonate	600.00
80.00	16	Flavors	80.00
QS	17	Saccharin sodium	QS

Manufacturing Directions

1. Granulate mixture of items 1 to 6 with solution of items 9 and 10 prepared at 70°C.
2. Dry and sieve, add items 11 to 17, pass through a 0.4-mm sieve, and press with high compression force at maximum 30% of relative atmospheric humidity.
3. Compress 1.63 g using 16-mm biplanar punches.

Multivitamin Infant Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1125 IU	1	Vitamin A palmitate (1.7 MM IU/g, 50% excess)	1.324
416 IU	2	Vitamin D (40 MM IU/g, cholecalciferol, 25% excess)	0.013
5.00	3	Vitamin E (oily; alpha-tocopheryl acetate)	5.00
52.50	4	Ascorbic acid (50% excess)	52.50
0.375	5	Thiamine hydrochloride (50% excess)	0.75
0.40	6	Pyridoxine hydrochloride	0.40
8.00	7	Nicotinamide	8.00
0.00125	8	Cyanocobalamin (50% excess)	0.0025
0.82	9	Riboflavin sodium phosphate (5% excess as riboflavin)	0.865
2.50	10	Polyoxyl 20 cetostearyl ether (Cetomacrogol 1000)	2.50
12.50	11	Polysorbate 80 (Tween 80)	12.50
0.50	12	Edetate disodium (sodium EDTA)	0.50
3.75	13	Sodium hydroxide	3.75
0.25	14	Saccharin sodium	0.25
300.00	15	Glycerin (glycerol)	300.00
500.00	16	Sorbitol (70% solution)	500.00
50.00	17	Propylene glycol	50.00
1.50	18	Flavor	1.50
3.00	19	Flavor	3.00
1.50	20	Flavor	1.50
–	21	Purified water	QS to 1 L

Manufacturing Directions

The product is a microemulsion and thermolabile. The temperature of solution must not exceed 25°C at the time of processing. Store bulk at temperature 15°C to 20°C under nitrogen protection to avoid discoloration and precipitation. Period of storage should not exceed 48 hours prior to filling in the bottle.

1. Check and record pH of item 21 (limit: 5.0–6.5) and collect 250 g of it in manufacturing vessel. Heat to 90°C to 95°C for 10 minutes, then cool to 20°C to 25°C.
2. Bubble nitrogen gas into cooled item 21 for 20 minutes.
3. Load 200 g of item 21 from first step to the manufacturing vessel.
4. Bubble nitrogen gas during all stages of the process.
5. Charge items 4 to 9 and 12 to 14 one by one to the manufacturing vessel while mixing.
6. Check that all materials are dissolved completely. Solution should be clear.
7. Add item 11 in a separate stainless steel container and heat to 45°C.
8. Mix items 1, 2, 3, and 10 one by one.
9. Mix for 1 hour at slow speed.
10. Add oil phase preparation to the aqueous phase at a rate of 2 mL/min while mixing. Keep on bubbling nitrogen gas throughout the process.
11. Add items 15 and 16 to the manufacturing vessel one by one while mixing.
12. Keep on bubbling nitrogen gas throughout the process.
13. Add items 18, 19, and 20 in item 17 and add to the manufacturing vessel while mixing.
14. Adjust the volume to 1 L using nitrogen-bubbled item 21.
15. Mix for 10 minutes at slow speed without aeration.
16. Check pH (limit: 3.7–4.5).
17. Filter the product at 1.5 bar.
18. Recirculate approximately 100 to 150 mL of product.
19. Transfer the filtered product to the storage vessel under a nitrogen blanket.

Multivitamin Infant Drops

Bill of Materials			
Scale (mg/0.6 mL)	Item	Material Name	Qty/L (g)
675.00	1	Glycerin, USP (96%)	675.00
10.00	2	Nicotinamide niacinamide (white powder) (5% excess)	17.50
2.74	3	Riboflavin-5′-phosphate sodium (0% excess)	2.74
0.50	4	Methyl paraben (powder)	500.00 mg
1.00	5	Benzoic acid	1.00
2.10	6	Saccharin sodium (powder)	2.10
1.50	7	Thiamine HCl (45% excess)	3.625
0.60	8	Pyridoxine HCl	833.34 mg
50.00	9	Ascorbic acid (white powder) (20% excess)	100.00
0.257	10	Orange oil terpeneless No. 54125	257.789 mg
0.095	11	Alcohol (ethanol)	95.50 mg
80.00	12	Polysorbate 80	80.00
0.186	13	Butylated hydroxyanisole	186.92 mg
400 IU	14	Vitamin D viosterol in corn oil (oleovitamin D) (25% excess)	833.34 mg
5000 IU	15	Vitamin A; use vitamin A palmitate (1,500,000 AU/g) (50% excess[a])	16.66
QS	16	Purified water	329
QS	17	Carbon dioxide gas	QS

[a]Excess includes 20% manufacturing loss and 30% stability excess.

Manufacturing Directions

Use carbon dioxide cover at all time and use stainless steel 316 or higher resistant equipment.

1. Add 300 mL of purified water and the glycerin into a suitable jacketed tank. Start mixing.
2. Add, in this order, nicotinamide, riboflavin-5-phosphate sodium, Aspetoform M, benzoic acid, and saccharin sodium.
3. Continue mixing for balance of process.
4. Heat to 90°C to 100°C to dissolve ingredients.
5. In a separate tank, boil at least 15 mL of purified water for at least 15 minutes.
6. Cool while bubbling CO_2 gas into it and hold at 30°C or lower for use later for making up the volume.
7. Start cooling the main tank. When the temperature reaches 50°C to 60°C, start bubbling CO_2 gas through the solution from the bottom of the tank.
8. Continue cooling to 25°C. Continue the CO_2 gas protection for the balance of the process.
9. Add and dissolve thiamine HCl, pyridoxine HCl, and ascorbic acid.
10. Dissolve orange oil in alcohol and add.
11. Load approximately 5.25 g of Polysorbate 80 into a separate stainless steel container.
12. Heat to 50°C to 60°C. Add the butylated hydroxyanisole and dissolve with mixing. Remove heat.
13. Add remaining Polysorbate 80 into the container, setting aside a sufficient quantity for rinsing the vitamin containers.
14. Bubble in CO_2 gas while mixing slowly. Stop mixing.
15. Add viosterol and vitamin A palmitate.
16. Rinse bottles with remaining Polysorbate 80 and drain.
17. Mix slowly for at least 30 minutes or longer, if necessary, to provide a clear solution. Continue to bubble CO_2 gas for the entire mixing period.
18. Change CO_2 gas protection on main mixing tank to the top to prevent excessive foaming upon addition of Polysorbate 80 solution.
19. Add Polysorbate 80 solution to the main tank from the bottom of the tank to the top to prevent excessive foaming. Stop mixing.
20. If the volume is less than 1000 mL, adjust the volume with CO_2-saturated purified water made above to 1000 mL. Mix for at least 1 hour.
21. In a separate tank, boil at least 115 mL of purified water for at least 15 minutes.
22. Cool while bubbling CO_2 gas into it and hold at 30°C or lower for use later. Stop mixing.
23. Allow to stand for at least 4 hours to eliminate entrappped CO_2 gas.
24. Readjust volume to 1000 mL with CO_2-saturated purified water. Mix for at least 1 hour. Stop mixing.
25. Filter through lint-free paper and do not use filter aids.
26. Recirculate product back to mixing tank until clear.
27. Flush storage tank with CO_2 gas and continue CO_2 gas protection until product has been filled.
28. Average intake dose is 0.60 mL.

Multivitamin Instant Granules

Bill of Materials			
Scale (mg/sachet)	Item	Material Name	Qty/30 kg (g)
40.00	1	Vitamin A and vitamin D (dry powder + 50,000 IU/g CWD)	200.00
5.00	2	Thiamine mononitrate	26.00
6.00	3	Riboflavin	33.00
22.00	4	Nicotinamide	110.00
4.50	5	Pyridoxine hydrochloride	22.00
30.00	6	Calcium D-pantothenate	150.00
0.013	7	Cyanocobalamin; use cyanocobalamin (gelatin-coated, 0.1%)	66.00
230	8	Ascorbic acid powder	1150.00
–	9	Vitamin E acetate dry powder	210.00
4000	10	Sucrose (finely ground)	20,000.00
1000	11	Kollidon CL-M	5000.00
200	12	Orange flavor	1000.00
400	13	Kollidon VA 64	2000.00
–	14	Ethanol or isopropanol	~7.00 L

Manufacturing Directions

1. Pass mixture through a 0.8-mm sieve and granulate with solution of items 13 and 14 in the fluidized bed.
2. Fill 6 to 12 g of the granules in sachets.
3. If the technology of a fluidized bed is not available, the dry powders of vitamins A, B_{12}, and E should be added after granulation of the other components.
4. Suspend 6 to 12 g (= 1 sachet) in a glass of water (corresponds to 2 to 4 RDA of vitamins).

Multivitamin Mineral Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
6.65	1	Acid hypophosphorous (50% pure)	6.65
16.47	2	Calcium hypophosphite	16.47
31.68	3	Calcium lactate (powder)	31.68
1.00	4	Methyl paraben	1.00
0.20	5	Propyl paraben	200.00 mg
1.00	6	Benzoic acid	1.00
150.00	7	Sucrose (granular)	150.00
5.20	8	Ferrous gluconate	5.20
2.00	9	Niacinamide (5% excess)	2.10
0.32	10	Riboflavin-5-phosphate sodium	328.77 mg
1.00	11	D-Pantothenyl alcohol (dexpanthenol) (20% excess)	1.20
0.60	12	Vitamin B_{12} (cyanocobalamin) (35% excess)	810.00 μg
0.20	13	Pyridoxine hydrochloride	200.00 mg
0.30	14	Thiamine hydrochloride (regular powder) (55% excess)	465.00 mg
4.78	15	Flavor	4.78
1.94	16	Flavor	1.94
0.64	17	Orange oil, terpeneless	642.00 mg
0.21	18	Lime oil, distilled	214.97 mg
4.28	19	Alcohol (190 proof)	4.28
2.50	20	Saccharin sodium	2.50
14.50	21	Acid ascorbic (white powder/EP) (45% excess)	14.50
3.00	22	Caramel (acid proof)	3.00
2.00	23	Anhydrous citric acid (powder/EP)	2.00
0.01	24	Butylated hydroxyanisole (BHA)	10.00 mg
3.39	25	Corn oil	3.39
0.40	26	Vitamin A palmitate (TN, 1.5 MM UA/g) (40% excess)	560.00 mg
0.08	27	Viosterol in corn oil (syn. oleovitamin D; 1000 mD/g; D_3 in arachis oil) (40% excess)	112.00 mg
1.50	28	Acacia	1.50
0.12	29	Sodium lauryl sulfate (acetone washed)	127.41 mg
171.00	30	Deionized, purified water	171.00
QS	31	Glucose liquid	QS to 1 L

Manufacturing Directions

Do not expose this preparation during manufacturing to direct sunlight. Riboflavin is sensitive to light.

1. Add 83.7 mL of purified water to a stainless steel jacketed tank.
2. Add calcium hypophosphite, calcium lactate, parabens, and benzoic acid.
3. Heat mixture to 60°C with agitation.
4. Shut off mixer and wash tank free of all powders with 25.9 mL purified water.
5. Heat mixture to and maintain a maximum temperature of 100°C until solution is complete. Do not agitate. Avoid loss of water through evaporation. Cover opening of tank.
6. After solution occurs, take sample from bottom of tank and examine for clarity. Solution must be clear.
7. Add acid hypophosphorous (if used) with mixing.
8. Turn off heat and add 222 g glucose and start agitator. (*Caution*: Use CO_2 cover throughout. Wherever water is used, it should be CO_2-saturated water.) Dissolve ferrous gluconate in 7.4 mL water CO_2 saturated by heating.
9. Add 278 g glucose with mixing. Add and dissolve sugar.
10. Allow solution to cool to 35°C and mix well.
11. To 29.6 mL water, add and dissolve nicotinamide, riboflavin, D-pantothenyl alcohol, vitamin B_{12}, pyridoxine,

and thiamine. Mix until solution is complete and add to tank. Dissolve by heat, if necessary.
12. Charge flavors into tank.
13. Charge saccharin into tank and mix until dissolved.
14. Charge ascorbic acid into tank and mix well.
15. Charge caramel into tank and mix well. Dissolve citric acid in 3 mL water and add to above.
16. Heat corn oil to 50°C to 60°C and add and dissolve BHA. Be sure the BHA is completely dissolved before continuing.
17. Cool to room temperature. While cooling oil mixture, saturate with CO_2 and maintain heavy CO_2 coverage for balance of operation.
18. Set aside a small amount of this mixture as a rinse for the vitamin A and viosterol containers above.
19. Add vitamin A palmitate TN and viosterol to the cool corn oil mixture, rinsing the containers with the oil reserved above.
20. Add the rinse to the bulk. Mix well.
21. Add the acacia to the oil mixture with good mixing.
22. Dissolve sodium lauryl sulfate in 3 mL CO_2-saturated purified water.
23. To avoid excessive foaming, do not bubble CO_2 gas through the water/sodium lauryl sulfate solution.
24. Add the sodium lauryl sulfate solution to the oil mixture and stir to a thick creamy emulsion.
25. Add 7.56 g glucose to the emulsion with mixing.
26. Blend 13.33 mL CO_2-saturated purified water with 77.04 g glucose and add emulsion with stirring.
27. Recycle primary emulsion back into holding tank while setting mill.
28. Homogenize until all oil globules are less than 8 μm in diameter using colloid mill with a fine setting.
29. Add primary emulsion to syrup solution with mixing. Add glucose QS to 965 mL and mix well.
30. Allow to stand overnight to vent entrapped air.
31. Adjust the volume to 1 L using glucose or glucose and CO_2-saturated water.
32. Strain through 149-μm aperture or similar screen into clean reserve tank and recheck volume.
33. Seal tank under heavy CO_2 until filled.

Multivitamin + Minerals Tablets with Beta-Carotene (1 RDA of Vitamins)

Formulation

Beta-carotene dry powder, Betavit 20%, 16.5 g; thiamine mononitrate, 1.7 g; riboflavin, 1.9 g; nicotinamide (Degussa), 22.0 g; calcium D-pantothenate, 12.0 g; pyridoxine hydrochloride, 2.2 g; ascorbic acid, crystalline, 72.0 g; vitamin E acetate dry powder 50%, 66.0 g; ferrous fumarate, 54.7 g; magnesium oxide, high density type, 165.8 g; copper II oxide, powder, 2.5 g; manganese sulfate, 6.9 g; zinc oxide, 18.7 g; potassium chloride (Baker), 76.3 g; dicalcium phosphate, DI-TAB [9], 550.0 g; Avicel PH 102, 60.0 g; croscarmellose, 32.0 g; Syloid® 244 FP (Grace), 6.0 g; stearic acid. 6.0 g; magnesium stearate. 6.0 g.

Manufacturing Directions

1. All ingredients are passed through a 0.8-mm sieve, blended in a mixer, and then compressed with medium to high compression force at 1193 mg.

Multivitamin Oral Gel

Formulation

I. Vitamin A palmitate, 1.7 million IU/g, 110 mg; vitamin E acetate, 1060 mg; BHT, 500 mg; Cremophor RH 40 [1], 20 g.
II. Water, 725 g.
III. Thiamine hydrochloride, 355 mg; riboflavin, 35 mg; pyridoxine hydrochloride, 177 mg; cyanocobalamin gelatin coated 1%, 35 mg; nicotinamide, 353 mg; folic acid, 35 mg; dexpanthenol, 353 mg; EDTA sodium, 300 mg; ferrous sulfate (7 H_2O), 438 mg; manganese chloride (4 H_2O), 638 mg; potassium iodide, 115 mg.
IV. Kollidon 90 F, 50 g; Lutrol F 127, 100 g; Lutrol F 127 [1], 100 g; Total amount: approximately 1000 g.

Manufacturing Directions

1. Heat mixture I to approximately 60°C to obtain a clear solution.
2. Add slowly the water II to the well-stirred solution I.
3. Dissolve III and IV in this mixed solution (step 2) at room temperature, cool to approximately 6°C, add IV, and stir until all Lutrol F 127 is dissolved.
4. Maintain the cool temperature until the air bubbles escaped.

Multivitamin Oral Gel Veterinary

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (mg)
18,700 IU	1	Vitamin A palmitate (1.7 MM IU/g)	110.00
1.06	2	Vitamin E acetate	1060.00
0.50	3	BHT	500.00
20.00	4	Cremophor RH 40	20.00 g
725.00 g	5	Water	725.00 g
0.355	6	Thiamine hydrochloride	355.00
0.035	7	Riboflavin	35.00
0.177	8	Pyridoxine hydrochloride	177.00
0.035	9	Cyanocobalamin (gelatin coated, 1%)	35.00
0.353	10	Nicotinamide	353.00
0.035	11	Folic acid	35.00
0.353	12	Dexpanthenol	353.00
0.30	13	EDTA sodium	300.00
0.438	14	Ferrous sulfate ($7H_2O$)	438.00
0.638	15	Manganese chloride ($4H_2O$)	638.00
0.115	16	Potassium iodide	115.00
50.00	17	Kollidon 90 F	50.00 g
100.00	18	Lutrol F 127	100.00 g
100.00	19	Lutrol F 127	100.00 g

Manufacturing Directions

1. Heat mixture of items 1 to 4 to approximately 60°C to obtain a solution.
2. Slowly add the water (item 5) to the well solution.
3. Dissolve items 6 to 16 and item 17 separately in this mixed solution at room temperature, cool to approximately 6°C, add item 19, and stir until all Lutrol F 127 clear is dissolved.
4. Maintain the cool temperature until the air stirred bubbles escape.

Multivitamin Oral Gel with Linoleic and Linolenic Acid

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/100 mL (mg)
0.05	1	Evening primrose oil (Epopure®, Prima Rosa/SA)	5.00 mL
0.30	2	Vitamin A palmitate (1.7 million IU/g)	30.00
0.19	3	Vitamin E acetate	19.00
0.00150	4	Vitamin D_3 (40 million IU/g)	150.00 μg
200.00	5	Cremophor RH 40	20.00 g
550.00	6	Water	55.00 g
0.03	7	Thiamine hydrochloride	3.00
0.03	8	Riboflavin	3.00
0.15	9	Pyridoxine hydrochloride	15.00
0.001	10	Cyanocobalamin (crystalline)	10.00 μg
0.001	11	Calcium D-pantothenate	10.00
0.005	12	Nicotinamide	50.00
10.00	13	Ascorbic acid (crystalline)	1.00 g
140.00	14	Lutrol F 127	14.00 g
50.00	15	Lutrol F 127	5.00 g

Manufacturing Directions

1. Prepare mixture of items 1 to 5 and heat to approximately 65°C.
2. Slowly add the warm water (item 6) (65°C) to the well-stirred mixture as before.
3. Dissolve items 7 to 14 at 20°C to 25°C in this clear solution.
4. Cool the obtained solution to approximately 5°C and dissolve the rest of the Lutrol F 127 (item 15).
5. Maintain the cool temperature until the air bubbles escape.
6. A clear yellow gel is obtained. 5 mL of evening primrose oil Epopure® contains 3.5 g linoleic acid and 0.45 g gamma-linolenic acid.

Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/100 mL (mg)
170 IU	1	Vitamin A palmitate (1.7 million IU/g)	10.00
2.00 IU	2	Vitamin D (40 million IU/g)	0.05
1.00	3	Vitamin E acetate	100.00
0.02	4	BHT	2.00
45.00	5	Cremophor RH 40	4.50 g
100.00	6	Water	10.00 g
450.00	7	Saccharose	45.00 g
2.00	8	Methyl paraben	200.00
0.08	9	Citric acid	80.00
9.60	10	Glycerol	9.60 g
250.00	11	Water	25.00 g
0.15	12	Thiamine hydrochloride	15.00
0.15	13	Riboflavin 5′-phosphate sodium	15.00
0.55	14	Nicotinamide	55.00
0.15	15	Pyridoxine hydrochloride	15.00
3.00	16	Ascorbic acid (crystalline)	300.00
1.00	17	Sorbic acid	100.00
5.00	18	Propylene glycol (Pharma)	5.00 g

Manufacturing Directions

1. Mix items 1 through 5 and heat to 60°C.
2. Separately heat item 2 to approximately 60°C.
3. Mix these two solutions slowly, stirring well to obtain a clear solution.
4. Dissolve items 7 to 9 in the hot solution of items 10 and 11 to obtain a clear solution.
5. Add to solution above.
6. Add items 12 to 18 and adjust the pH to 4.0 to 4.2.
7. Pass nitrogen through the solution for 10 minutes and fill under nitrogen cover.
8. Provides 1 to 2 RDA/20 mL.

Multivitamin Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/100 mL (mg)
0.17	1	Vitamin A palmitate (1.7 MM IU/g)	17.00
0.001	2	Vitamin D_3 (40 MM IU/g)	0.10
0.01	3	BHT	1.00
30.00	4	Cremophor RH 40	3.00 g
1.00	5	Parabens	100.00
170.00	6	Water	17.00 g
0.50	7	Thiamine hydrochloride	50.00
0.20	8	Riboflavin phosphate sodium	20.00
0.20	9	Pyridoxine hydrochloride	20.00
2.50	10	Ascorbic acid (crystalline)	250.00
50.00	11	Water	5.00 g
–	12	Sugar syrup	Add 100 mL

Manufacturing Directions

1. Heat mixture of items 1 to 4 to approximately 65°C.
2. Stir well and very slowly add item 6 to warm solution (65°C).
3. Mix with solution of items 7 to 11 and add item 12 to make up the volume.
4. *Note*: Parabens are generally a 1:10 ratio of methyl and propyl parabens.

Multivitamin Tablet Cores with Beta-Carotene (1–2 RDA of Vitamins)

Formulation

Vitamin A acetate dry powder, 500,000 IU/g, 1.27%; beta-carotene dry powder Betavit 10%, 11.50%; thiamine mononitrate, 1.24%; riboflavin, 0.96%; nicotinamide, 11.50%; calcium D-pantothenate, 1.91%; pyridoxine hydrochloride, 1.15%; cyanocobalamin gelatin coated 1%, 2.86%; D-biotin, 1% trituration, 1.91%; folic acid, 0.09%; ascorbic acid, 38.20%; vitamin D_3 dry powder, 100,000 IU/g, 0.76%; vitamin E acetate dry powder 50 DC, 28.40%; phytomenadione dry powder 5% GFP, 0.19%,. 270.2 g; Ludipress, 69.1 g; magnesium stearate, 3.3 g.

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix and press with high compression force at 459 mg.

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
10.00	1	Thiamine mononitrate (powder), USP (5% excess; 5–10%)	10.50
5.00	2	Riboflavin, USP	5.00
100.00	3	Nicotinamide niacinamide (white powder), USP	100.00
200.00	4	Ascorbic acid, use sodium ascorbate (microcrystalline) (2% excess)	229.47
20.00	5	Calcium pantothenate; use calcium pantothenate racemic (20% excess)	48.00
5.00	6	Pyridoxine hydrochloride, USP	5.00
6.10	7	Povidone (PVP K-25), USP	6.10
—	8	Alcohol dehydrated (200 proof), USP	25.00 mL
21.90	9	PEG-8000, NF	21.90
25,000 IU	10	Vitamin A (275,000 IU[a]) (20% excess)	7.50 mg
400 IU	11	Vitamin D as D_2 powder (850 mD[a])	1.77
6.00	12	Vitamin B_{12} oral powder in gelatin (5% excess)	6.30
16.00	13	PEG-8000 (milled), NF	16.00
5.30	14	Magnesium stearate	5.30
23.20	15	Talc	23.20

[a]Adjust quantities according to regulatory allowance for OTC label.

Manufacturing Directions

Vitamin A is susceptible to destruction by oxidation and also excessive exposure to actinic light and moisture. Oxidation and destruction are catalyzed by traces of copper and other heavy metals. Dry granulation and compression of this tablet should be done where RH is less than 40%. Protect with CO_2 at blending and storage stages.

1. Charge the following into a suitable mixer (screen if necessary): thiamine mononitrate, riboflavin, nicotinamide, sodium ascorbate, calcium pantothenate, and pyridoxine HCl.
2. Dissolve the PVP (item 7) in approximately 16 mL alcohol.
3. Add PVP solution to the powders from first step and QS with alcohol to mass.
4. Granulate the mass through a 4-mesh (4.76-mm aperture or similar) screen.
5. Dry at 50°C until the LOD is less than 1%.
6. Grind to 16 mesh (1.2 mm or similar).
7. Melt the PEG-8000 (item 10) and incorporate vitamins A and D with thorough agitation.
8. Mix until mass cools and becomes granular.
9. Screen through a 16-mesh (1.2-mm aperture or similar) screen and grind coarse material through a Fitz mill or similar No. 2 band (1.59-mm aperture or similar) at slow speed or a 16-mesh (1.2-mm aperture or similar).
10. Reserve for lubrication.
11. Mix milled PEG-8000 (item 13) with talc and magnesium stearate and pass through a Fitz mill using a 60-mesh (250-μm aperture or similar) screen (impact forward, high speed).
12. If a Fitz mill is unavailable, pass the mixture through a 30-mesh (595-μm aperture or similar) screen.
13. Load base granulation into a mixer along with vitamin B_{12}, the mixture from above, and the PEG-coated vitamins A and D mixture from the first step. Blend thoroughly.
14. Store dry mixed granulation with CO_2 protection.
15. Compress.
16. Apply a PVP subcoat, a CAP-carbowax, or other aqueous coating and finish with a polish coat (see appendix).

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Riboflavin	10.00
100.00	2	Niacinamide (white powder)	100.00
5.00	3	Pyridoxine hydrochloride (15% excess)	5.75
15.00	4	Thiamine mononitrate (powder) (5% excess)	15.75
500.00	5	Ascorbic acid, EP	500.00
100.00	6	Lactose	100.00
40.00	7	Povidone (K-29–32)	40.00
100.00	8	Cellulose microcrystalline (Avicel PH101)	100.00
–	9	Alcohol SD 3A (200 proof)	QS
20.00	10	Calcium pantothenate; use racemic calcium pantothenate, USP (80 mesh; 15% excess)	46.00
11.50	11	Magnesium oxide (light powder calcined)	11.50
500.00	12	Ascorbic acid	500.00
3.83	13	Povidone (K-29–32)	3.83
–	14	Alcohol SD 3A (200 proof)	QS
4.00 μg	15	Vitamin B_{12}; use vitamin B_{12} oral powder in gelatin (15% excess)	4.60
28.00	16	Acid stearic	28.00
9.60	17	Magnesium stearate	9.60

Manufacturing Directions

1. Dry blend the riboflavin, niacinamide, pyridoxine hydrochloride, thiamine mononitrate, ascorbic acid (item 5), and lactose for 10 minutes.
2. Dissolve the povidone (item 7) in 75 mL of alcohol (item 9).
3. While mixing in mass mixer, add the povidone solution to mass and continue mixing for 10 minutes or until a satisfactory granule mass is obtained.
4. Additional alcohol may be added, if required.
5. Granulate the mass through a 15.9-mm screen using a comminuting mill (knives forward, slow speed) or a 4-mm screen on an oscillating granulator.
6. Dry the granules between 41°C and 49°C in a hot air oven (for approximately 8 hours) or fluid-bed dryer until moisture content is less than 1.5%.
7. Dry screen the granule through a 1-mm screen on an oscillating granulator.
8. Dry blend the calcium pantothenate and magnesium oxide in a suitable mixer for 10 minutes.
9. Dissolve the povidone (item 13) in 20 mL alcohol (item 14).
10. While mixing, add the povidone solution and mix to produce a suitable mass.
11. Additional alcohol may be added, if required.
12. Granulate the mass through a 15.9-mm aperture screen using a comminuting mill (knives forward, slow speed) or a 4-mm screen on an oscillating granulator.
13. Dry the granule at 45°C in a hot air oven until moisture content is less than 1.5%.
14. Dry screen granule through a 1.0-mm screen on an oscillating granulator.
15. Mix the two granules made separately in a suitable mixer.
16. Add vitamin B_{12} powder and blend for 10 minutes. If necessary, screen the stearic acid and magnesium stearate through a 250-μm screen.
17. Add the remainder of the granule together with the magnesium stearate and stearic acid to the mixer and blend for 10 minutes.
18. Compress and coat (see appendix).

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Riboflavin	10.00
100.00	2	Niacinamide (white powder)	100.00
5.00	3	Pyridoxine hydrochloride (15% excess)	5.75
15.00	4	Thiamine mononitrate (powder) (5% excess)	15.75
40.00	5	Povidone (K-29–32)	40.00
25.00	6	Povidone (K-29–32)	25.00
–	7	Alcohol SD 3A (200 proof)	QS
13.50	8	Stearic acid (fine powder)	13.50
2.70	9	Magnesium stearate	2.70

Manufacturing Directions

1. Mill the niacinamide, riboflavin, pyridoxine hydrochloride, and thiamine mononitrate through a 500-μm screen on a comminuting mill (impact forward, slow speed).
2. Load screened material from previous step into a mass mixer, add the Povidone (item 5) and the cellulose microcrystalline, and dry blend for 5 to 15 minutes.
3. While mixing in the mass mixer, add alcohol (item 7) to mass and continue mixing for 10 minutes or until a satisfactory granule mass is obtained.
4. If necessary, granulate the mass through a 15.9-mm screen using a comminuting mill (knives forward, slow speed) or a 4-mm screen on an oscillating granulator.
5. Dry the granule between 41°C and 49°C in a hot air oven (for approximately 8 hours) or fluid-bed dryer until moisture content is less than 1.5%.
6. Dry screen the granules through a 1-mm screen on an oscillating granulator.
7. Load ascorbic acid and povidone (item 6) into the mixer and dry-blend for 10 minutes.
8. While mixing, add 15 mL of alcohol (item 7) and mix until a satisfactory mass is formed, adding more alcohol if necessary. If necessary, screen through a 4.00-mm screen and load onto trays.
9. Dry at 49°C for 8 hours.
10. Dry screen the granules through a 1-mm aperture screen on an oscillating granulator.
11. Screen the magnesium stearate and stearic acid through a 500-μm aperture screen.
12. Mix the two granules, add the screened lubricants, and blend for 20 minutes.
13. Coat with a protective subcoat, a color coat, and a polish coat (see appendix).

Multivitamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Vitamin A acetate (dry powder; 500,000 IU/g)	10.00
2.20	2	Thiamine mononitrate	2.20
2.20	3	Riboflavin	2.20
16.50	4	Nicotinamide	16.50
11.50	5	Calcium D-pantothenate	11.50
2.20	6	Pyridoxine hydrochloride	2.20
6.00	7	Cyanocobalamin (dry powder, 0.1%)	6.00
85.00	8	Ascorbic acid (powder)	85.00
31.00	9	Vitamin E acetate (dry powder; SD 50)	31.00
321.00	10	Ludipress[a]	321.00
21.00	11	Kollidon VA 64	21.00
3.00	12	Magnesium stearate	3.00
7.20	13	Orange flavor	7.20
2.50	14	Saccharin sodium	2.50

[a]Can be replaced with 300 g of microcrystalline cellulose (Vitacel®).

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, mix, and press with medium compression force (15 kN).
2. Compress 500 mg in 12-mm biplanar punches.

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
2.00	1	Thiamine hydrochloride	2.20
2.20	2	Riboflavin	2.20
11.00	3	Calcium D-pantothenate	11.00
2.20	4	Pyridoxine hydrochloride	2.20
300.00	5	Mannitol	300.00
20.00	6	Kollidon 30 or Kollidon VA 64	20.00
–	7	Isopropanol	~80
5000 IU vitamin A, 500 IU vitamin D	8	Vitamins A and D; use crystallets of vitamin A acetate + vitamin D_3 dry powder (500,000 + 50,000 IU/g) (10% excess)	11.00
31.00	9	Vitamin E acetate (dry powder; SD 50)	31.00
0.06	10	Cyanocobalamin; use gelatin-coated cyanocobalamin (0.1%)	6.00
80.00	11	Ascorbic acid (crystalline)	80.00
20.00	12	Nicotinamide	20.00
65.00	13	Avicel PH101	65.00
7.00	14	Orange flavor	7.00
2.00	15	Saccharin sodium	2.00
3.00	16	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate mixture of items 1 to 5 with solution of items 6 and 9.
2. Pass through a 0.8-mm sieve, mix with items 8 to 16, and press with medium compression force.
3. Compress 560 mg in 12-mm biplanar punches.

Multivitamin Tablets, DC (1–2 RDA of Vitamins)

Formulation

Vitamin A acetate dry powder, 500,000 IU/g, 10.0 g; thiamine mononitrate, 2.2 g; riboflavin, 2.2 g; nicotinamide, 16.5 g; calcium D-pantothenate, 11.5 g; pyridoxine hydrochloride, 2.2 g; cyanocobalamin, 0.1% dry powder, 6.0 g; ascorbic acid, powder, 85.0 g; vitamin E acetate dry powder SD 50, 31.0 g; Ludipress, 321.0 g; magnesium stearate, 3.0 g; orange flavor, 7.2 g; saccharin sodium, 2.5 g.

Manufacturing Directions

Mix all components, pass through a 0.8-mm sieve, mix and press with medium compression force (15 kN).

Multivitamin Tablets for Dogs

Formulation

Vitamins A and D_3 dry powder, 500,000 and 50,000 IU/g, 4.0 g; thiamine mononitrate, 0.5 g; riboflavin, 0.7 g; nicotinamide, 5.0 g; calcium D-pantothenate, 1.0 g; pyridoxine hydrochloride, 0.5 g; cyanocobalamin gelatin coated 1%, 0.5 g; folic acid, 0.05 g; choline bitartrate, 20.0 g; vitamin E acetate dry powder SD 50, 20.0 g; Ludipress, 196.0 g; magnesium stearate, 2.0 g.

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with low compression force at 250 mg.

Multivitamin Tablets for Dogs

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
2000 IU Vitamin A, 200 IU Vitamin D	1	Vitamin A + vitamin D_3 (dry powder; 500,000 + 50,000 IU/g)	4.00
0.50	2	Thiamine mononitrate	0.50
0.70	3	Riboflavin	0.70
5.00	4	Nicotinamide	5.00
1.00	5	Calcium D-pantothenate	1.00
0.50	6	Pyridoxine hydrochloride	0.50
0.50	7	Cyanocobalamin (gelatin coated, 1%)	0.50
0.05	8	Folic acid	0.05
20.00	9	Choline bitartrate	20.00
20.00	10	Vitamin E acetate (dry powder, SD 50)	20.00
196.00	11	Ludipress	196.00
2.00	12	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with low compression force.
2. Compress 250 mg using 8-mm biplanar punches.

Multivitamin Tablets with Beta-Carotene

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
1.00	1	Beta-carotene; use beta-carotene dry powder (Betavit, 10%)	10.00
2.00	2	Thiamine mononitrate	2.00
2.00	3	Riboflavin	2.00
16.00	4	Nicotinamide	16.00
11.00	5	Calcium D-pantothenate	11.00
2.00	6	Pyridoxine hydrochloride	2.00
0.06	7	Cyanocobalamin; use cyanocobalamin dry powder (0.1%)	6.00
85.00	8	Ascorbic acid (powder)	85.00
31.00	9	Vitamin E acetate (dry powder; SD 50)	31.00
321.00	10	Ludipress	321.00
7.00	11	Kollidon VA 64	7.00
3.00	12	Magnesium stearate	3.00
7.00	13	Orange flavor	7.00
2.00	14	Saccharin sodium	2.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, mix, and press with medium compression force.
2. Compress 508 mg using 12-mm planar punches.

Multivitamin Tablets with Copper and Zinc

Formulation

Vitamin mixture (thiamine mononitrate), 3.9%; riboflavin 100, 0.4%; nicotinamide 10.1%; calcium D-pantothenate, 2.9%; pyridoxine hydrochloride, 1.2%; cyanocobalamin gelatin coated 0.1%, 2.6%; folic acid, 0.1%; ascorbic acid fine powder, 63.4%; vitamin E acetate dry powder 500 SD, 9.1%; copper oxide, 0.3%; zinc sulphate, 6.0%, 1000 g; Aerosil, 200, 5 g; Ludipress, 150 g; Avicel PH102 [5], 120 g; Kollidon VA64 [1], 25 g; magnesium stearate, 10 g; talc, 10 g.

Manufacturing Directions

Pass all components through a 0.8-mm sieve, mix, and press with high compression force at 1350 mg.

Multivitamin with Beta-Carotene Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
2.85 IU	1	Vitamin A acetate (dry powder; 500,000 IU/g)	5.47
5.00	2	Beta-carotene; use beta-carotene dry powder (Betavit, 10%)	50.00
15.34	3	Thiamine mononitrate	15.34
4.13	4	Riboflavin	4.13
50.00	5	Nicotinamide	50.00
8.23	6	Calcium D-pantothenate	8.23
5.00	7	Pyridoxine hydrochloride	5.00
0.04	8	Cyanocobalamin; use gelatin-coated cyanocobalamin (1%)	4.00
0.04	9	D-Biotin; use 1% trituration	4.00
0.38	10	Folic acid	0.38
165.00	11	Ascorbic acid	165.00
327.00	12	Vitamin D_3 (dry powder; 100,000 IU/g)	3.27
122.00	13	Vitamin E acetate (dry powder; SD 50)	122.00
0.41	14	Phytomenadione; use phytomenadione dry powder (5% GFP)	0.82

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high compression force.
2. Compress 432 mg in 12-mm biplanar punches.

Multivitamin with Fluoride Infant Drops

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
8.00	1	Niacin; use niacinamide (5% excess)	8.332
0.60	2	Riboflavin, USP; use riboflavin-5′–phosphate sodium (2% excess)	0.83
0.50	3	Methyl paraben	0.50
1.00	4	Benzoic acid	1.00
5000 IU	5	Vitamin E; use D-alpha-tocopheryl PEG-1000 succinate (20% excess)	13.826
400 IU	6	Vitamin D; use viosterol in corn oil (syn. oleovitamin D) (25% excess)	0.522
1500 IU (0.45)	7	Vitamin A palmitate (synthetic A palmitate, 1 MM U/g), USP	1.44
35.00	8	Ascorbic acid (white powder), USP (33% excess)	46.55
0.50	9	Thiamine hydrochloride (44% excess)	0.72
0.40	10	Pyridoxine; use pyridoxine hydrochloride	0.486
0.25	11	Fluoride; use sodium fluoride (powder)	0.5526
4.013	12	Caramel (acid proof)	4.013
0.257	13	Orange oil terpeneless	0.257
QS	14	Alcohol (ethanol; 190 proof)	10.00 mL
QS	15	Distilled purified water	QS
QS	16	Hydrochloric acid	QS
QS	17	Sodium hydroxide	QS
QS	18	Carbon dioxide gas	QS

Manufacturing Directions

Use only stainless steel tanks and minimize vortex formation to prevent aeration. Product attacks glass, so avoid contact with glass.

1. Charge 350 mL of purified water into the stainless steel jacketed main tank.
2. Start mixing.
3. Add, in this order, niacinamide, riboflavin, sodium fluoride, methyl paraben, and benzoic acid.
4. Rinse the interior walls of the tank with approximately 16 mL purified water.
5. Continue mixing for the balance of the process.
6. Heat the main tank to 95°C to dissolve ingredients.
7. When the solution is complete, cool to less than 85°C (range: 80–90°C).
8. The main tank will have to be heated to 85°C for this step.
9. Add vitamin E to another tank, if necessary, by heating vitamin E container.
10. Melt vitamin E in the tank.
11. Add viosterol and vitamin A and heat to 60°C to 65°C with mixing.
12. Start bubbling in CO_2.
13. Mix slowly for 10 minutes or longer to produce a clear solution.
14. Start CO_2 gas protection on the main mixing tank and continue for the balance of the process.
15. With the main batch at 85°C to 90°C, add the solution of vitamins A, D, and E at 60°C to 65°C, with mixing.
16. The addition may cause the temperature of the main batch to drop below the specified range, so readjust to 85°C to 90°C.
17. Mix and maintain at this temperature until solution is complete, after which cool to less than 30°C.
18. Add the glycerin with mixing.
19. Adjust the temperature to 25°C±5°C and maintain at this temperature before proceeding.
20. Add and dissolve with mixing, in this order, ascorbic acid, thiamine, pyridoxine, and caramel.
21. Rinse the caramel container with approximately 3 mL of water and add the rinsings.
22. Rinse the tank inner walls and mixer shaft with approximately 3 mL water.
23. Dissolve the orange oil with mixing in the alcohol and add to solution above.
24. Continue mixing for at least 30 minutes to ensure a homogeneous product.
25. Stop mixing and take pH (range: 3.1–3.3). If necessary, adjust with 10% sodium hydroxide or 10% hydrochloric acid, prepared by adding 1 mL hydrochloric acid (reagent-grade) with 3.3 mL purified water. Mix.
26. Stop mixing and allow to stand for at least 4 hours to eliminate entrapped CO_2 gas.
27. In a properly cleaned separate tank, boil at least 65 mL of purified water for at least 15 minutes.
28. Cool while bubbling CO_2 into it and hold at 30°C.
29. Adjust pH to the range of 3.1 to 3.3.
30. Filter using a lint-free paper. Do not use filter aids.
31. Recirculate product back to main mixing tank until clear.
32. Flush a storage tank with CO_2 for at least 10 minutes with the CO_2 valve completely open.
33. Filter product into this storage tank.
34. Fill under CO_2 cover.

Multivitamin with Zinc Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Niacin; use niacinamide (white powder)	99.20
750.00	2	Ascorbic acid; use microcrystalline sodium ascorbate[a]	843.68
20.00	3	Vitamin B_6; use pyridoxine hydrochloride	34.03
QS	4	Povidone	40.00
15.00	5	Thiamine hydrochloride; use thiamine mononitrate (powder)	17.47
15.00	6	Riboflavin	16.50
20.00	7	Pantothenic acid; use calcium pantothenate	32.60
0.49	8	Folic acid (powder)	0.52
12.00 μg	9	Vitamin B_{12}; use cyanocobalamin oral powder in gelatin 1:1000	15.00
60.00	10	Vitamin E (D,L-alpha-tocopherol acetate)	60.00
–	11	Alcohol SD 3A (200 proof)	138 mL 23 mL
22.50	12	Elemental zinc (pure zinc sulfate powder)	55.61
4.00	13	Povidone	4.00
–	14	Alcohol SD 3A (200 proof)	4 mL
–	15	Alcohol SD 3A (200 proof)	9 mL
10.80	16	Magnesium stearate	10.80
40.00	17	Cellulose microcrystalline	40.00
3.20	18	Silicon dioxide colloidal	3.20
6.00	19	Colloidal silicon dioxide	6.00

[a]May use ascorbic acid (750.00 g) instead. The quantity of povidone is reduced to 6.34 g and the amount of alcohol SD used is adjusted.

Manufacturing Directions

1. Mill niacinamide, sodium ascorbate, pyridoxine, povidone (item 4), and thiamine through a comminuting mill with hammers (impact forward) at high speed and fitted with a 0 band (686-μm aperture or similar) screen.
2. Charge millings into mass mixer.
3. Screen riboflavin, calcium pantothenate, folic acid, vitamins B_{12} and E through an 840-μm screen.
4. Charge into mass mixer and dry mix for 5 to 10 minutes.
5. Add 89 mL alcohol to powder while mixing.
6. Add additional alcohol, if required (approximately 49 mL) to achieve satisfactory granulation.
7. Pass wet mass through 5/8-in band (15.88-mm aperture or similar) screen and spread out on paper-lined trays.
8. Dry granulation at 49°C and dry until LOD is NMT 1.5%.
9. Sift dry granule through 1.19-mm screen and coarse grind granule through a No. 2 band (1.59-mm aperture or similar) screen fitted on a comminuting mill (knives forward, medium speed) to polyethylene-lined drums.
10. Mill zinc sulfate and povidone through a comminuting mill fitted with a 0 band (686-μm aperture or similar) screen at high speed with impact (hammers) forward.
11. Charge millings into mass mixer for 5 to 10 minutes.
12. Add 3.3 mL alcohol (item 14) to powders from first step while mixing.
13. If necessary, use additional alcohol (up to 0.83 mL) to achieve satisfactory granulation.
14. Granulate wet mass through 5/8-in band (15.88-mm aperture or similar) screen and spread out on paper-lined trays.
15. Dry granule at 49°C and dry until LOD is NMT 1.5%.
16. Sift dry granule through 1.19-mm screen and coarse grind granule through a No. 2 band (1.59-mm aperture or similar) screen fitted on a comminuting mill (knives forward, medium speed) and transfer to polyethylene-lined drums.
17. Charge approximately one-tenth of vitamin granulation into blender.
18. Premix magnesium stearate, microcrystalline cellulose, and silicon dioxide in a bowl and sift through 840-μm screen into blender.
19. Charge another one-tenth more of vitamin granulation into blender and blend for 5 minutes.
20. Discharge a portion of granulation from the blender and check for white lumps.
21. If lumps are present, discharge entire granulation through a 1.68-mm aperture screen to break lumps, then return it to blender.
22. Charge zinc granulation into the blender.
23. Charge remaining vitamin granulation into blender and blend for 15 minutes.
24. Discharge blender into polyethylene-lined drums, tie liners, close and seal drums, and deliver to storage area.
25. Compress and coat (see appendix).

Naphazoline Eye Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
17.71	1	Acid boric	17.71
1.50	2	Hydroxypropylmethylcellulose 2910 (400 cps)	1.50
0.36	3	Borax (sodium borate)	0.36
1.00	4	Disodium edetate	1.00
0.12	5	Naphazoline hydrochloride	0.12
0.17 mL	6	Benzalkonium chloride; use benzalkonium chloride solution (17%)	0.63 mL
QS	7	Water for injection	QS to 1 L

Manufacturing Directions

Use thoroughly cleaned and rinsed, steam-jacketed glass-lined or stainless steel tank equipped with a speed-controlled agitator. The tank should have a cover. Foaming occurs because of benzalkonium chloride, which concentrates in foam. Processing and filling systems should be designed to minimize foaming and allow rapid dissipation of foaming.

1. Charge 80% of final volume of water into mixing tank. Heat deionized water to 90°C.
2. While agitating, add and disperse methyl cellulose by slowly sprinkling it on the surface of solution. Mix to avoid excessive foaming.
3. Allow 15 minutes for hydration of methyl cellulose before discontinuing heating and allowing cooling to 40°C.
4. While agitating, add and dissolve disodium edetate, benzalkonium chloride, boric acid, and sodium borate.
5. Continue cooling to 30°C (25–30°C). Discontinue agitation and QS to 950 mL with deionized water.
6. Start agitator and mix for at least 15 minutes at 30°C. Discontinue agitation and cooling.
7. Naphazoline hydrochloride concentrate solution: dissolve naphazoline hydrochloride in 50 mL of deionized water and sterile-filter solution through a previously sterilized millipore filter unit containing 0.22-μm membrane.
8. Hold naphazoline solution under aseptic conditions for addition to bulk solution (after it has been autoclaved and cooled).
9. Prefiltration: Methyl cellulose solutions filter at a slow rate, so use an appropriate filter.
10. Recirculate solution until clear and transfer to holding or sterilization.
11. Sterilization and filling: Use either heat sterilization or sterile filtration.
12. Heat sterilization: Sterilize at 112°C to 115°C for 60 minutes, cool solution to 25°C to 30°C, and aseptically add the sterile naphazoline solution. Mix well.
13. Set up a previously sterilized filter and transfer line with 10-μm stainless steel FulFlo filter or equivalent.
14. Aseptically fill sterile solution into sterilized containers and apply sterile closure components.
15. Sterile filtration: Use Pall cartridge AB 1 NR 7p (pr 8P) with Sartorius Cartridge 526-07 H 1. Prepare and steam sterilize the recommended filter units.
16. Aseptically fill the sterilized solution to which the naphazoline solution has been added into each sterilized container and apply sterile closure.

Neomycin Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.50	1	Neomycin sulfate	0.50
50.00	2	Propylene glycol	50.00
5.00	3	Parabens	5.00
200.00	4	Lutrol F 127	200.00
745.00	5	Water	745.00

Manufacturing Directions

1. Dissolve the parabens and Lutrol F 127 in water heated to approximately 80°C.
2. Add the propylene glycol and dissolve neomycin sulfate.
3. Cool to room temperature when the air bubbles escape.
4. Alternative: Dissolve parabens in hot water, cool to 5°C to 10°C, dissolve Lutrol F 127, add propylene glycol, and dissolve neomycin sulfate.
5. Maintain the cool temperature until the air bubbles escape.

Nicotinamide Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
300.00	1	Nicotinamide (Degussa)	320.00
160.00	2	Avicel PH101	160.00
16.00	3	Kollidon VA 64	16.00
3.00	4	Magnesium stearate	3.00
3.00	5	Aerosil 200	3.00

Manufacturing Directions

With medium compression force, compress 506 mg using 12-mm biplanar punches.

Nicotinic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
375.00	1	Nicotinic acid	375.00
188.70	2	Hydroxypropylmethylcellulose E10 M premium	188.70
12.90	3	Povidone K90	12.90
5.80	4	Stearic acid (Hystrene 5016)	5.80

Manufacturing Directions

1. Charge one-half of the quantity of item 1 to 3 and the powder bed is dry mixed in a Littleford granulator, with choppers on, for approximately 1 minute.
2. At the completion of the 1-minute premix cycle, an appropriate quantity approximately 3 times the quantity of item 3 is sprayed slowly for a period of 5 minutes.
3. The granulated unit is discharged into double polyethylene-lined containers and then manually loaded into a Glatt bowl while being passed through a No. 4 mesh screen. The Glatt bowl is loaded into a Glatt fluid-bed drier with an inlet air temperature setting of approximately 70°C±5°C.
4. The unit is dried until a moisture level of approximately 1% is obtained as determined using a Computrac® Moisture Analyzer.
5. The dried granulation is discharged into appropriately labeled, double polyethylene-lined drums and reconciled.
6. The dried and reconciled granulation is passed through a Kemutec BetaGrind mill equipped with an l.5-mm screen and running at approximately 1500 rpm.
7. The milled granulation is collected into appropriately labeled, double polyethylene-lined drums and reconciled.
8. The milled granulation is sampled and tested by quality control and released prior to further processing.
9. The released granulation units are charged to a Patterson-Kelley 20 ft^3 V-blender after which they are blended together for approximately 10±1 minutes and then discharged to appropriately labeled, double polyethylene-lined containers.
10. Add item 4, blend, and compress at 582.40 mg in caplet shaped punches. Compress 727.50 for 500-mg strength and 990.50 mg for 750-mg strength.

Nicotinic Acid (Niacin) Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Nicotinic acid	200.00
200.00	2	Ludipress	200.00
5.00	3	Kollidon CL	5.00
1.50	4	Magnesium stearate	1.50
3.00	5	Aerosil 200	3.00
10.00	6	PEG-6000	10.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve.
2. Mix and press with very low compression force.
3. Compress 410 mg using 12-mm biplanar punches.

Nicotinic Acid (Niacin) Tablets (200 mg)

Formulation

Nicotinic acid (Lonza), 200.0 g; Ludipress, 200.0 g; Kollidon CL, 5.0 g; magnesium stearate, 1.5 g; Aerosil 200, 3.0 g; polyethylene glycol 6000, powder, 10.0 g.

Manufacturing Directions

Pass all components through a 0.5-mm sieve, mix, and press with very low compression force at 419 mg.

Niacin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
1000.00	1	Niacin	1000.00
40.00	2	PVP	40.00
10.00	3	Silicon dioxide	10.00
15.00	4	Sodium stearyl fumarate	15.00
400.00	5	Water	400.00

Manufacturing Directions

1. Niacin is placed in a fluidized bed apparatus.
2. An aqueous PVP solution (in 85 g of water) is sprayed to get granules.
3. The granules thus obtained are subsequently dried and passed through a sieve (1-mm mesh) and sodium stearyl fumarate is weighed, added, and blended in a drum mixer.
4. The resulting mixture is pressed into tablets 1065 mg.
5. These tablet cores are then coated with the following formulation: ethyl cellulose (Ethocel), 10, 10; PVP (Povidone), 5.50 mg; stearic acid, 2.40 mg.
6. Ethocel, povidone, and stearic acid are first dissolved in denatured alcohol (180 g).
7. The coating solution is then sprayed onto the tablet cores in a coating pan.

Nondetergent Neutral Dry Skin Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
60.00	1	Stearic acid	60.00
145.00	2	White petrolatum jelly	145.00
116.00	3	Mineral oil (25 cS)	116.00
10.00	4	Lanolin	10.00
20.00	5	Cetearyl alcohol	20.00
QS	6	Deionized water	QS to 1 kg
14.00	7	Triethanolamine (99%)	14.00
QS	8	Perfume, preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool, adding triethanolamine at 60°C and perfuming at 40°C to 50°C.
4. This cream serves as a base for drugs as well.
5. Triethanolamine may be omitted, as it gives a higher pH.

Norephedrine Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
40.00	1	DL-norephedrine hydrochloride	40.00
4.00	2	Parabens	4.00
5.00	3	Saccharin sodium	5.00
3.00	4	Kollidon 90 F	3.00
500.00	5	Sorbitol solution	500.00
460.00	6	Water	460.00

Manufacturing Directions

1. Dissolve the parabens in the hot water, add the sorbitol, cool to room temperature, and dissolve the other components.
2. To prevent discoloration of Kollidon in the solution during storage, 0.1% to 0.5% cysteine could be added as an antioxidant.
3. Flavors should be added to adjust the taste, as needed.

Nystatin Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
80.00	1	Cetostearyl alcohol	80.00
20.00	2	Polyoxyl 20 cetostearyl ether (Cetomacrogol 1000)	20.00
80.00	3	Mineral oil (liquid paraffin)	80.00
2.00	4	Methyl paraben	2.00
100,000 IU	5	Nystatin microfine[a] (30% excess) 5420 IU/mg	24.00
1.00	6	Propyl paraben	1.00
100.00	7	Propylene glycol	100.00
4.86	8	Dibasic sodium phosphate	4.86
2.36	9	Monobasic sodium phosphate	2.36
180.00	10	Petrolatum (soft white paraffin)	180.00
506.00	11	Purified water	506.00

[a]Particle size NLT 90% less than 45 μm and 100% less than 80 μm.

Manufacturing Directions

1. Charge item 3 to the fat-melting vessel.
2. Heat to 70°C while stirring.
3. Charge items 1, 2, and 10 to the fat-melting vessel while stirring.
4. Mix well and maintain the temperature at 65°C to 70°C.
5. Load 466 g of item 11 and item 7 into mixer and heat to 90°C.
6. Add items 4 and 6 to dissolve, while stirring on manual mode.
7. Mix for 15 minutes at 10 rpm.
8. Cool to 65°C to 70°C.
9. Add items 8 and 7 to the parabens solution to dissolve.
10. Mix for 5 to 10 minutes at 10 rpm.
11. Maintain temperature at 65°C to 70°C.
12. Take a sample of approximately 0.40 mL from mixer and cool to 25°C.
13. Check the pH (6.3–7.0).
14. Withdraw 80 g of preservative/buffer solution from mixer at 65°C to 70°C in a stainless steel container.
15. Cool the solution in stainless steel container to 30°C to 35°C.
16. Disperse item 5, carefully using a spatula.
17. Homogenize using homogenizer to make a smooth dispersion.
18. Transfer the molten fat to the mixer containing the preservative/buffer solution through a stainless steel sieve by vacuum at 0.6 bar while mixing at 10 rpm in manual mode at a temperature of 65°C.
19. Homogenize and mix the cream for 10 minutes at low speed (10 rpm, manual mode) and vacuum of 0.6 bar.
20. Cool to 40°C±5°C.
21. Transfer 104 g of drug phase (35°C±5°C) to the mixer while mixing.
22. Rinse the stainless steel container of the drug phase with 40 g of item 11 (25–35°C) and transfer to the mixer while mixing.
23. Rinse the homogenizer and the container with item 11 and transfer the rinsing to the mixer.
24. Mix for 5 minutes.
25. Set the mixer at a mixing speed of 10 rpm (manual mode) and the homogenizer at low speed with a vacuum of 0.6 bar.
26. Mix and homogenize for 15 minutes.
27. Cool to 30°C with mixer speed of 10 rpm and vacuum of 0.6 bar.
28. Transfer the cream to a stainless steel drum.

Nystatin Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100,000 IU	1	Nystatin microfine[a], 5420 IU/mg, 15% excess	21.05
22.00	2	Cetostearyl alcohol	22.00
8.00	3	Paraffin (hard paraffin)	8.00
100.00	4	Mineral oil (liquid paraffin)	100.00
848.95	5	Petrolatum (soft white paraffin)	848.95

[a]Particle size NLT 90% less than 45 μm and 100% less than 80 μm.

Manufacturing Directions

1. Melt items 2, 3, and 5 at 70°C in fat-melting vessel.
2. Disperse item 1 in 80 g of item 4 in a separate stainless steel container by using a spatula.
3. Pass the dispersion through a homogenizer twice, then transfer the dispersion to the mixer.
4. Rinse the homogenizer and container with 20 g of item 4 and transfer the rinsings to the mixer.
5. Homogenize the dispersion at high speed for 15 minutes.
6. Set the mixer at a temperature of 40°C to 45°C.
7. Transfer the molten mass from the fat-melting vessel to the mixer at a temperature of 45°C to 50°C.
8. Mix for 10 minutes in manual mode and 10 minutes in automode at 12 rpm and vacuum 0.4 to 0.6 bar.
9. Homogenize at high speed for 10 minutes with recirculation.
10. Mix until the temperature of ointment reaches to 28°C to 30°C.
11. Transfer the ointment to a stainless steel drum.
12. Keep drum tightly closed.

Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100,000 IU	1	Nystatin microfine,[a] 5420 IU/mg 20% excess	22.96
4.43	2	Neomycin sulfate[b]	4.43
0.28	3	Gramicidin[c]	0.28
1.00	4	Triamcinolone acetonide micronized	1.00
80.00	5	Cetostearyl alcohol	80.00
20.00	6	Poloxyl 20 cetostearyl ether (Cetomacrogol 1000)	20.00
80.00	7	Mineral oil (liquid paraffin)	80.00
2.00	8	Methyl paraben	2.00
1.00	9	Propyl paraben	1.00
60.00	10	Propylene glycol	60.00
4.86	11	Dibasic sodium phosphate	4.86
2.36	12	Monobasic sodium phosphate	2.36
180.00	13	Petrolatum (soft white paraffin)	180.00
531.86	14	Purified water	531.86

For items 1–3, actual quantity to be calculated per actual potency.
Difference in quantity is to be adjusted by purified water.
[a] Particle size NLT 90% less than 45 μm and 100% less than 80 μm.
[b] Particle size NLT 99% less than 20 μm and 75% less than 10 μm.
[c] Particle size NLT 98% less than 50 μm.

Manufacturing Directions

1. Load items 5, 6, 7, and 13 in fat-melting vessel.
2. Heat to 70°C. Stir to melt.
3. Maintain temperature at 70°C to 75°C.
4. Heat 420 g of item 14 to 90°C in mixer.
5. Dissolve items 8 and 9 by stirring.
6. Mix for 15 minutes at 10 to 12 rpm.
7. Cool to 65°C to 70°C.
8. Dissolve items 11 and 12 in 71.86 g of item 14 at 40°C to 45°C in a stainless steel drum.
9. Check the pH (limit: 6.3–7.0 at 25°C).
10. Dissolve item 2 into 79.08 g of phosphate solution. The solution should be clear.
11. Disperse item 1 in the neomycin/phosphate solution from above.

12. Homogenize 2 times with homogenizer (gap setting 1) to make smooth dispersion.
13. Dispersion should be smooth with no lumps.
14. Add 50 g of item 10 in a separate stainless steel container and heat to 40°C to 45°C, then dissolve item 3 by using a homogenizer. The solution should be clear.
15. Disperse item 4 in the clear solution of gramicidin/propylene glycol by using homogenizer.
16. Homogenize until no lumps are present.
17. Maintain temperature at 40°C to 45°C.
18. Transfer the melt from step above to the mixer through a stainless steel sieve while mixing at 1012 rpm (manual mode) at a temperature of 65°C.
19. Homogenize at high speed for 10 to 12 minutes at a temperature of 60°C to 65°C and a vacuum of 0.6 bar. Scrape the sides and blade.
20. Cool down to 50°C.
21. Transfer the homogenized dispersion to the mixer.
22. Rinse the container with 10 g of item 10.
23. Add the rinsing to the mixer and mix for 10 minutes.
24. Transfer the dispersion to the mixer.
25. Rinse the container with 40 g of item 14.
26. Add to the mixer and mix for 10 minutes.
27. Homogenize at high speed for 20 minutes at a temperature of 45°C, mixer speed of 10 to 12 rpm, and vacuum of 0.6 bar.
28. Cool down to 25°C to 30°C while mixing.
29. Transfer the cream to a stainless steel drum.

Nystatin, Neomycin Sulfate, Gramicidin, and Triamcinolone Acetonide Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
22.96	1	Nystatin microfine[a]	22.96
4.43	2	Neomycin sulfate[a]	4.43
0.28	3	Gramicidin[a]	0.28
1.00	4	Triamcinolone acetonide (micronized)	1.00
100.00	5	Mineral oil (liquid paraffin)	100.00
10.00	6	Syncrowax	10.00
861.33	7	Petrolatum (soft white paraffin)	861.33

[a]Actual quantity to be calculated per actual potency. Difference in quantity to be adjusted by use of soft white paraffin.

Manufacturing Directions

1. Melt item 7 at 70°C in fat-melting vessel.
2. Add item 6 to the melt while mixing.
3. Transfer the melt to the mixer through filters and cool to 40°C while mixing.
4. Add 60 g of item 5 in a stainless steel container and disperse item 1 manually by using a spatula.
5. Homogenize 2 times with homogenizer (gap setting 1) to make a smooth dispersion and then transfer to the mixer.
6. Add 20 g of item 5 in a stainless steel container and disperse items 2, 3, and 4 by using the homogenizer to make a smooth dispersion.
7. Homogenize until no lumps are present.
8. Transfer the dispersion to the mixer.
9. Rinse the homogenizer and stainless steel container with 20 g of item 5 and transfer the rinsing to the mixer.
10. Mix for 10 minutes at a mixer speed of 10 rpm and vacuum of 0.4 to 0.6 bar.
11. Set thermostat at 28°C to 30°C.
12. Homogenize at high speed for 20 minutes with recirculation.
13. Mix until the temperature of ointment reaches to 28°C to 30°C.
14. Transfer the ointment to a stainless steel drum.
15. Keep drum tightly closed.

Omega Fatty Acids Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
140.00	1	Omega fatty acids dry N-3	140.00
140.00	2	Avicel PH101	140.00
8.40	3	Kollidon VA 64	8.40
2.00	4	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high compression force.
2. Compress 289 mg in 9-mm biconvex punches.
3. The dry powder omega fatty acids dry N-3 contains 25% fish oil; this fish oil consists of approximately 30% EPA+DHA.
4. These tablet cores could be coated with an enteric coating of Kollicoat MAE 30 D.
5. See appendix for more choices.

Orlistat Chewable Tablets

Manufacturing Directions

1. Orlistat (60g) and myristic acid (30g) are melted together at 50°C.
2. Mannitol (400g) and lactose (400g) are added and the mixture is cooled to room temperature under continuously stirring.
3. Talcum (10 g) is added and homogeneously distributed.
4. The powder is pressed into tablets of 960 mg weight (= orlistat content of 120 mg).

Orlistat Chewable Tablets

Manufacturing Directions

1. Orlistat (120 g) and myristic acid (30 g) are melted together at 50°C.
2. Sucrose palmitate (PEG-40 stearate, 12 g) and lactose (15 g) are added and the mixture is cooled to room temperature under continuously stirring.
3. The powder is pressed into tablets of 960 mg weight (= orlistat content of 120 mg).

Orlistat Chewable Tablets

Manufacturing Directions

1. Mix together orlistat, 120 g; sodium laurate, 30 g; mannitol, 80 g; and HPMC 3cp, 60 g, with stepwise addition of a (50:50% m/m) ethanol/water mixture (0.2 mL/g).
2. The formed granules are dried in vacuum at 30°C to constant weight and pressed into tablets (each containing 120 mg orlistat).

Oral Rehydration Salt (45 mEq)

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
811.90	1	Cerelose powder	811.90
66.57	2	Sodium chloride	66.57
31.82	3	Sodium citrate dihydrate, USP	31.82
70.14	4	Potassium citrate monohydrate (food grade)	70.14
19.57	5	Povidone (PVP K-29–32), USP/BP	19.57
–	6	Alcohol SD 3A (200 proof/190 proof), USP	500.00 mL
–	7	Purified water, USP	50.00 mL

Manufacturing Directions

1. Mill the dextrose through a 1.2-mm aperture screen or similar on a comminuting mill (knives forward, medium speed).
2. Individually mill the sodium chloride, sodium citrate, and potassium citrate through a 1.2-mm aperture screen on a comminuting mill (knives forward, medium speed).
3. *Note*: Do not mix the milled items until ready to add them to the dextrose.
4. Charge the powders from steps above into a suitable mass mixer and mix for 10 minutes.
5. Screen the Povidone through a 1.2-mm aperture screen and transfer to the mixer.
6. Mix all the powders for 5 minutes.
7. Mix 500 mL of alcohol with 50 mL of water and slowly add to the mixer while mixing.
8. Continue to mix for 5 to 10 minutes. Do not overwet the mass.
9. Granulate the wet mass through a 4.76-mm screen using an oscillating granulator and spread on stainless steel trays.
10. Dry the granules at 45°C for approximately 16 hours, or until LD is less than 0.8%.
11. Turn the granules over after 3 to 4 hours of drying.
12. Screen dry granules through an 840-μm screen.
13. Transfer the fines to a suitable blender.
14. Pass coarse granules through 840-μm screen using an oscillating granulator and transfer to the blender.
15. Blend for 5 to 10 minutes.
16. Discharge into polyethylene-lined drums.
17. Fill 3.08 g for 100 mL, 7.70 g for 250 mL, and 30.80 g for 1000 mL of reconstituted solution. Prorate weights for different volumes.

Pancreatin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
30.00	1	Pancreatin	30.00
308.00	2	Ludipress	308.00
10.00	3	Kollidon CL	10.00
2.00	4	Magnesium stearate	2.00

Manufacturing Directions

1. Mix the components, pass through a 0.8-mm sieve, and press with low compression force.
2. Compress 355 mg using 8-mm biconvex punches.
3. Coat by enteric coating. (See appendix in Volume 1.)

Pancreatin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
300.00	1	Pancreatin	300.00
290.00	2	Ludipress	290.00
25.00	3	Kollidon CL	25.00
3.00	4	Magnesium stearate	3.00

Manufacturing Directions

1. Mix the components, pass through a 0.8-mm sieve, and press to tablets with low compression force.
2. Compress 615 mg in 11-mm biconvex punches.
3. Coat by enteric coating. (See Volume 1.)

Pancreatin and Cholic Acid Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
130.00	1	Pancreatin	130.00
2.00	2	Cholic acid	2.00
127.00	3	Avicel PH101	127.00
56.00	4	Lactose monohydrate	56.00
2.00	5	Magnesium stearate	2.00
3.00	6	Aerosil 200	3.00

Manufacturing Directions

1. Mix the components and press with high compression force.
2. Compress 324 mg in 9-mm biconvex punches.
3. Coat by enteric coating. (See Volume 1.)

Panthenol Lotion

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L Tablets (g)
26.25	1	D-Panthenol (2.5%)[a]	26.25
2.50	2	DL-Lactone (pure)	2.50
1.00	3	Sequestrene disodium	1.00
3.00	4	Chlorhexidine hydrochloride (micropowder)	3.00
5.00	5	POEG 300-stearate[b]	5.00
50.00	6	Paraffin oil (low viscosity)	50.00
5.00	7	Polydimethylsiloxane M 350	5.00
3.00	8	Perfume PCV 1155/8	3.00
—	9	Purified water	QS to 1 L

[a] Based on 100% content; adjust for assay.

[b] POEG 300 is a mixture of monoesters and diesters of polyoxyethylene glycol 300, with palmitic and stearic acids and free polyoxyethylene glycol 300.

Manufacturing Directions

1. Aqueous phase: Prepare a solution of DL-lactone (previously liquefied at approximately 100°C) in water.
2. Add the DL-lactone solution to the main part of water at 70°C.
3. Incorporate the D-panthenol (previously liquefied at approximately 45°C).
4. Admix and dissolve sequestrene disodium.
5. Fatty phase: Melt at approximately 65°C under stirring POEG 300-stearate, paraffin oil, and polydimethylsiloxane M 350.
6. Emulsion: Add the fatty phase at 65°C to the aqueous phase at approximately 45°C.
7. Cool to approximately 36°C while stirring and homogenizing.
8. Chlorhexidine suspension: Suspend chlorhexidine in water.
9. Lotion: Add the chlorhexidine suspension to the emulsion at approximately 36°C.
10. Stir, homogenize, and deaerate.
11. Finally, add the perfume, homogenize again, and filter.

Panthenol Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Protegin X	50.00
18.00	2	Cetyl alcohol	18.00
12.00	3	Stearyl alcohol	12.00
40.00	4	Wax (white)	40.00
250.00	5	Wool fat (deodorized)	250.00
130.00	6	Vaseline® (white)	130.00
50.00	7	Almond oil	50.00
150.00	8	Paraffin oil	150.00
50.00	9	D-Panthenol	50.00
250.00	10	Deionized water	250.00

Manufacturing Directions

1. Place in a heating vessel wool fat, Vaseline, almond oil, and paraffin.
2. Heat and melt the fats together at 80°C with stirring to keep the fatty phase at this temperature until further processing.
3. In a separate container, add Protegin X, cetyl alcohol, stearyl alcohol, and white wax. Melt these fats with stirring at 80°C.
4. Add to above.
5. The final temperature in the melt should be approximately 70°C.
6. Keep this temperature until further processing.
7. Transfer D-panthenol into a 10-L container by pouring, then rinse it with hot deionized water.
8. Continue to mix for another 5 minutes, check the final weight, and make up for evaporated water (5.67 kg).
9. Place in kettle and heat to 70°C while stirring. Transfer the melted fatty mass under vacuum (–0.3 mm) through the inline sieve (0.150-mm mesh).
10. After the addition, evacuate again to –0.3 atm.
11. Then, stir for another 15 minutes and homogenize for 5 minutes under the same conditions.
12. Cool to 30°C (the cooling should occur within 4 hours).
13. When this temperature is reached, continue stirring until the ointment has reached 24°C to 26°C.
14. Stop cooling, then evacuate quickly to –0.3 atm and stir for 5 minutes.
15. Transfer the ointment in a storage vessel and mix for 5 minutes with electric mixture.
16. Fill the ointment.

Papain Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
1.00	1	Papain	1.00
150.00	2	Lycasin	150.00
17.40	3	Hydrogenated vegetable oil	17.40
9.60	4	Water	9.60
5.80	5	Gelatin (40% solution)	5.80
17.40	6	Starch coated dicalcium phosphate	17.40
1.60	7	Mono- and diglyceride mixture	1.60
0.60	8	Lecithin	0.60
0.10	9	Aspartame	0.10
0.10	10	Vanillin	0.10
0.20	11	Glycerin	0.20
0.20	12	Sodium bicarbonate	0.20
0.38	13	Mint flavor	0.38

Manufacturing Directions

1. Boil isomalt, lycasin, water, fat, mono- and diglyceride mixture, glycerin, and lecithin to 131°C.
2. Glycerin is added to the mixture and cooled to 60°C.
3. Thereafter, sodium bicarbonate, papain, dicalcium phosphate, and the remaining ingredients are added.
4. Thereafter, the mixture cooled to room temperature is ground into powder and compressed into 205-mg tablets using a tablet press.

Papain Chewing Gum

Formulation

Gum base, 31.20%; sorbitol, 28.08%; mannitol, 5.23%; papain, 1.00%; acesulfame K, 0.16%; aspartame, 0.16%; menthol powder, 1.00%; liquid flavor, 0.47%; isomalt PF, 11.70%; isomalt DC, 16.00%; anticaking agents (magnesium stearate, talc, or silica gel), 4.00%; flavor, 2.00%.

Peppermint Rub Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
25.00	1	Sorbitol stearate	25.00
15.00	2	Polysorbate 60	15.00
300.00	3	Peppermint oil	300.00
20.00	4	Cetyl alcohol	20.00
40.00	5	Stearic acid	40.00
10.00	6	Triethanolamine (99%)	10.00
2.00	7	Carbopol 980	2.00
QS	8	Deionized water	QS
QS	9	Preservative, color	QS

Manufacturing Directions

1. Hydrate Carbopol in water at 60°C to 65°C.
2. Add remaining water-phase ingredients.
3. Heat oil and water phases separately to 70°C to 75°C.
4. Add water phase to oil phase while stirring.
5. Stir to cool, neutralizing at 65°C with triethanolamine.

Peptide Sublingual Tablet

Formulation

The individual component peptides, each has a molecular weight of less than 20,000 Da. Thymosin fraction, 5%; water, 5.0%; sucrose/lactose, 69.5%; propylene glycol, 0.5%; silicon dioxide, 15.0%; methyl nicotinate, 0.5%.

Manufacturing Directions

The wetted mixture is formed into tablets of a desired weight and the tablets are then dried at 30°C for 36 hours.

Peptide Topical Liquid

Formulation

Peptide such as thymic fraction, 5; glycerin, 44.5; propylene glycol, 44.9; methyl nicotinate, 0.1; water, 50; polysorbate 80, 0.5% by weight.

Phenindione Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50.00	1	Phenindione	50.00
165.00	2	Ludipress	165.00
2.00	3	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compression force.
2. Compress 230 mg in 8-mm biplanar punches.

Phenolphthalein Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Phenolphthalein	200.00
150.00	2	Dibasic calcium phosphate	150.00
11.00	3	Kollidon 30	11.00
–	4	Isopropanol or ethanol (96%)	QS
19.00	5	Kollidon CL	19.00
3.00	6	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 3 and 4, mix with items 5 and 6, pass through a 0.8-mm sieve, and press with low compression force.
2. Compress 385 mg using 9-mm biconvex punches.

Phenolphthalein Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
90.00	1	Yellow phenolphthalein	90.00
64.80	2	Microcrystalline cellulose	64.80
187.20	3	Dicalcium phosphate	187.20
3.60	4	Croscarmellose sodium	3.60
3.60	5	Fumed silica	3.60
7.20	6	Stearic acid	7.20
3.60	7	Magnesium stearate	3.60

Manufacturing Directions

1. Screen items 6 and 7 through a 40-mesh sieve.
2. Blend items 1 and 5 in a V-blender for 3 minutes.
3. Add items 2 and 4 to the blender and mix for 5 minutes.
4. Add item 3 to the blender and mix for 12 minutes.
5. Add item 6 and blend for 3 minutes.
6. Add item 7 and mix for another 5 minutes.
7. Compress using 3/8-in flat, bevel-edged punches to hardness of 10 kg; average tablet weight is 360 mg.

Phenylpropanolamine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
60.00	1	Phenylpropanolamine hydrochloride, USP	60.00
180.00	2	Calcium sulfate dihydrate	180.00
—	3	Starch paste 10%	QS
12.00	4	Starch 1500 (StarX)	12.00
6.00	5	Magnesium stearate	6.00

Manufacturing Directions

1. Add starch to cold water in 1:10 ratio. Heat to boil with constant stirring until a thick, translucent white paste is formed.
2. Keep it for use in granulation below.
3. Mix the phenylpropanolamine hydrochloride with the calcium sulfate in a Sigma blade mixer for 15 minutes.
4. Add starch paste in sufficient quantity to form a suitable wet mass of desirable consistency.
5. Allow to mix for 30 minutes.
6. Pass the wet mass through a No.14 screen and distribute on drying trays.
7. Dry in a forced-air oven at 49°C to 54°C or in a fluid-bed dryer.
8. Pass the dried granules through a No. 18 mesh screen.
9. Transfer granules to a twin-sell blender, add items 4 and 5, and blend for 6 to 8 minutes.
10. Compress the granulation in a rotary press using 3/8-in standard punches. Tablet weight is 260 mg.

Phenylpropanolamine and Brompheniramine Fast-Dissolving Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
6.25	1	Phenylpropanolamine hydrochloride	6.25
1.00	2	Brompheniramine maleate	1.00
6.00	3	Citric acid	6.00
1.80	4	Magnasweet 135	1.80
4.50	5	Aspartame	4.50
3.60	6	Cherry flavor	3.60
21.00	7	Croscarmellose sodium	21.00
3.00	8	Lecithin	3.00
30.00	9	Cornstarch	30.00
3.00	10	Silicon dioxide	3.00
2.10	11	Magnesium stearate	2.10
219.25	12	Fast-dissolving granulation (see below)	219.25

Manufacturing Directions

1. Fast-dissolving granulation is made by combining 400 g of melted PEG-900 with fructose powder (100 g) in a planetary mixer (low shear mixer) and mixing until the granules formed.
2. The granulations are allowed to cool, then screened.
3. All ingredients are mixed in a V-blender.
4. Tablets are compressed (301.5 mg) at approximately 3 kN.
5. Tablet hardness is 0.2 to 0.5 kp and disintegration time is 10 seconds.

Phenylpropanolamine, Chlorpheniramine, Dextromethorphan, Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
150.00	1	PEG-400 (low color), NF	150.00
21.66	2	Acetaminophen, USP	21.66
0.075 mL	3	Glycerin, USP (96%)	75.00 mL
0.35 mL	4	Sorbitol; use sorbitol solution, USP	350.00 mL
1.00	5	Benzoic acid, USP	1.00
1.75	6	Saccharin sodium (dihydrate powder), USP	1.75
0.91	7	Phenylpropanolamine hydrochloride, USP	916.70 mg
0.06	8	Chlorpheniramine maleate, USP (plus 10% manufacturing)	73.30 mg
0.66	9	Dextromethorphan hydrobromide, USP	667.00 mg
20.00	10	Sodium CMC (premium low viscosity)	20.00
70.00	11	Dye	70.00 mg
6.00	12	Dye	6.00 mg
5.00	13	Ascorbic acid; use sodium ascorbate (fine powder)	5.62
0.50	14	Flavor, orange	500.00 mg
0.25	15	Flavor, orange	250.00 mg
QS	16	Carbon dioxide gas	QS
QS	17	Purified water, USP	QS to 1 L

Manufacturing Directions

Manufacture under complete CO_2 protection. Bubble the CO_2 gas through the solution from the bottom of the tank.

If excessive foaming occurs, change CO_2 gas protection from the bottom to the top of the tank. Minimize vortex formation while mixing to prevent aeration of the product.

1. In a covered stainless steel container, heat 500 mL of water to boiling. Boil for 30 minutes.
2. Turn off the heat. While keeping the container covered, cool the water to 30°C while purging the water with CO_2.
3. Keep this water in a covered container blanketed with CO_2 gas and use where indicated.

4. Transfer the PEG-400 to the main stainless steel mixing tank and cover.
5. Start bubbling CO_2 gas. While mixing, slowly heat to 60°C to 65°C. Maintain at this temperature.
6. While mixing, add and dissolve the acetaminophen. Maintain the temperature and CO_2 protection.
7. When all the acetaminophen has dissolved, add, while mixing, the glycerin and sorbitol.
8. Continue mixing while maintaining the temperature and CO_2 gas protection until mixture is used later.
9. Do not allow the temperature to go more than 65°C.
10. During this mixing period, remove samples through the bottom valve of the mixing tank and inspect for clarity. Return samples to the mixing tank. Continue mixing and sampling until absolutely clear.
11. In a separate stainless steel mixing tank, heat 300 mL of water covered to 90°C.
12. While maintaining at this temperature, start bubbling CO_2 gas.
13. While mixing, add and dissolve successively the benzoic acid, saccharin sodium, and phenylpropanolamine hydrochloride. Continue mixing until all have dissolved.
14. Reduce the temperature to 60°C to 65°C while mixing. Do not force cool.
15. Add the solution from step above to the solution in the main mixing tank, while mixing and bubbling CO_2 gas.
16. Rinse the container with 2 lots of 5 mL of CO_2-saturated water and add the rinsings to the batch while mixing.
17. Continue mixing for 15 minutes while maintaining the temperature at 60°C to 65°C and under CO_2 gas protection.
18. While mixing the batch, sprinkle on the sodium CMC.
19. Continue mixing until all the sodium CMC has been dispersed.
20. Check on the absence of any undissolved lumps.
21. Add CO_2-saturated water from step 3 to 900 mL and mix while cooling the batch to 30°C.
22. Dissolve the dyes in 10 mL of CO_2-saturated water, then add to the batch with mixing.
23. Rinse the container with two lots of 5 mL of the same water and add the rinsings to the batch.
24. Mix until a homogenously colored batch is formed.
25. Stop bubbling in CO_2 gas but maintain CO_2 protection of the tank headspace.
26. In a stainless steel container, dissolve the sodium ascorbate in 25 mL of CO_2-saturated water, taking care to minimize exposure of the solution to air or light.
27. Mix all solutions, add rinsings where necessary, and continue mixing for 15 minutes.
28. Add the flavors, complete the batch to 1 L with CO_2-saturated water, and mix well for 1 hour.
29. Stop mixing, saturate the headspace with CO_2, and leave overnight to release any entrapped air.

Placebo Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
299.70	1	Ludipress	299.70
0.30	2	Magnesium stearate	0.30

Manufacturing Directions

1. Mix the components, sieve, and press.
2. For this formulation, compress 300 mg.
3. The compression force determines hardness and friability.
4. At 7 kN, the hardness is 45 N; at 22 kN, the hardness is 160 N.
5. The disintegration time increases from 1 minute to 4 minutes.

Polidocanol Wound Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Polidocanol	5.00
50.00	2	Kollidon VA 64	50.00
50.00	3	Ethocel® 20	50.00
20.00	4	Lutrol E 400	20.00
675.00	5	Ethyl acetate	675.00
200.00	6	Isopropanol	200.00

Manufacturing Directions

1. Dissolve items 1 to 4 in the solvent mixture of items 5 and 6.
2. Fill the solution into spray cans with the necessary quantity of propellant (e.g., propane/butane) or in a mechanical pump bottle.

Potassium Bicarbonate-Coated Tablet

Manufacturing Directions

1. Preparation of the potassium bicarbonate crystals: U.S. Patent 5,445,805 describes how to prepare crystals of size within the range of 800 to 900 μm, a BET surface area of 0.004 to 0.01 m^2/g, and particle distributions such that greater than 90% by weight of the crystals are within the range of 700 to 1000 μm. [At least 90% of the crystals are retained on a 25-mesh screen (707 μm) and less than 10% are retained on an 18-mesh screen (1000 μm)].
2. Preparation and application of controlled-release coating lacquers: Coating lacquer composition: Cutina HR, 23.45 g; Ethocel, 163.45 g; acetyl tributyl citrate, 8.75 g; isopropyl alcohol, 3304.35 g; total, 3500.00 g.
3. Coating conditions: process air flow (m^3/h), 100–171; spray period (minutes), 135; spray temperature, 60.1°C to 68.1°C; spray pressure (bar), 2; liquid flow rate, 26–28 g/min; product temperature, 46°C to 52°C; coated crystals: theoretical yield (g), 3191.1; actual yield approximately 98% giving w/w dry matter of 6.37% (coated/uncoated crystals).
4. Hydrogenated castor oil (Cutina HR), ethyl cellulose (Ethocel Standard 100 premium), and acetyl tributyl citrate are dissolved in isopropyl alcohol to provide the controlled-release coating lacquers.
5. Cutina HR, Ethocel, and acetyl tributyl citrate are dissolved in the isopropyl alcohol solvent by heating in a mixer equipped with a heating jacket set at 60°C to 70°C with vigorous agitation. The agitation is continued for approximately 1 hour. When dissolved, the mixture is clear to translucent.
6. The coating lacquer composition is maintained at temperatures of 60°C to 70°C.
7. The lacquers are coated on the potassium bicarbonate particles by co-current flow through a fluidized bed in which the moisture content is controlled. The coating lacquer is sprayed from a spray nozzle positioned at the bottom of a Glatt fluidized bed apparatus equipped with a Wurster tube.
8. The potassium bicarbonate crystals are fluidized and the warm coating lacquer is sprayed on the crystals in multiple coating cycles.
9. The process air-flow rate is adjusted as necessary to provide adequate movement of the crystals through the fluidized bed as they are coated. During the coating process, the isopropyl alcohol solvent is flash-evaporated from the crystals as they cycled through the fluidized bed.
10. After completing the application of the coating lacquer to the crystals, any trace residual solvent remaining on the coated crystals is removed by cycling in the fluidized bed without lacquer spray for 10 minutes.
11. Following the residual solvent removal, the coated crystals are cooled in the bed.
12. The amount of coating lacquer applied on the crystals is calculated as the % w/w of the dry matter of the respective coatings, relative to the uncoated potassium bicarbonate crystals.
13. Compression: potassium, 85.00%; bicarbonate coated crystals, Cutina HR, 1.50%; Avicel PH, 7.68%; cornstarch, 5.12%; Syloid, 0.40%; Lubritab, 0.30%. Compress tablets of 1500 mg of potassium bicarbonate.

Povidone–Iodine and Lidocaine Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
10.00	2	Lidocaine hydrochloride	10.00
10.00	3	Sodium chloride	10.00
200.00	4	Lutrol F 127	200.00
79.00	5	Sodium hydroxide (1-M solution)	79.00
61.10	6	Water	61.10

Manufacturing Directions

1. Dissolve items 1 to 3 in item 6, cool to approximately 6°C, dissolve item 4, and adjust the pH to a value of 4.5 to 5.0 with item 5.
2. Maintain the cool temperature until the air bubbles escape.
3. Viscosity (Brookfield, 23°C) is 54,000 mPa.

Povidone–Iodine Bar Soap

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PVP–iodine 30/06	50.00
10.00	2	Fragrance	10.00
75.00	3	Water	75.00
940.00	4	Syndet base	940.00

Manufacturing Directions

1. Dissolve PVP–iodine in water and mix the solution with the fragrance and the syndet base.
2. Pass the blend 4 times through a three-roller mill.
3. Blend 3 times through a plodder with a narrow-sieve hole disk.
4. Pass the blended material through a wide-sieve hole disk combined with a mouth hole disk.
5. Heat the area of the two disks to 50°C using a heating collar.
6. Cut the bar in pieces on a lab stamper.
7. Composition of the syndet base (in sequence of concentration): disodium lauryl sulfosuccinate, sodium lauryl sulfate, cetyl stearyl alcohol, paraffin, glycerol stearate, water, titanium dioxide.

Povidone–Iodine Bar Soap

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PVP–iodine 30/06	50.00
75.00	2	Water	75.00
241.5	3	Texapon® K 12	241.5
241.5	4	Setacin® F special paste	241.5
241.5	5	Emcol® 4400.1	241.5
145.00	6	Cetylstearyl alcohol	145.00
96.50	7	Paraffin	96.50
226.00	8	Glycerol monostearate	226.00

Manufacturing Directions

1. Heat mixture of items 3 to 8 to 75°C to 80°C and cool to approximately 50°C, stirring well.
2. Add solution of items 1 and 2 and let cool to room temperature, stirring continuously.
3. Pass the blend 4 times through a three-roller mill and let dry overnight at room temperature.
4. Cut the bar into pieces on a lab stamper.

Povidone–Iodine Bar Soap

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	PVP–iodine 30/06	50.00
75.00	2	Water	75.00
241.50	3	Texapon® K 12	241.50
145.00	4	Cetylstearyl alcohol	145.00
96.50	5	Paraffin	96.50
226.00	6	Glycerol monostearate	226.00

Manufacturing Directions

1. Heat mixture of items 3 to 6 to 75°C to 80°C and cool to approximately 50°C, stirring well.
2. Add solution of item 1 and let cool to room temperature, stirring continuously.
3. Pass the blend 4 times through a three-roller mill and let dry overnight at room temperature.
4. Cut the bar into pieces on a lab stamper.

Povidone–Iodine Concentrates for Broilers and Cattle

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
200.00	1	PVP–iodine 30/06	200.00
50.00	2	Texapon® K 12	50.00
50.00	3	Cremophor NP 14	50.00
73.00	4	Tartaric acid	73.00
43.00	5	Sulfuric acid, diluted	43.00
100.00	6	Ethanol 96%	100.00
QS	7	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve surfactant items 2 and 3 in solution of items 4 to 7 and slowly add PVP–iodine.
2. Brown transparent liquid having a pH of approximately 1 is obtained.
3. Dilute approximately 3 mL of the concentrate with 1 L of water prior to use.

Povidone–Iodine Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
241.00	2	Citric acid (0.1-M solution)	241.00
369.00	3	Na_2HPO_4 (0.2-M solution)	369.00
20.00	4	Cremophor A 6	20.00
20.00	5	Cremophor A 25	20.00
100.00	6	Cetylstearyl alcohol	100.00
100.00	7	Liquid paraffin	100.00
50.00	8	Glycerol	50.00

Manufacturing Directions

1. Prepare a basic cream from the emulsifying agents and the fatty substances (items 4–8).
2. Stir in the PVP–iodine dissolved in the buffer solutions made from items 2 and 3.
3. A brown cream having a pH of 4.5 is obtained.

Povidone–Iodine Effervescent Vaginal Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
350.00	1	PVP–iodine 30/06, with excess	360.00
1450.00	2	Ludipress	1450.00
360.00	3	Tartaric acid	360.00
265.00	4	Sodium bicarbonate	265.00
19.00	5	Talc	19.00
2.00	6	Calcium arachinate	2.00
2.00	7	Aerosil 200	2.00

Manufacturing Directions

1. Dry the mixture of items 2 to 4 for 4 hours at 60°C, mix with item 1 and items 5 to 7, and press to tablets.
2. Compress 2.5 g in 20-mm biplanar punches.
3. The tablet is dissolved in water to obtain a vaginal douche solution.

Povidone–Iodine Foam Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
0.10	2	Cremophor A 25	0.10
QS	3	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve PVP–iodine in the solution of Cremophor A 25 in water.
2. Fill the aerosol cans with 90 parts of this solution and 10 parts of propane + 1 part butane.

Povidone–Iodine Gargle

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Polyvinylpyrrolide-iodine (powder) (35% excess)	13.50
10.00	2	Glycerin, USP (96%)	10.00
–	3	Purified water, USP	QS to 1 L

Manufacturing Directions

Wear gloves and mask during all phases of manufacturing and filling. Do not keep the lid of the manufacturing or storage tank open, unless necessary, as iodine may be liberated.

1. Add 600 mL purified water to a suitable stainless steel manufacturing tank.
2. Slowly add povidone–iodine powder to the water (with continuous stirring).
3. Stir for 30 minutes or until a clear, brown solution is obtained.
4. Add glycerin to the manufacturing tank.
5. Stir until uniform solution is obtained.
6. Make up volume to 1 L with purified water and mix well for 5 minutes.
7. Check pH (range: 2–4).
8. Filter the solution through a 100-mesh nylon cloth and transfer to a stainless steel storage tank.
9. Keep the storage tank tightly closed.

Povidone–Iodine Gargle Solution Concentrate

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	PVP–iodine 30/06	100.00
10.00	2	Propylene glycol	10.00
90.00	3	Ethanol (96%)	90.00
800.00	4	Water	800.00

Manufacturing Directions

1. Dissolve the PVP–iodine in the solvent mixture to produce a brown transparent liquid.
2. Dilute 10 mL of the concentrate with approximately 100 mL of water prior to use.

Povidone–Iodine Gel Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
359.00	2	Citric acid (0.1-M solution)	359.00
181.00	3	$NA_2HPO_4 \cdot 12H_2O$ (0.2-M solution)	181.00
50.00	4	Lutrol E 400	50.00
100.00	5	Liquid paraffin	100.00
150.00	6	Lutrol F 127	150.00
70.00	7	Lutrol F 127	70.00

Manufacturing Directions

1. Dissolve item 1 in solution of items 2 to 4, mix with item 5, and dissolve item 6 at approximately 20°C.
2. Cool to 5°C to 8°C and dissolve item 7.
3. Maintain cool temperature until all air bubbles have disappeared.
4. A brown, turbid gel is obtained.

Povidone–Iodine Gels

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
10.00	2	Sodium chloride	10.00
200.00	3	Lutrol F 127	200.00
79.00	4	Sodium hydroxide (1-M solution)	79.00
610.00	5	Water	610.00

Manufacturing Directions

1. Dissolve items 1 and 2 in item 5 and cool to approximately 6°C.
2. Dissolve Lutrol F 127 and item 2 and adjust the pH value with item 4.
3. Maintain cool until all air bubbles escape.
4. Viscosity (Brookfield, 23°C) is 61,000 to 54,000 mPa; pH value (20% in water) is 2.2 to 4.6.

Povidone–Iodine Glucose Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	PVP–iodine 30/06, with excess	26.00
45.00	2	Ethanol (96%)	45.00
849.00	3	Glucose	849.00
34.00	4	Lutrol E 4000	34.00
6.00	5	Glycerol	6.00
6.00	6	Water	6.00

Manufacturing Directions

1. Dissolve Lutrol E 4000 in the hot mixture of glycerol and water and add the glucose warmed to 60°C to 80°C.
2. Incorporate item 4 to obtain a brown, viscous, and turbid paste.

Povidone–Iodine Liquid Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
150.00	2	Kollidon VA 64	150.00
750.00	3	*N*-Propanol	750.00
750.00	4	Ethanol	750.00

Manufacturing Directions

1. Dissolve Kollidon VA 64 in the mixture of solvents and slowly add PVP–iodine to the well-stirred solution.
2. Fill in aerosol cans with propellants such as propane and butane or with manual valves.

Povidone–Iodine Lozenges

Bill of Materials			
Scale (mg/lozenge)	Item	Material Name	Qty/1000 Lozenges (g)
5.00	1	PVP–iodine 30/06	5.00
150.00	2	Sorbitol (crystallized)	150.00
4.00–5.00	3	Menthol (crystalline)	4.00–5.00
4.00–5.00	4	Eucalyptol (crystalline)	4.00–5.00
1.00	5	Aspartame, potassium	1.00
0.10	6	Saccharine sodium	0.10
1.00	7	Aerosil 200	1.00
1.00	8	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium compression force.
2. Compress 176 mg in 8-mm biplanar punches.

Povidone–Iodine Mastitis Cream for Cattle

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
100.00	2	Liquid paraffin	100.00
100.00	3	Vaseline®	100.00
50.00–80.00	4	Cetylstearyl alcohol	50–80
20.00	5	Cremophor A 6	20.00
20.00	6	Cremophor A 25	20.00
50.00	7	Propylene glycol	50.00
QS	8	Water	530.00–560.00

Manufacturing Directions

1. Dissolve PVP–iodine in the solvents (items 7 and 8).
2. Mix items 2 to 6 by heating, stir the solution in the previous mixture, and cool by stirring.

Povidone–Iodine Mouthwash and Gargle Solution Concentrate

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
75.00	1	PVP–iodine 30/06	75.00
5.00	2	Saccharin sodium	5.00
150.00	3	Water	150.00
2.00	4	Menthol	2.00
1.00	5	Anise oil + eucalyptus oil (1+1)	1.00
150.00	6	Lutrol E 400	150.00
500.00	7	Ethanol (96%)	500.00

Manufacturing Directions

1. Dissolve PVP–iodine and saccharin in water and mix with solution of items 4 to 7.
2. Brown transparent liquid has a fresh odor.
3. Dilute 10 to 20 mL with a glass of water.
4. A brown liquid with a fresh taste is obtained.

Povidone–Iodine Powder Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
250.00	1	PVP–iodine 30/06	250.00
250.00	2	Maize PO_4 aerosol	250.00
15.00	3	Isopropyl myristate	15.00
100.00	4	Dow Corning® 344 fluid	100.00
500.00	5	Pentane	500.00
220.00	6	Propane + butane (1+3)	220.00

Manufacturing Directions

1. Suspend PVP–iodine and maize PO_4 aerosol in the liquid mixture of items 3 to 5.
2. Fill in aerosol cans with the propellants.

Povidone–Iodine Pump Spray

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	PVP–iodine 30/06	10.00
100.00	2	Water	100.00
1.00	3	Potassium iodide	1.00
100.00	4	Xylitol	100.00
787.50	5	Propylene glycol	787.50
1.00	6	Menthol (crystalline)	1.00
0.50	7	Peppermint oil (double rectified)	0.50

Manufacturing Directions

1. Dissolve potassium iodide in water, warm up to 40°C, and dissolve xylitol.
2. At room temperature, dilute with propylene glycol, dissolve PVP–iodine, and add flavors to produce a clear, brown liquid with a sweet, refreshing taste.

Povidone–Iodine Shampoo

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
75.00	1	PVP–iodine 30/06	75.00
250.00	2	Neutronyx® S 60	250.00
40.00	3	Super Amide® L 9	40.00
5.00–7.00	4	Natrosol® HR 250	5.00–7.00
–	5	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve Super Amide and Natrosol in hot water (approximately 60°C), then dissolve PVP–iodine.
2. After cooling, incorporate Neutronyx.
3. A brown, clear solution is obtained.
4. The viscosity can be changed by modification of the amount of Natrosol 250 HR.

Povidone–Iodine Soft Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	PVP–iodine 30/06	10.00
25.00	2	Natrosol HR 250	25.00
QS	3	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve PVP–iodine and Natrosol HR 250 in the water and stir well to produce a clear, brown gel.
2. Viscosity (Brookfield, 23°C) is 31,500 mPa.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100.00	1	Povidone–iodine powder (35% excess)	135.00
9.318	2	Anhydrous citric acid (powder)	9.318
14.62	3	Anhydrous sodium phosphate (dibasic)	14.62
QS	4	Purified water	QS to 1 L

Manufacturing Directions

Wear gloves and mask during all phases of manufacturing and filling. Do not keep the lid of the manufacturing or storage tank open, unless necessary, as iodine may be liberated.

1. Citric acid–phosphate buffer solution (pH 5): Add 600 mL purified water to a suitable stainless steel manufacturing tank.
2. With gentle stirring, add citric acid to the purified water in the manufacturing tank.
3. Stir for 10 minutes or until completely dissolved.
4. During this mixing period, remove samples from the bottom valve of the manufacturing tank and inspect for clarity.
5. Return samples to the manufacturing tank.
6. Continue mixing and sampling until the solution is completely clear.
7. With gentle stirring, add dibasic sodium phosphate to the solution.
8. Stir for 10 minutes or until completely dissolved.
9. During this mixing period, remove samples from the bottom valve of the manufacturing tank and inspect for clarity.
10. Return samples to the manufacturing tank.
11. Continue mixing and sampling until the solution is completely clear.
12. Make up volume to 1 L with purified water and mix well for 5 minutes.
13. Check and record pH (range: 4.8–5.2).
14. Filter the solution through a 100-mesh nylon cloth.
15. Transfer into a suitable stainless steel storage tank and keep tightly closed.
16. This solution should be freshly prepared and should not be stored for more than 24 hours.
17. Preparation of solution: Dissolve povidone–iodine in approximately 600 mL of citric acid/phosphate buffer (pH 5) solution in a suitable stainless steel mixing tank.
18. Stir evenly for 10 minutes or until a clear, brown solution is obtained.

19. Make up volume to 1 L with citric acid/phosphate buffer solution.
20. Mix well for 10 minutes.
21. Check and record pH (range: 3.0–4.5).
22. Filter the solution through a 100-mesh nylon cloth.
23. Transfer into a suitable stainless steel storage tank and keep it tightly closed.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
3.00	2	Lutrol F 127	3.00
5.00	3	Lutrol E 400	5.00
432.00	4	Citric acid (0.1-M solution)	432.00
460.00	5	$Na_2HPO_4 \cdot 12H_2O$ (0.2-M solution)	460.00

Manufacturing Directions

1. Dissolve the PVP–iodine (and Lutrol F 127) in the mixture of buffer solutions (and Lutrol E 400).
2. Brown clear solutions having a low viscosity and pH of approximately 4.5.
3. Items 2 and 3 can be deleted and compensated with item 5.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
0.23	2	Texapon® K 12	0.23
1.40	3	Sodium biphosphate	1.40
0.30	4	Sodium citrate	0.30
20.80	5	Sodium hydroxide (1-M solution)	20.80
10.00	6	Glycerol	10.00
QS	7	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve Texapon K 12 in solution of items 3 to 7 and slowly add PVP–iodine to the well-stirred solution.
2. The brown transparent liquid has a pH of 4.5.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
10.00	2	Natrosol HR 250	10.00
2.00	3	Lutrol F 127	2.00
32.00	4	Sodium hydroxide (1-M solution)	32.00
QS	5	Water	QS to 1 kg

Manufacturing Directions

1. Dissolve Lutrol F 127 and then Natrosol in the water.
2. As soon as both are dissolved, slowly add the PVP–iodine to the well-stirred solution.
3. Adjust the pH with the sodium hydroxide solution to approximately 3.5.

Povidone–Iodine Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
20.00	1	Tylose® M 300	20.00
2.00	2	Texapon® K 12	2.00
595.00	3	Citric acid (0.1-M solution)	595.00
283.00	4	Sodium biphosphate (0.2-M solution)	283.00

Manufacturing Directions

1. Dissolve Tylose M 300 in the mixture of the citric acid and sodium biphosphate solutions.
2. Add Texapon and slowly dissolve the PVP–iodine.
3. The brown, clear solution has a pH of 3 to 4.

Povidone–Iodine Scrub

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
75.00	1	PVP–iodine (powder) (40% excess)	105.00
250.00	2	Sodium lauryl sulfate	250.00
35.00	3	Lauric diethanolamide	35.00
–	4	Distilled purified water, USP	QS to 1 L

Manufacturing Directions

1. Add 600 mL purified water to a suitable stainless steel manufacturing tank.
2. Add, by sprinkling, the sodium lauryl sulfate to the manufacturing tank.
3. Continue to mix slowly under vacuum and begin to heat until product temperature is 70°C.
4. Continue to mix vigorously under vacuum at 65°C to 70°C for 15 minutes or until completely dissolved.
5. (*Note*: Do not add detergent quickly, as a gel may form that is difficult to dissolve.) Stop mixer, release vacuum, and open tank.
6. Add and disperse the previously broken lauric diethanolamide in the warmed solution from the step above.
7. Maintain vacuum and mix vigorously for 30 minutes at 65°C to 70°C or until completely dissolved.
8. Slowly cool under vacuum to room temperature with slow mixing. (*Note*: Do not force cool with cold water; otherwise the mixture will adhere to the walls of the manufacturing tank.) When temperature reaches 30°C, release vacuum and open tank.
9. While mixing slowly, add povidone–iodine in small portions.
10. Rinse the container of povidone–iodine with 150 mL purified water and add to the main tank. (*Note*: Do not keep the lid of the manufacturing or storage tank open, unless necessary, as iodine may liberate.) Mix under vacuum until a clear reddish-brown solution is obtained.
11. Make volume up to 1 L with purified water and mix well under vacuum for at least 15 minutes to ensure product uniformity and to deaerate the product.
12. Stop mixing, release the vacuum, then open the tank.
13. Check and record pH (range: 3–6).
14. Filter the solution through 100-mesh nylon cloth.

Povidone–Iodine Surgical Scrub

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
75.00	1	PVP–iodine 30/06	75.00
250.00	2	Neutronyx® S 60	250.00
40.00	3	Super Amide® L 9	40.00
QS	4	Floral bouquet	QS
QS	5	Water	QS to 1 kg

Manufacturing Directions

Dissolve Super Amide in hot water, cool, dissolve PVP–iodine, and add Neutronyx to produce a brown, clear viscous solution with pH of approximately 3.4.

Povidone–Iodine Surgical Scrub

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
75.00	1	PVP–iodine 30/06	75.00
250.00	2	Lutensit® AES	250.00
40.00	3	Monoamide® 150 MAW	40.00
QS	4	Floral bouquet	QS
QS	5	Water	QS to 1 kg

Manufacturing Directions

Dissolve monoamide in hot water, cool, dissolve PVP–iodine, and add Lutensit to produce a brown, clear, viscous solution.

Povidone–Iodine Transparent Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
600.00	2	Lutrol E 400	600.00
46.00	3	Sodium hydroxide (1-M solution)	46.00
4.00	4	Water	4.00
250.00	5	Lutrol E 4000	250.00

Manufacturing Directions

1. Prepare solution of items 1 to 4, heat to approximately 60°C, incorporate item 5 (stirring well), and cool to room temperature.
2. The transparent ointment, similar to a gel, has a pH of 4 and is miscible and washable with water.

Povidone–Iodine Vaginal Douche Concentrate

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine 30/06	100.00
5.00	2	Lutrol E 400	5.00
3.00	3	Lutrol F 127	3.00
432.00	4	Citric acid (0.1-M solution)	432.00
460.00	5	$Na_2HPO_4 \cdot 12H_2O$ (0.2-M solution)	460.00

Manufacturing Directions

1. Dissolve PVP–iodine and Lutrol F 127 in the mixture of buffer solutions with Lutrol E 400.
2. The brown, clear solution has a low viscosity and pH of approximately 4.3.

Povidone–Iodine Vaginal Ovule

Bill of Materials			
Scale (mg/Ovule)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	PVP–iodine 30/06	5.00
200.00	2	Lutrol E 400	10.00
170.00	3	Lutrol E 4000	85.00

Manufacturing Directions

1. Melt the Lutrol E grades by gentle heating.
2. Stir in the micronized PVP–iodine product in small portions into the melt.
3. After a uniform suspension has been obtained, pour it into polyethylene molds.
4. The homogeneous, brown-colored ovule has a weight of 2 g.

Povidone–Iodine Vaginal Ovule

Bill of Materials			
Scale (mg/Ovule)	Item	Material Name	Qty/kg (g)
200.00	1	PVP–iodine 30/06	200.00
100.00	2	Lutrol E 400	100.00
100.00	3	Lutrol E 1500	100.00
700.00	4	Lutrol E 4000	700.00

Manufacturing Directions

1. Melt the Lutrol E grades by gentle heating.
2. Stir in the micronized PVP–iodine product in small portions into the melt.
3. After a uniform suspension has been obtained, pour it into polyethylene molds.
4. The homogeneous, brown-colored ovule has a weight of 2 g.

Povidone–Iodine Viscous Solution

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
10.00	1	PVP–iodine 30/06	10.00
15.00	2	Natrosol HR 250	15.00
QS	3	Buffer	QS
QS	4	Water	975.00

Manufacturing Directions

1. Dissolve PVP–iodine and Natrosol in the well-stirred buffered solution in water to produce a clear, brown, viscous liquid.
2. Viscosity (Brookfield) is 7500 mPa.

Promethazine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1.00	1	Promethazine HCl (5% excess)	1.05
675.00	2	Sucrose	675.00
1.00	3	Citric acid (monohydrate)	1.00
2.40	4	Sodium citrate	2.40
0.50	5	Ascorbic acid	0.50
0.25	6	Sodium metabisulfite (sodium disulfite)	0.25
0.25	7	Anhydrous sodium sulfite	0.25
50.00	8	Alcohol (ethanol, 95%)	50.00
0.15	9	Flavor	0.15
0.30	10	Flavor	0.30
0.50	11	Polysorbate 80 (Tween 80)	0.50
0.15	12	Caramel color	0.15
QS	13	Purified water	QS to 1 L

Manufacturing Directions

Promethazine HCl undergoes thermal and photochemical oxidation. Protect from light, heat, and oxygen as practicable. Avoid vortex or overmixing to avoid air entrapment. Use nitrogen gas whenever necessary to expel air.

1. Add 400 g of item 13 to the manufacturing vessel and heat to 90°C to 95°C.
2. Add item 2 while mixing at slow speed.
3. After addition of item 2, mix for 30 minutes at high speed and a temperature of 90°C to 95°C.
4. Cool down to 30°C to 35°C while mixing at low speed.
5. Add items 3 and 4 to the manufacturing vessel while mixing and mix until dissolved.
6. Add items 6 and 7 to the manufacturing vessel while mixing and mix until dissolved.
7. Add item 5 to the manufacturing vessel while mixing and mix until dissolved.
8. Mix items 9 and 10 with items 8 and 11 in a separate container by using stirrer.
9. Mix for 10 minutes and add to the manufacturing vessel while mixing.
10. Add 8 g of cold purified water (25–30°C) to a separate container and dissolve item 12 by using stirrer.
11. Mix for 10 minutes and add to the manufacturing vessel while mixing.
12. Start flushing the syrup with nitrogen gas pressure at 20 to 40 psi.
13. Add 10 g of cold purified water (cooled and flushed with N_2 gas) in a separate container with lid.
14. Pass nitrogen gas at 20 to 40 psi pressure for 15 minutes.
15. Dissolve item 1 in nitrogen-flushed, cold purified water (25–30°C) by using stirrer.
16. Mix for 10 minutes and add to the manufacturing vessel while mixing. Do not produce vortex.
17. Bring volume up to 1 L with nitrogen-flushed purified water.
18. Continue flushing nitrogen gas at 20 to 40 psi pressure for 30 minutes while mixing at slow speed.
19. Check and record the pH (limit: 4.5–5.5). If required, adjust pH with 10% citric acid or 10% sodium citrate solution.
20. Filter the syrup at 1.5 bar.
21. Recirculate approximately 20 to 30 mL syrup.
22. Transfer the filtered syrup to the storage vessel.
23. Flush with nitrogen gas and seal the tank.

Promethazine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Promethazine HCl	10.50
41.95	2	Lactose monohydrate	41.95
20.00	3	Maize starch	20.00
0.05	4	Sodium metabisulfite (sodium disulfite)	0.05
2.00	5	Povidone (PVP K-30)	2.00
5.00	6	Maize starch (dried)	5.00
0.50	7	Magnesium stearate	0.50
–	8	Alcohol (ethanol, 95%)	6.07
–	9	Purified water	8.67

Manufacturing Directions

Avoid overmixing of lubricants; otherwise, hardness will be reduced.

1. Mix items 8 and 9 in a stainless steel container.
2. Dissolve items 4 and 5 by slow stirring with stirrer until mixture becomes clear.
3. Sift items 1, 2, and 3 through a stainless steel 500-μm sieve in sifter.
4. Load into mixer and mix for 5 minutes at low speed.
5. Add binding solution at a rate of 5 to 7 g/min to the dry powders, while mixing at low speed.
6. After addition is complete, scrape sides and blades.
7. Mix further for 2 minutes using a mixer and chopper at low speed.
8. Scrape sides and blades.
9. Check for the end point of granulation, which is the point where the granulation consists of few or no lumps.
10. If required, add purified water.
11. Dry the wet granules with the air circulation heater to expel alcohol for 2 hours.
12. Then dry at 55°C for 14 hours.
13. After 4 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying.
14. Check the LOD (limit: 1.0–1.5%).
15. If required, dry further at 55°C for 2 hours.
16. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed.
17. Collect in stainless steel drums.
18. Load granules into the blender.
19. Sift item 6 material through a 500-μm sieve using a sifter and add it into blender.
20. Mix for 3 minutes.
21. Sift item 7 through a 500-μm sieve and add 1 to 2 g of granules from above.
22. Mix in polyethylene bag for 1 minute.
23. Add to blender.
24. Mix for 30 seconds.
25. Compress 0.80 g.
26. Coat using one of the HPMC coatings in the appendix.

Promethazine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
25.00	1	Promethazine HCl	26.00
103.75	2	Lactose monohydrate	103.75
50.00	3	Maize starch	52.50
1.50	4	Sodium metabisulfite (sodium disulfite)	1.50
5.00	5	Povidone (PVP K-30)	5.00
12.50	6	Maize starch (dried)	12.50
1.25	7	Magnesium stearate	1.25
–	8	Alcohol (ethanol, 95%)	15.00
–	9	Purified water	21.67

Manufacturing Directions

Avoid overmixing of lubricants; otherwise, hardness will be reduced.

1. Mix items 8 and 9 in a stainless steel container.
2. Dissolve items 4 and 5 by slow stirring with stirrer until mixture becomes clear.
3. Sift items 1, 2, and 3 through a stainless steel 500-μm sieve in sifter.
4. Load into mixer and mix for 5 minutes at low speed.
5. Add binding solution at a rate of 5 to 7 g/min to the dry powders, while mixing at low speed.
6. After addition is complete, scrape sides and blades.
7. Mix further for 2 minutes using a mixer and chopper at low speed.
8. Scrape sides and blades.
9. Check for the end point of granulation, which is the point where the granulation consists of few or no lumps.
10. If required, add purified water.
11. Dry the wet granules with the air circulation heater to expel alcohol for 2 hours.
12. Then dry at 55°C for 14 hours.
13. After 4 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying.
14. Check the LOD (limit: 1.0–1.5%).
15. If required, dry further at 55°C for 2 hours.
16. Grind the dried granules through a 1.25-mm sieve using a granulator at medium speed.
17. Collect in stainless steel drums.
18. Load granules into the blender.
19. Sift item 6 material through a 500-μm sieve using a sifter and add it into blender.
20. Mix for 3 minutes.
21. Sift item 7 through a 500-μm sieve and add 1 to 2 g of granules from above.
22. Mix in polyethylene bag for 1 minute.
23. Add to blender.
24. Mix for 30 seconds.
25. Compress 0.80 g.
26. Coat using one of the HPMC coatings in the appendix.

Pseudoephedrine Hydrochloride Fast-Disintegrating Tablets

1. To the vortex of a rapidly stirred vessel containing 345 g of deionized water is added 30 g of croscarmellose sodium.
2. This slurry is mixed for 10 minutes.
3. Concurrently, 300 g of pseudoephedrine hydrochloride and 300 g of microcrystalline cellulose (Avicel PH-101) are placed in the bowl of a mixer.
4. This mixture is stirred for 10 minutes.
5. At the conclusion of the mixing time, the slurry is added slowly to the contents of the mixing bowl, forming a granulation, which is then placed in trays and dried in a 65°C oven for 3 hours.
6. The dried granulation is passed through a U.S. standard 16-mesh screen (1190 μm).
7. The dried granulation is then placed in a twin shell blender and to it are added 300 g of Avicel AC-815 (85% microcrystalline cellulose coprocessed with 15% of a calcium, sodium alginate complex) and 300 g of microcrystalline cellulose (Avicel PH-102).
8. This is thoroughly blended for 10 minutes, after which 10.05 g of magnesium stearate is added and mixed for an additional 5 minutes.
9. Prior to being added to the blender, the magnesium stearate had been passed through a U.S. standard 30-mesh screen.
10. The resulting blend is compressed into tablets using 6.35-mm (0.25-in) round standard concave tooling to give average weight of 0.1299 g and an average thickness of 4.864 mm (0.1915 in).
11. The hardness of these tablets averaged 1.38 kp.
12. Friability is measured at 0.077% after 4 minutes.
13. The average disintegration time is 15 seconds in 10 mL of deionized water, forming a suspension with minimal shaking.

Pseudoephedrine Hydrochloride Capsules

Bill of Materials			
Scale (mg/capsule)	Item	Material Name	Qty/1000 Capsules (g)
24.00	1	Pseudoephedrine hydrochloride	24.00
15.00	2	Hyroxyethylcellulose, NF	15.00
60.00	3	Anhydrous lactose	60.00
1.00	4	Magnesium stearate	1.00

Manufacturing Directions

1. Blend all the ingredients in a twin-shell blender for 10 minutes.
2. Fill No. 0 capsules with fill weight of 500 mg using a tamping force of 200 N.

Pseudoephedrine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
6.00	1	Pseudoephedrine HCl (3% excess)	6.18
600.00	2	Sucrose	600.00
100.00	3	Glycerin (glycerol)	100.00
100.00	4	Sorbitol (70% solution)	100.00
15.00	5	Propylene glycol	15.00
1.00	6	Methyl paraben	1.00
0.30	7	Propyl paraben	0.30
0.50	8	Saccharin sodium	0.50
0.02	9	Dye (if needed)	0.02
0.05	10	Menthol	0.05
0.13	11	Citric acid	0.13
1.15	12	Sodium citrate	1.15
QS	13	Purified water	QS to 1 L

Manufacturing Directions

1. Add 390 g of purified water to the manufacturing vessel and heat to 90°C to 95°C.
2. Add items 6 and 7 while mixing to dissolve at high speed.
3. Add item 2 while mixing at slow speed at a temperature of 90°C to 95°C.
4. Mix for 1 hour at high speed.
5. Cool down to 50°C while mixing at slow speed.
6. Dissolve items 8 and 12 in 10 g of item 13 and add to the manufacturing vessel while mixing at high speed.
7. Dissolve item 11 in 10 g of purified water and add to the manufacturing vessel while mixing at high speed.
8. Load items 4 and 3 into the manufacturing vessel using a transfer pump while mixing at high speed.
9. Mix for 5 minutes.
10. Cool down to 30°C while mixing at slow speed.
11. Add 20 g of item 13 (30°C) in a separate container and dissolve item 1 by using stirrer.
12. Mix for 10 minutes and add to the manufacturing vessel while mixing at high speed.
13. Add 6 g of item 13 in a separate container and dissolve item 9 manually.
14. Add color to the manufacturing vessel while mixing at high speed.
15. Dissolve item 10 in item 5.
16. Add this flavor mixture to the manufacturing vessel while mixing at high speed.
17. Bring the volume up to 1 L with item 13 and finally mix for 15 to 20 minutes at high speed.
18. Check and record the pH (limit: 5.5–6.5 at 25°C).
19. If required, adjust pH with 20% citric acid or 20% sodium citrate solution.
20. Filter the syrup at 1.5 bar.
21. Recirculate approximately 100 to 150 mL syrup.

Pseudoephedrine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
60.00	1	Pseudoephedrine HCl[a]	63.00
120.20	2	Lactose monohydrate	120.20
25.00	3	Maize starch	25.00
1.00	4	Povidone (PVP K-30)	1.00
4.00	5	Povidone (PVP K-30)	4.00
1.80	6	Magnesium stearate	1.80
–	7	Alcohol (ethanol, 95%)	29.00

[a]Pseudoephedrine HCl 3 mg/tablet can be added in excess to compensate for moisture and handling loss.

Manufacturing Directions

Avoid overmixing of lubricants; otherwise, hardness is reduced.

1. Dissolve item 5 in item 7 while mixing at slow speed using a stirrer.
2. Sift items 1 to 4 through a 500-μm sieve.
3. Load into mixer and mix for 5 minutes at low speed.
4. Add binding solution to the dry powders while mixing at low speed for 2 minutes.
5. After addition is complete, mix further for 1 minute using mixer and chopper at low speed.
6. Scrape sides and blade.
7. Check for the end point of granulation, which is when the granulation consists of wet granules with few or no lumps.
8. If required, add ethanol 95% to achieve desired granules.
9. Record extra quantity of ethanol 95% used.
10. Dry the wet mass at 55°C for 7 hours.
11. After 4 hours of drying, scrape the semidried granules to break the lumps to promote uniform drying.
12. Check the moisture content (limit: 1.5–2.5%).
13. Sift the dried granules through a 1.25-mm sieve using a granulator at medium speed.
14. Collect in stainless steel drums.
15. Load granules into the drum blender.
16. Sift item 6 through a stainless steel 250-μm sieve in sifter.
17. Add 8 to 12 g granules in mixer to sieved item 6.
18. Mix manually for 1 minute.
19. Add to drum blender and blend for 1 minute.
20. Compress 215 mg in 8-mm round punches.

Pseudoephedrine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
60.00	1	(+) Pseudoephedrine hydrochloride	60.00
95.00	2	Dicalcium phosphate (Di-Tab)	95.00
5.00	3	Kollidon 30	5.00
–	4	Water	QS
20.00	5	PEG-6000 (powder)	20.00
2.00	6	Aerosil 200	2.00

Manufacturing Directions

1. Granulate dicalcium phosphate with solution of items 3 and 4, dry, pass through a 0.8-mm sieve, and mix with item 1.
2. Add items 5 and 6 and press with low compression force.
3. Compress 192 mg using 8-mm biplanar punches.

Pseudoephedrine Hydrochloride, Carbinoxamine Maleate Oral Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
500.00	1	Sucrose	500.00
300.00	2	Glucose liquid	300.00
150.00	3	Glycerin (96%)	150.00
30.00	4	D-Pseudoephedrine hydrochloride	30.00
1.00	5	Carbinoxamine maleate	1.00
4.00	6	Saccharin sodium (powder)	4.00
2.50	7	Sodium benzoate (powder)	2.50
1.25	8	Flavor	1.25
0.03	9	Dye	0.03
0.03	10	Dye	0.03
QS	11	Hydrochloric acid reagent-grade bottles	QS
QS	12	HyFlo filter aid	1.32
QS	13	Purified water	455.00
QS	14	Sodium hydroxide for pH adjustment	QS

Manufacturing Directions

1. Charge 315 mL of deionized water into a suitable tank.
2. Begin heating water to 60°C to 70°C while adding sucrose with stirring.
3. Stir until sugar is dissolved.
4. Remove heat.
5. Add glucose liquid and 125 g of glycerin in this step.
6. Add and dissolve D-pseudoephedrine HCl, carbinoxamine maleate, saccharin sodium, and sodium benzoate with mixing.
7. Cool solution to 30°C to 35°C.
8. Mix flavor with 25 g of glycerin.
9. (*Note*: Temperature of syrup must not be higher than 35°C.) Dissolve dyes, if used, in 5 mL of deionized water and add to syrup with mixing.
10. Adjust to pH 4.25 (range: 4.0–4.5), if necessary, with hydrochloric acid or sodium hydroxide.
11. QS to 1 L with deionized water and mix well.
12. Allow product to stand overnight to let entrapped air escape.
13. Readjust volume to 1 L with deionized water.
14. Add and mix 1.320 g of HyFlo filter aid to the product.
15. Circulate through a press.
16. Filter into tank for filling.

Psoriasis Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
40.00	1	Lanolin alcohol	40.00
50.00	2	White petroleum jelly	50.00
120.00	3	Paraffin wax 140F	120.00
300.00	4	Mineral oil (70 cS)	300.00
20.00	5	Coal tar	20.00
2.50	6	Allantoin	2.50
QS	7	Deionized water	QS to 1 kg
QS	8	Preservative	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Slowly add water phase in increments to the oil phase.
3. Allow each addition time to be fully incorporated.
4. Stir to cool.
5. Fill just above melting point.
6. Further homogenization may improve stability prior to filling.

Psoriasis Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
160.00	1	Stearic acid	16.00
60.00	2	Oleyl alcohol	6.00
20.00	3	Lanolin	2.00
20.00	4	Coal tar	2.00
6.00	5	Triethanolamine (99%)	0.60
2.50	6	Allantoin	0.25
QS	7	Deionized water	QS to 1 kg
–	8	Preservative	QS

Manufacturing Directions

1. Heat water and oil phases separately to 80°C.
2. Add water phase to oil phase while stirring.
3. Stir to cool.
4. Pass through homogenizer.
5. Fill at 40°C.

Psyllium and Dioctyl Sodium Sulfosuccinate Powder

Manufacturing Directions

1. Psyllium husk, 5.1 g; dioctyl sodium sulfosuccinate, 240 mg.
2. The psyllium husk is milled to a small particle size: NMT 4% on 100 mesh and between 25% and 50% through 200 mesh.
3. These psyllium particles are then agglomerated with maltodextrin and citric acid is sprayed on.
4. Dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, can be substituted for the dioctyl sodium sulfosuccinate, or two or three of these can be combined.
5. Methyl cellulose, polycarbophil, calcium polycarbophil, bran, malt soup extract, karaya, guar gum, or mixtures of these can be substituted for the psyllium.
6. The amounts of psyllium and/or dioctyl sulfosuccinate can be varied within the ranges specified herein.

Psyllium and Docusate Sodium Tablets

Formulation

Psyllium, 71.0%; ethyl cellulose, 4.8%; isopropyl alcohol, QS; microcrystalline cellulose, 16.7%; PVP cross-linked, 1.9%; carnauba wax, 2.3%; docusate sodium, 3.3%.

Manufacturing Directions

1. Soak ethyl cellulose in isopropyl alcohol overnight.
2. Granulate psyllium with isopropyl/ethyl cellulose mixture in mixer.
3. Dry at 49°C for 3 hours.
4. Mill through 12-mesh screen.
5. Mix in a mixer the following: psyllium, microcrystalline cellulose and carnauba wax.
6. Compress the tablet per granulation specifications using a tableting press.
7. Coat the core tablets.

Methyl cellulose, polycarbophil, calcium polycarbophil, bran, malt soup extract, karaya, guar gum, or mixtures of these can be substituted for the psyllium. The amounts of psyllium and/or dioctyl sulfosuccinate can be varied. Dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, can be substituted for the dioctyl sodium sulfosuccinate, or two or three of these can be combined.

Psyllium and Docusate Sodium Wafer

Formulation

Ascorbic acid, 0.15%; natural and artificial flavors, 1.54%; corn oil, 14.80%; cornstarch, 1.97%; fructose crystalline, 6.82%; lecithin oil, 0.99%; molasses granular light, 0.39%; oat hull fiber, 6.42%; psyllium husk, 13.32%; sodium bicarbonate, 0.20%; sucrose white granulated, 17.40%; table oats, 8.89%; water purified USP, QS; wheat flour, 19.21%; docusate sodium, 0.63%; sorbitan tristearin, 0.20%.

Manufacturing Directions

1. In an appropriate mixer, add corn oil and lecithin and mix for 1 minute using low speed.
2. *Note*: Preheat (microwave) lecithin, if necessary.
3. Add psyllium, docusate (which has been coated with the sorbitan tristearin) and mix for 1 minute using low speed.
4. Into a separate bowl, add part of the sucrose, fructose, molasses, and half of the water.
5. Mix for 1 minute using low speed.
6. Add psyllium/oil/lecithin premix and oat fiber.
7. Mix for 1 minute. Add rest of water, soda, flavors, ascorbic acid, and starch.
8. Mix for 1 minute at low speed.
9. Add flour to the mixer and mix for 1 minute at low speed.
10. Roll dough into sheets approximately 0.1 in thick.
11. Cut dough into rectangles of approximately 2.5 in × 1.6 in.
12. Place bars on baking trays and bake at 375°C for 10 to 12 minutes.
13. Ethyl cellulose, polycarbophil, calcium polycarbophil, bran, malt soup extract, karaya, guar gum, or mixtures of these can be substituted for the psyllium. The amounts of psyllium and/or dioctyl sulfosuccinate can be varied within the ranges specified herein. Dioctyl calcium sulfosuccinate, dioctyl potassium sulfosuccinate, can be substituted for the dioctyl sodium sulfosuccinate, or two or three of these can be combined.

Psyllium Husk Granules

1. Raw, unmilled psyllium seed husk (2 g) is stirred with 0.2 N sodium hydroxide (400 mL) containing sodium

borohydride (400 mg) in a nitrogen atmosphere at ambient temperature for 90 minutes.
2. The pH of the solution is from 10 to 11.
3. The solution is passed through a pasteurizer at a temperature of 100°C for a period of 50 seconds.
4. Once pasteurized, the mixture is centrifuged for 20 minutes at 23,500 g.
5. The supernatant is decanted from an insoluble fraction that settles out in the centrifuge bottle.
6. The insoluble fraction is mixed with fresh sodium hydroxide/sodium borohydride solution (100 mL) and recentrifuged for 15 minutes to increase yield of the soluble fraction.
7. The pH of the supernatant is adjusted to 5.5 by the addition of acetic acid at ambient temperature with stirring, forming a gel.
8. The gel is desiccated with isopropanol added with high shear mixing.
9. The isopropanol solution is then decanted from the gel.
10. The solids content of the gel is 30%.
11. The gel material is passed through an extruder and extruded into individual particles with an average particle size of 500 μm.
12. The extruded particles enter a fluidized bed dryer fitted with a cyclonic airflow screen, such as a Conidur screen.
13. The air temperature is maintained at 80°C.
14. The gel temperature remains below 70°C throughout the drying process.
15. The particles are dried to a powder, with 90% of the water being removed.
16. The yield of the gel-forming polysaccharide is 85%.
17. The final compositions comprise the following components by weight: gel-forming, 50.0%; polysaccharide sorbitol neosorb P20, 48.16%; magnesium stearate, 0.5%; flavorant, 0.4%; colorant, 0.14%; citric acid, 0.8%.
18. The granules can be coated using the coating formulation: isopropanol, 94.5%; Eudragit RD100, 5%; polyethylene glycol, 0.5%.
19. The coated gel-forming polysaccharide particles are dried and combined with the excipients as described above.

Psyllium Husk Tablets

Manufacturing Directions

1. Raw, unmilled psyllium seed husk (2 g) is stirred with 0.2 N sodium hydroxide (400 mL) containing sodium borohydride (400 mg) in a nitrogen atmosphere at ambient temperature for 90 minutes.
2. The pH of the solution is from 10 to 11.
3. The solution is passed through a pasteurizer at a temperature of 100°C for a period of 50 seconds.
4. Once pasteurized, the mixture is centrifuged for 20 minutes at 23,500 g.
5. The supernatant is decanted from an insoluble fraction that settles out in the centrifuge bottle.
6. The insoluble fraction is mixed with fresh sodium hydroxide/sodium borohydride solution (100 mL) and recentrifuged for 15 minutes to increase yield of the soluble fraction.
7. The pH of the supernatant is adjusted to 5.5 by the addition of acetic acid at ambient temperature with stirring, forming a gel.
8. The gel is desiccated with isopropanol added with high shear mixing.
9. The isopropanol solution is then decanted from the gel.
10. The solids content of the gel is 30%.
11. The gel material is passed through an extruder and extruded into individual particles with an average particle size of 500 μm.
12. The extruded particles enter a fluidized bed dryer fitted with a cyclonic airflow screen, such as a Conidur screen.
13. The air temperature is maintained at 80°C.
14. The gel temperature remains below 70°C throughout the drying process.
15. The particles are dried to a powder with 90% of the water being removed.
16. The yield of the gel-forming polysaccharide is 85%.
17. Chewable tablets, total weight 2.5 g, are manufactured while step 8 is dry blended with sorbitol for 10 minutes, each component having an average particle size of approximately 500 μm.
18. The premix, if desired, is added and the mixture is blended for an additional 10 minutes.
19. Magnesium stearate is added and the composition is blended for another 5 minutes.
20. The mixture is directly compressed into tablets using pressure from 2000 to 4000 psi.
21. The final compositions comprise the following components by weight: gel-forming, 50.0%; polysaccharide sorbitol neosorb P20, 48.16%; magnesium stearate, 0.5%; flavorant, 0.4%; colorant, 0.14%; citric acid, 0.8%.
22. Optionally, the coating can be applied directly to a chewable tablet containing the gel-forming polysaccharide.
23. Additionally, it may be desired to include a flavorant within the coating composition: ethanol, 94%; polyethylene glycol, 5%; flavorant, 1%.

PVP–Iodine Mouthwash

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	PVP–iodine	100.00
5.00	2	Saccharin sodium	5.00
2.00	3	Menthol	2.00
0.50	4	Aniseed oil	0.50
0.50	5	Eucalyptus oil	0.50
160.00	6	PEG-400	160.00
300.00	7	Ethanol	300.00
QS	8	Purified water	QS to 1 kg

Manufacturing Directions

1. Dissolve PVP–iodine powder and saccharin sodium in 440 g of water to obtain a clear solution.
2. In a separate container, add alcohol.
3. Mix and dissolve aniseed oil, eucalyptus oil, menthol, and PEG-400 to obtain a clear solution.
4. QS with water.
5. Add solution from step above and mix with stirring.
6. Package in HDPE plastic bottles.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
40.00	1	Pyridoxine hydrochloride	40.00
150.00	2	Lactose monohydrate	150.00
150.00	3	Avicel PH101	150.00
15.00	4	Kollidon VA 64	15.00
10.00	5	Kollidon CL	10.00
1.00	6	Magnesium stearate	1.00
1.00	7	Aerosil 200	1.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with high compression force.
2. Compress 361 mg in 12-mm biplanar punches; items marked with asterisk can be deleted when the compression weight becomes 340 mg.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
40.00	1	Pyridoxine hydrochloride	40.00
300.00	2	Cornstarch	300.00
15.00	3	Kollidon 30	15.00
80.00	4	Water + isopropanol	80.00
1.00	5	Magnesium stearate	1.00
2.00	6	Aerosil 200	2.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 3 and 4, dry, pass through an 0.8-mm sieve, mix with items 5 and 6, and press with high compression force.
2. Compress 354 mg in 12-mm biplanar punches.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Pyridoxine hydrochloride	100.00
200.00	2	Tabletlose®	200.00
10.00	3	Kollidon VA 64	10.00
3.00	4	Kollidon CL	3.00
1.00	5	Magnesium stearate	1.00
1.00	6	Aerosil 200	1.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium compression force.
2. Compress 363 mg in 12-mm biplanar punches.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Pyridoxine hydrochloride	100.00
150.00	2	Lactose monohydrate	150.00
83.00	3	Avicel PH101	83.00
10.00	4	Kollidon VA 64	10.00
3.00	5	Kollidon CL	3.00
1.00	6	Magnesium stearate	1.00
1.00	7	Aerosil 200	1.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium compression force.
2. Compress 360 mg in 12 mm-biplanar punches.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Pyridoxine hydrochloride	250.00
100.00	2	Avicel PH101	100.00
12.00	3	Kollidon VA 64	12.00
5.00	4	Magnesium stearate	5.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high compression force.
2. Compress 361 mg in 12-mm biplanar punches.

Pyridoxine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
300.00	1	Pyridoxine hydrochloride	300.00
100.00	2	Lactose monohydrate D 20	100.00
20.00	3	Kollidon 30	20.00
QS	4	Isopropanol + water (1+1)	60.00
10.00	5	Kollidon CL	10.00
2.00	6	Aerosil 200	2.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 3 to 6, dry, and sieve through a 0.8-mm screen.
2. Press with medium compression force.
3. Compress 440 mg using 12-mm biplanar punches.

Ranitidine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Quantity/1000 Tablets (g)
	1	Ranitidine HCl USP (Orchev Pharma)	167.39
	2	Microcrystalline Cellulose NF (Avicel PH-102, FMC)	78.28
	3	Pregelatinized Starch NF (Starch 1500, Colorcon)	62.00
	4	Fumed silica NF (Aerosil 200, Degussa AG)	1.55
	5	Magnesium Stearate NF (Peter Greven)	0.78

Manufacturing Directions

1. All materials, with the exception of magnesium stearate, are blended for 10 minutes in a blender.
2. Magnesium stearate is added and blended for an additional 2 minutes.
3. Tablets compressed at 310 mg.

Ranitidine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
75.00	1	Ranitidine; use Ranitidine HCl[a]	85.00
95.00	2	Microcrystalline cellulose (Avicel PH102)	95.00
7.00	3	Croscarmellose sodium (Ac-Di-Sol)	7.00
6.60	4	Microcrystalline cellulose (Avicel PH102)	6.60
1.40	5	Magnesium stearate	1.40

[a]Ranitidine HCl (1.5%) is added to compensate LOD and process loss.

Manufacturing Directions

1. Process the product in an area where the RH is 40% to 45% and temperature does not exceed 25°C.
2. Store the bulk tablets in polyethylene-lined stainless steel containers at a controlled RH of 45% to 50% and temperature not exceeding 25°C.
3. Pass items 1, 2, and 3 through a sifter using a 900-μm sieve.
4. Load into a blender and mix for 3 minutes.
5. Manually mix items 4 and 5 in a polyethylene bag for 1 minute.
6. Pass through a sifter using a 500-μm sieve.
7. Collect in a polyethylene bag.
8. Add to blender and blend for 1 minute.
9. Check temperature and humidity before start of slugging (at a temperature not exceeding 25°C and a RH of 40–45%).
10. Slug 240 g of mixed powder in a rotary tableting machine.
11. Grind the slugs in a granulator using a 3-mm sieve followed by a 1-mm sieve.
12. Compress 195 mg using oblong biconvex punches.
13. Check temperature and humidity before start of compression (limit: temperature not exceeding 25°C and RH of 40–45%).
14. Coat using a hydroalcoholic HPMC coating.

Ranitidine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
75.00	1	Ranitidine; use Ranitidine HCl	88.88
65.00	2	Microcrystalline cellulose, NF	65.00
1.12	3	Magnesium stearate, NF	1.12

Manufacturing Directions

1. Pass Ranitidine and microcrystalline cellulose through a 595-μm screen and transfer to a suitable mixer.
2. Mix for 10 minutes.
3. Screen the magnesium stearate through a 400-μm screen and add to the blender.
4. Blend for 2 minutes.
5. Compress using slightly convex round punches at hardness 8 ppi and disintegration time NMT 15 minutes in water.
6. Coat using a methocel-ethocel coating solution (see appendix).

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
3.00	1	Riboflavin	3.00
195.00	2	Ludipress	195.00
2.00	3	Magnesium stearate	2.00
1.00	4	Aerosil 200	1.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with very low compression force (4 kN).
2. Compress 202 mg using 8-mm biplanar punches.
3. This is a very low active ingredient formulation (3 mg).
4. If content uniformity is a problem, prepare a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Riboflavin	10.00
75.00	2	Lactose monohydrate	75.00
20.00	3	Cornstarch	20.00
15.00	4	Avicel PH101	15.00
5.00	5	Kollidon 30	5.00
25.00	6	Water	25.00
0.80	7	Aerosil 200	0.80
2.50	8	Talc	2.50
1.70	9	Hydrogenated castor oil	1.70

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with solution of items 5 and 6, dry, pass through a 0.8-mm sieve, mix with items 7 to 9, and press with low compressive force.
2. Compress 134 mg in 8-mm biplanar punches.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
75.00	1	Riboflavin	75.00
375.00	2	Sorbitol (crystalline)	375.00
23.00	3	Kollidon VA 64	23.00
4.00	4	Magnesium stearate	4.00
12.00	5	Aerosil 200	12.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with low compressive force.
2. Compress 493 mg using 12-mm biplanar punches.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Riboflavin	100.00
250.00	2	Sorbitol (crystalline)	250.00
19.00	3	Kollidon VA 64	19.00
5.00	4	Magnesium stearate	5.00
10.00	5	Aerosil 200	10.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium compression force.
2. Compress 384 mg using 12-mm biplanar punches.

Riboflavin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
150.00	1	Riboflavin, with excess	156.00
150.00	2	Ludipress	150.00
4.00	3	Magnesium stearate	4.00
2.00	4	Aerosil 200	2.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress 308 mg using 8-mm biplanar punches.

Rubefacient Analgesic Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Polawax, NF	150.00
100.00	2	Methyl salicylate	100.00
50.00	3	Menthol	50.00
100.00	4	Mineral oil (70 cS)	100.00
QS	5	Deionized water	QS to 1 kg
QS	6	Preservative, color	QS

Manufacturing Directions

1. Heat oil and water phases separately to 70°C.
2. Add water phase to oil phase while stirring. Stir to cool.
3. Fill at 30°C.

Saccharin Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
15.00	1	Saccharin sodium	15.00
10.00	2	Tartaric acid	10.00
14.00	3	Sodium bicarbonate	14.00
2.00	4	Kollidon VA 64	2.00
2.00	5	PEG-6000 (powder)	2.00

Manufacturing Directions

1. Dry saccharin sodium and tartaric acid for 1 hour at 100°C.
2. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force.
3. Compress 42 mg in 5-mm biplanar punches.

Saccharin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
37.50	1	Sodium cyclamate	37.50
17.00	2	Mannitol	17.00
6.35	3	Soda ash (light-milled powder, 58% Na_2O)	6.35
3.75	4	Saccharin sodium (dihydrated powder)	3.75
1.40	5	Povidone (PVP K-29–32)	1.40
8.00	6	Purified water	8.00
11.00	7	Tartaric acid	11.00
0.80	8	Soda ash (light-milled powder, 58% Na_2O)	0.80
1.00	9	Anhydrous sodium citrate	1.00
1.00	10	Sodium benzoate	1.00
0.20	11	PEG-8000	0.20

Manufacturing Directions

1. This product is hygroscopic and should be processed in a low-humidity area not exceeding 50% RH at 24°C.
2. Maintain at 35 to 40% RH at 24°C if possible.
3. If necessary, pass sodium cyclamate and mannitol (if used) through a Fitz mill or similar type using a 420-μm or similar screen, then charge into a suitable mixer.
4. To this mixture, add soda ash (item 3) and blend for 30 minutes or until uniform.
5. Dissolve povidone in 4 mL of warm purified water.
6. Dissolve saccharin sodium in 3 mL of warm purified water.
7. Add solutions from previous steps together plus sufficient purified water.

8. Mass with blended powders.
9. Blend for 1 hour or until uniform.
10. Pass the wet mass through a 4.76-mm or similar screen in an oscillating granulator and spread onto trays.
11. Oven dry at 50°C to 55°C for 16 to 24 hours using a full oven load of trays (LOD NMT 0.9%).
12. Pass dried granulation through a 1.19-mm or similar screen in an oscillating granulator or through a 1.68-mm or similar screen using a comminuting mill (knives forward, slow speed).
13. Lubricants must meet LOD/moisture content before proceeding.
14. If lubricants fail, dry them at 80°C for 8 hours.
15. Use 60°C for tartaric acid.
16. Mill lubricants (except tartaric acid and granulated lactose, if used) through a 600-µm or similar screen in a comminuting mill (hammers forward, medium speed).
17. Load dried granulation, coated tartaric acid, lactose (if used), and milled lubricants into a suitable mixer and blend for 30 to 40 minutes.
18. Compress 80 mg per tablet in 7/32-in punches.

Saccharin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
15.00	1	Saccharin sodium	15.00
31.00	2	Ludipress	31.00
2.00	3	Kollidon CL	2.00
0.30	4	Magnesium stearate	0.30
2.00	5	PEG-6000 (powder)	2.00
2.00	6	Lutrol F 68	2.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium compression force.
2. Compress 51 mg (or 50 mg, if items 5 and 6 are omitted) using 5-mm punches.

Salicylic Acid Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Glyceryl stearate and PEG-75 stearate	150.00
5.00	2	Stearic acid	5.00
80.00	3	Mineral oil	80.00
665.00	4	Deionized water	665.00
100.00	5	Salicylic acid	100.00

Manufacturing Directions

1. Mix and heat items 1 to 4 to 75°C.
2. Allow to cool with gentle stirring.
3. At 30°C, add item 5. Homogenize if necessary.

Scopolamine Tablets

Manufacturing Directions

1. To 0.2 g of scopolamine hydrobromide, 29.4 g of calcium hydrogen phosphate (anhydrous) is added in small portions and well mixed in a mortar to form a triturate.
2. The triturate (29.6 g) is well mixed with fumaric acid (60 g) and calcium stearate (0.4 g) in a polyethylene bag to form a mixed powder A.
3. 25 g of fumaric acid, 9.8 g of potassium hydrogen phosphate (anhydrous), and 0.2 g of calcium stearate are intimately mixed in a polyethylene bag to make a mixed powder B.
4. To 0.1 g of scopolamine hydrobromide, 10 g of crystalline cellulose is added in small portions and mixed well in a mortar to make a triturate.
5. This triturate (10.1 g) is mixed well with 24.7 g of lactose and 0.2 g of calcium stearate in a polyethylene bag to make a mixed powder C.
6. Multilayer tableting is performed on a single-punch machine equipped with a die (8 mm) and flat-faced punches: First, 90 mg of the mixed powder A is placed in the die and precompressed lightly; 35 mg of the mixed powder B is placed on the first fill and lightly precompressed; thereafter, 35 mg of the mixed powder C is placed on the second fill and compressed with a total pressure of approximately 1.2 tonnes.

Selegiline Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
5.00	1	Selegiline	5.00
94.00	2	Ludipress	94.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components intensively, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress 99 mg in 6-mm biplanar punches.

Selenium Sulfide Shampoo with Conditioner

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
10.00	1	Selenium sulfide	10.00
2.00	2	Methyl paraben	2.00
10.00	3	Magnesium aluminum silicate type IIA	10.00
20.00	4	Titanium	20.00
0.17	5	Dye	0.17
230.00	6	Sodium alkyl ether sulfate/sulfonate	230.00
30.00	7	Cocamide DEA surfactant	30.00
40.00	8	Cocoamphocarboxyglycinate	40.00
10.00	9	Hydrolyzed protein	10.00
4.00	10	Perfume	4.00
QS	11	Citric acid	QS
QS	12	Sodium chloride	QS
QS	13	Deionized purified water	QS to 1 L

Note: Item 11 is used for pH adjustment, if necessary, and item 12 is used for viscosity adjustment, if necessary.

Manufacturing Directions

1. Selenium sulfide is toxic. Handle carefully and use approved respiratory protection.
2. Add 7 mL of purified water to an appropriate mill containing full-charge alumina grinding cylinder media.
3. Add selenium sulfide.
4. Seal the mill and agitate for approximately 10 minutes to wet down the powdered material.
5. Recycle for approximately 5 minutes with the pump set at 1040 mmHg.
6. Stop agitation.
7. If necessary, add purified water (25–30°C) to nearly cover the grinding media.
8. Seal the mill and recirculate the slurry for 1 to 2 hours with the pump set to obtain the required particle size specifications for the selenium sulfide.
9. Load 250 mL of purified water into a suitable jacketed mixing tank and heat to 60°C to 70°C.
10. With good stirring, add and dissolve methyl paraben.
11. Slowly add and disperse the magnesium aluminum silicate. Continue mixing until fairly smooth.
12. Stop mixing and allow to hydrate for 1 hour.
13. Add and disperse titanium dioxide.
14. Mix for 30 minutes.
15. With good stirring, add the selenium sulfide slurry and rinse the mill with purified water.
16. Mix for 30 minutes.
17. Stop mixing and add sodium lauryl ether sulfate/sulfonate.
18. Mix slowly for 5 minutes.
19. Add cocamide DEA.
20. Mix slowly for approximately 3 minutes.
21. Add cocoamphocarboxyglycinate.
22. Mix slowly for 30 minutes.
23. Separately dissolve hydrolyzed protein (hydrogel) in 4 mL of purified water and mix until uniform.
24. Add solution from above to the tank and mix until uniform.
25. Add perfume and mix for 1 minute.
26. Dissolve dye in 2 mL of warm purified water (50–60°C) and add to mixing tank.
27. Mix until uniform.
28. Check and record pH. Adjust to 4.5 to 5.0, if necessary, using citric acid. Record amount of citric acid used and the adjusted pH.
29. Add purified water QS to 980 mL and mix for 30 minutes.
30. Check and record viscosity.
31. If necessary, adjust by adding sodium chloride.
32. Deaerate by slow stirring under vacuum or use of a suitable deaerator.
33. Mix for 1 hour.

Sertraline L-Lactate Osmotic Tablets

Manufacturing Directions

1. Tablet cores comprising sertraline L-lactate (13.8 wt%), L-aspartic acid (11 wt%), calcium acetate (5 wt%), microcrystalline cellulose (29.5 wt%), and fructose (38.2 wt%) are blended, then run through a roller compactor and milled.
2. This milled material is then blended with 2.5 wt% magnesium stearate to form the final blended material that is used to make tablets having a total weight of 470 mg on a conventional tablet press.
3. Semipermeable asymmetric membrane coatings comprised 10 wt% cellulose acetate 398-10, 2.5 wt% polyethylene glycol 3350, 15 wt% water, and 72.5 wt% acetone.
4. The coating solution is spray-coated onto the tablets at a rate of 20 g/min until a 10 wt% coating level on the tablets had been achieved.

Serratio Peptidase Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Serratio peptidase	10.00
228.00	2	Ludipress	228.00
2.00	3	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix intensively, and press with low compressive force (6 kN).
2. Compress 238 mg in 8-mm biplanar punches.

Silicone Protective Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Polawax, NF	150.00
40.00	2	Oleyl alcohol	40.00
50.00	3	PEG-75 lanolin	50.00
150.00	4	Mineral oil (70 cS)	150.00
50.00–100.00	5	Dimethicone	50.00–100.00
QS	6	Deionized water	QS to 1 kg

Manufacturing Directions

1. Heat water and oil phase separately to 60°C to 65°C.
2. Add the water phase to the oil phase while stirring.
3. Stir to cool to 30°C.
4. May add perfume or color as desired.

Silymarin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
35.50	1	Silymarin	35.50
410.50	2	Ludipress	410.50
4.50	3	Magnesium stearate	4.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force (approximately 10 kN).
2. Compress 458 mg in 12-mm biplanar punches.

Simethicone and Magnesium Carbonate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
16.00	1	Dextrose monohydrate, USP 25.0 kg	16.00
0.16	2	Yellow No.10 D&C dye lake 250 g	0.16
0.06	3	Blue No.1 FD&C dye lake 90.0 g	0.06
80.00	4	Simethicone pwd GS (30%) 417 kg	266.40
64.00	5	Magnesium carbonate 100 kg	64.00
128.00	6	Microcrystalline cellulose 200 kg	128.00
175.68	7	Dextrates 275 kg	175.68
5.00	8	Stearic acid 8.00 kg	5.00

Manufacturing Directions

1. The simethicone mix is processed by preblending magnesium carbonate and simethicone powder GS 30% in a V-blender.
2. This preblended mix is then dry granulated and placed in a V-shell blender.
3. Dextrates and microcrystalline cellulose are then added to the preblended mix in the V-shell blender and the preblended mix, dextrates, and microcrystalline cellulose are blended for approximately 10 minutes.
4. Blue No. 1 FD&C dye lake, yellow No. 10 D&C dye lake, and dextrose are combined in a drum roller, dry granulated, and then placed in the V-shell blender with the preblended mix, dextrates, and microcrystalline cellulose.
5. An additional amount of dextrose is dry granulated in the same granulator that the colorants are granulated in, for the purpose of rinsing the granulator after the dry granulation of the colorants.
6. This amount of dextrose is also added to the V-shell blender.
7. An amount of stearic acid is then passed through a 30-mesh screen and added to the V-shell blender.
8. The preblended mix, dextrates, microcrystalline cellulose, colorants, dextrose, and stearic acid are then blended in the V-shell blender for 3 minutes.
9. A sample of the V-shell blender mix is then measured to test blend uniformity.
10. Upon meeting satisfactory blend uniformity requirements, the simethicone layer mix is transferred to tote bins and then compressed into 650-mg tablets.

Simethicone Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
70.00	1	Simethicone dry powder 25%	280.00
158.00	2	Sucrose, powder	158.00
7.00	3	Kollidon 90 F	7.00
3.50	4	Kollidon 90 F	3.50
QS	5	Isopropanol	QS
2.80	6	Aerosil 200	2.80

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with solution of items 4 and 5, dry, pass through a 0.8-mm sieve, add item 6, mix thoroughly, and press with high compressive force.
2. Compress 442 mg in 12-mm biplanar punches.

Simethicone Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
80.00	1	Simethicone (Wacker silicon oil, S184)	80.00
400.00	2	Sorbitol (crystalline)	400.00
20.00	3	Aerosil 200	20.00
390.00	4	Ludipress	390.00
2.00	5	Menthol (powder)	2.00
8.00	6	Magnesium stearate	8.00

Manufacturing Directions

1. Mix items 2 and 3 with item 1, pass through a 0.8-mm sieve, add mixture of items 4 to 6, mix thoroughly, pass again through a 0.8-mm sieve, and press with high compressive force.
2. Compress 870 mg using 16-mm biplanar punches.

Simethicone Instant Granules (60 mg and 120 mg)

Formulation

I. Simethicone (Abil® 200, Goldschmidt), 10.0 g; Cremophor RH 40 [1], 5.0 g.
II. Kollidon VA 64, 3.0 g; ethanol, 40.0 g.
III. Sorbitol, crystalline, 50.0 g; fructose, 50.0 g; Kollidon CL-M [1], 50.0 g; orange flavor (Dragoco), 0.5 g.

Manufacturing Directions

Introduce solution II into the mixture I.

1. Granulate the powder mixture III with the well-stirred mixture I/II, dry, and pass through a 1-mm sieve.
2. Fill 1 or 2 g in sachets.

Simethicone Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
70.00	1	Simethicone	70.00
71.40	2	Microcrystalline cellulose	71.40
71.40	3	Magnesium hydroxide	71.40
265.00	4	Mannitol	265.00
100.00	5	Lactose	100.00
395.10	6	Granular sugar	395.10
0.70	7	Menthol	0.70
10.00	8	Fumed silica	10.00
5.00	9	Fumed silica	5.00
10.00	10	Magnesium stearate	10.00

Manufacturing Directions

1. Blend item 2 and item 3 in a V-blender for 10 minutes.
2. Transfer to planetary mixer.
3. Slowly add weighted amount of item 1 to the mix and mix slowly using a "B" flat beater blade. After thorough mixing, pass through a No. 20-mesh screen.
4. Add the balance of the ingredients, mix, and compress.

Sodium Fluoride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
0.50	1	Sodium fluoride	0.55
56.25	2	Sorbitol, crystalline	56.25
56.25	3	Dicalcium phosphate	56.25
2.20	4	Kollidon VA 64	2.20
0.50	5	Magnesium stearate	0.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with high compressive force.
2. Compress 116 mg using 6-mm biplanar punches.
3. If the content uniformity is not sufficient, a premix of sodium fluoride and sorbitol or dicalcium phosphate should be prepared separately before mixing with the rest of the excipients.

Sodium Fluoride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
1.30	1	Sodium fluoride	1.30
76.70	2	Ludipress	76.70
0.40	3	Magnesium stearate	0.40

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress 78 mg using 5-mm biplanar punches.
3. If the content uniformity does not meet the requirements, prepare a premix of the active ingredient with a small part of the Ludipress or with lactose monohydrate before mixing with the other components of the formulation.

Spirulina Extract Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Spirulina extract (powder)	250.00
245.00	2	Ludipress	245.00
25.00	3	PEG-6000 (powder)	25.00
5.00	4	Aerosil 200	5.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium compressive force.
2. Compress 495 mg using 12-mm biplanar punches.

Sucralfate and Sodium Alginate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Sucralfate	500.00
20.00	2	Sodium alginate	20.00
70.00	3	Cornstarch	70.00
20.00	4	Kollidon 30	20.00
–	5	Ethanol (95%)	80.00 mL
30.00	6	Kollidon CL	30.00
3.00	7	Magnesium stearate	3.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with solution of items 4 and 5, pass through a sieve, mix the dry granules with items 6 and 7, and press with low compressive force.
2. Compress 660 mg using 12-mm biplanar punches.

Sulfur Antiseptic Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
15.00	1	Sulfur (precipitated)	15.00
85.00	2	Kaolin	85.00
QS	3	White petroleum jelly	QS to 1 kg
60.00	4	Isopropyl palmitate	60.00
13.00	5	Camphor	13.00
13.00	6	Methyl salicylate	13.00
20.00	7	Lanolin	20.00
50.00	8	Tribehenin	50.00
50.00	9	Ozokerite	50.00
35.00	10	Sorbitan oleate	35.00
15.00	11	Deionized water	15.00
4.00	12	Salicylic acid	4.00
24.00	13	Glycerin	24.00
QS	14	Preservative	QS

Manufacturing Directions

1. Heat oils, except sulfur and lanolin, to 70°C.
2. Disperse sulfur and kaolin in the oil phase.
3. Heat water, glycerin, and salicylic acid gently.
4. Add to oil phase while stirring.
5. Stir to 55°C.
6. Mill to disperse sulfur.

Tannin–Crospovidone Complex Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
55.00	1	Tannic acid	55.00
230.00	2	Water	230.00
230.00	3	Kollidon CL	230.00
33.00	4	Avicel PH101	33.00
2.60	5	Talc	2.60
0.30	6	Aerosil 200	0.30
0.30	7	Calcium arachinate	0.30

Manufacturing Directions

1. Prepare solution of items 1 and 2, suspend item 3, and filter the formed insoluble tannin–crospovidone complex.
2. Wash with water until the water is clear, pass the solids through a 0.8-mm sieve, and dry.
3. Add items 4 to 7 and press with low compressive force.
4. Compress 323 mg using 12-mm biplanar punches.

Tetrahydrozoline Eye Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
17.20	1	Acid boric	17.20
1.50	2	Hydroxypropylmethylcellulose 2910 (4000 cps)	1.50
0.40	3	Borax	0.40
1.00	4	Disodium edetate	1.00
0.50	5	Tetrahydrozoline hydrochloride	0.50
0.00063 mL	6	Benzalkonium chloride solution (17%)	0.63 mL
QS	7	Water purified	QS to 1 L

Manufacturing Directions

1. Use thoroughly cleaned and rinsed steam-jacketed, glass-lined, or stainless steel tank (No. 304 or better), equipped with a speed-controlled agitator. The tank should have a cover. Foaming occurs because of the benzalkonium chloride, which concentrates in the foam. Processing and filling systems should be designed to minimize foaming and allow rapid dissipation of foaming.
2. Charge 80% of the final volume of water into the mixing tank.
3. If using methyl cellulose, heat deionized water to 90°C.
4. While agitating, add and disperse methyl cellulose by slowly sprinkling it on the surface of solution. Mix to avoid excessive foaming.
5. Allow 15 minutes for hydration of the methyl cellulose before discontinuing heating and allow to cool to 40°C.
6. While agitating, add and dissolve disodium edetate, benzalkonium chloride, boric acid, sodium borate, and tetrahydrozoline. Continue cooling to 25°C.
7. Discontinue agitation and QS to 1 L with deionized water. (*Note*: Methylcellulose solutions filter at a slow rate.) Use inline Pall and Sartorius cartridges and recirculate solution until clear. Transfer to holding or sterilization.
8. Use either heat sterilization or sterile filtration.
9. Heat sterilization: Sterilize at 112°C to 115°C for 60 minutes, cool solution to 25°C to 30°C, and aseptically add the sterile tetrahydrozoline solution. Mix well.
10. Set up a previously sterilized filter and transfer line with 10-μm stainless steel FulFlo filter or equivalent.
11. Aseptically fill sterile solution into sterilized containers and apply sterile closure components.
12. Sterile filtration: Use Pall cartridge with Sartorius cartridge. Prepare and steam-sterilize the recommended filter units.
13. Aseptically fill the sterilize solution into each sterilized container and apply sterile closure.

Thiamine and Caffeine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Thiamine hydrochloride	500.00
100.00	2	Caffeine	100.00
30.00	3	Cornstarch	30.00
20.00	4	Kollidon VA 64	20.00
15.00	5	Kollidon VA 64	15.00
QS	6	Ethanol (96%)	QS
35.00	7	PEG-6000 (powder)	35.00

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with solution of item 5 and 6, dry, sieve, mix with item 7, and press with low compressive force.
2. Compress 698 mg using 16-mm biplanar punches.

Thiamine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Thiamine HCl with excess	110.00
43.50	2	Lactose monohydrate	43.50
4.00	3	Crospovidone (Kollidon CL)	4.00
5.50	4	Povidone (PVP K-90)	5.50
5.50	5	Crospovidone (Kollidon CL)	5.50
32.00	6	Microcrystalline cellulose (Avicel^{TM} PH112)	32.00
5.60	7	Talc (fine powder)	5.60
3.70	8	Glyceryl behenate (glyceryl monostearate)	3.70
0.20	9	Magnesium stearate	0.20
–	10	Alcohol (ethanol, 95%)	50.67

Manufacturing Directions

1. Sift items 1, 2, and 3 through a stainless steel 630-μm sieve.
2. Load into mixer.
3. Mix for 5 minutes at high speed.
4. Dissolve item 4 in item 10 under slow stirring by stirrer.
5. Add the binding solution while mixing at high speed over a period of 2 minutes. Scrape sides and blades.
6. Mix and chop at high speed for 2 minutes.
7. Check the end point of granulation.
8. If required, add additional item 10 to obtain the end point. (The end point of granulation occurs when the wet mass consists of few or no lumps.) Dry wet granules in oven at 55°C for 8 hours.
9. After 2 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying.
10. Check the LOD (limit: 1.0–1.5%).
11. If required, dry at 55°C for an additional hour.
12. Check the LOD again.
13. Grind the dried granules through a 1.25-mm sieve with the granulator set at medium speed.
14. Collect in stainless steel drums.
15. Load the granules into blender.
16. Sift items 5 and 6 through a 500-μm sieve and add to blender.
17. Mix for 2 minutes (do not overmix).
18. Sift items 8 and 9 through a 500-μm sieve.
19. Add 1.33 g to 2.67 g of granules.
20. Mix in a polyethylene bag for 1 minute.
21. Add to blender.
22. Blend for 1 minute.
23. Check temperature and humidity before start of compression (limit: temperature should not exceed 25°C; RH, 45–50%).
24. Compress using 8-mm round, beveled, concave punches.

Thiamine Hydrochloride Tablets (Sugar-Coated)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Thiamine hydrochloride monohydrate (with excess)	110.00
110.00	2	Lactose	110.00
5.00	3	Luviskol® K-98	5.00
1.00	4	Magnesium stearate	1.00
40.00	5	Ethyl alcohol (denatured)	40.00
251.44	6	Sugar (crystalline)	251.44
1.40	7	Sugar powder	1.40
14.50	8	Maize starch	14.50
14.81	9	Talcum	14.81
21.00	10	Copolymer lacquer	21.00
0.40	11	Paraffin (solid)	0.40
0.16	12	Gum acacia	0.16
0.228	13	Ethyl alcohol (denatured)	0.228
0.01	14	Paraffin (liquid)	0.01
QS	15	Purified water	QS

Manufacturing Directions

1. In a suitable stainless steel vessel, add denatured ethyl alcohol and Luviskol. Mix until homogeneous mixture is obtained. Set aside.
2. Pass lactose through a No. 2-mesh sieve, add thiamine, and mix for 10 minutes in an appropriate mixer.
3. Slowly add to this mixture the solution made earlier and stir until slightly lumpy mass is obtained.
4. If required, add ethyl alcohol to the mixture.
5. Pass the wet mass through an oscillating granulator with a 7-mm perforated sieve.
6. Spread the granules over paper-lined trays and dry at 40°C for 5 hours in a drying oven.
7. The RH of the granules should be 15% to 25%.
8. Pass magnesium stearate and talcum through a 1-mm hand sieve.
9. Compress on a rotary tablet machine at approximately 4 to 5 tonnes of pressure. The weight of each tablet should be approximately 230 mg.
10. In a suitable container, add purified water and acacia gum. Pass the resulting solution through a 0.8-mm sieve.
11. Charge the compressed tablets into a coating pan and apply the copolymer lacquer in ten portions. After the last application, apply neutral spray (crystalline sugar in demineralized water).
12. Dry the insulated tablets in a drying oven overnight at 45°C (minimum 14 hours). The tablet weight should be approximately 236 mg each.
13. In an electric-jacketed kettle, put demineralized water, crystalline sugar, maize starch, and talcum. Mix by stirring until homogeneous.
14. Pass through a sieve of mesh size 0.8 mm (pH: 6–8, density: 1.335–1.356).
15. Coat the tablets to 400 mg weight using the coating solution and a sugar-coating pan. Set pans at slow speed, open air inlets, and set air inflow at 80°C and maximum contact temperature set at 42°C.
16. Roll tablets to reach this temperature.
17. Turn pan to fast speed, close the inlet air flap, and make first application of syrup.
18. When all tablets are wet and distribution of syrup is uniform, open the air inlet flap and allow 80°C air to blow (tablet temperature falls 1–2°C for a short time and then slowly rises to 42°C).
19. The next application of the syrup cycle begins.
20. Coat the tablets with color solution as described above to 495-mg weight.
21. Set the air inflow temperature at 25°C and reduce the size of application with the falling temperature, whereby tablets are evenly and lightly moistened after each application. The temperature drops from 42°C to 32°C.
22. Turn the coating pans slowly during the drying phase. For the last three applications, keep the pan lids closed, as well as the air intake and outflow during this phase.
23. Drying only with outlet air may be extended for the last three applications up to 10 to 15 minutes.
24. Immediately after the last application of syrup has dried slightly, begin the polishing step.
25. The polishing paste is prepared in a suitable boiling vessel by adding stock gum solution, crystalline sugar, and demineralized water.
26. Boil until temperature reaches 106°C with stirring.
27. In a steam kettle, melt solid and liquid paraffin and pour melted paraffins into the mixture of gum. Make up the weight with demineralized water.
28. Polishing paste ready for use contains 0.75 kg of paste and 0.113 kg of ethyl alcohol.
29. Tablet temperature is 28°C to 32°C.
30. Shut off the inlet flaps and outlet flaps, set the pans at the fast speed, and add polishing paste (approximately 0.3% of tablet weight).
31. Close the pans with inner lids and allow them to rotate at fast speed for 90 seconds for even distribution.
32. Remove the inner lid of the pan and set it on slow speed.
33. Open the outlet air for 3 minutes, blow the inlet air at 40°C for 6 to 8 minutes until a good sheen appears.
34. Set the pans on automatic system for overnight, with intermission time of 5 minutes off and 10 seconds on.

Thiamine, Pyridoxine, and Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
110.00	1	Thiamine mononitrate	110.00
210.00	2	Pyridoxine hydrochloride	210.00
76.82	3	Lactose monohydrate	76.82
10.00	4	Crospovidone (Kollidon CL)	10.00
18.50	5	Povidone (PVP K-90)	18.50
0.30	6	Cyanocobalamin	0.30
85.00	7	Microcrystalline cellulose (Avicel PH102)	85.00
14.00	8	Crospovidone (Kollidon CL)	14.00
10.00	9	Glyceryl behenate (glyceryl monostearate)	10.00
0.49	10	Magnesium stearate	0.49
15.00	11	Talc (fine powder)	15.00
–	12	Alcohol (ethanol, 95%)	88.90

Manufacturing Directions

1. Dissolve item 5 in item 12 by using a stirrer to make a clear solution.
2. Dissolve item 6 carefully in the solution.
3. Sift items 1 to 4 through a 630-μm sieve.
4. Load the material into a mixer.
5. Mix and chop at high speed for 5 minutes.
6. Add binding solution from previous step to the dry powder in the mixer while mixing and chopping at high speed for 2 minutes.
7. Check for satisfactory wet mass.
8. Add additional item 12, if required, to obtain a satisfactory wet mass.
9. Do not allow big lumps.
10. Record the additional quantity of ethanol 95%.
11. Spread the granules onto stainless steel trays to a thickness of one-fourth of the tray thickness and load the trays onto a trolley.
12. Load the trolley into an oven.
13. Keep the door open, switch on the oven with air circulation, heater turned off for 2 hours.
14. Dry the granules at 55°C for 12 hours.
15. Check the LOD of dried granules (limit: NMT 0.7%).
16. Grind the dried granules through a 1.25-mm sieve using a granulator.
17. Collect in a stainless steel drum.
18. Load into the blender.
19. Sift items 7, 8, and 9 through a 500-μm sieve.
20. Collect in stainless steel container.
21. Load the sieved powder into the blender.
22. Blend for 3 minutes.
23. Sift items 11 and 10 through a 500-μm sieve.
24. Collect in a polyethylene bag.
25. Add 4.44 g to 6.67 g of granules from earlier step and mix manually for 1 minute.
26. Add this mixture to the blender and mix for 1 minute.
27. Compress the granules using a rotary tableting machine.
28. Compress 550 mg using round, biconvex punches at 9 to 16 kp.
29. Coat tablets using an HPMC coating (see appendix).

Thiamine, Pyridoxine, and Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Thiamine mononitrate (powder)	115.00
50.00	2	Pyridoxine hydrochloride	50.00
9.75	3	Anhydrous citric acid (powder)	9.75
20.10	4	Monohydrate lactose (powder, regular)	20.10
1.67	5	Saccharin sodium	1.67
0.24	6	Dye	0.24
0.009	7	Dye	0.009
0.02	8	Dye	0.02
2.00	9	Cornstarch	2.00
QS	10	Purified water	18.00 mL
50.00 μg	11	Vitamin B_{12}; use vitamin B_{12} oral powder cobalamin conc.	62.50
12.50	12	Monohydrate lactose (powder, regular)	12.50
1.50	13	Oil orange terpeneless	1.50
3.50	14	Magnesium stearate	3.50
1.50	15	Talc (powder)	1.50
17.70	16	Cornstarch, light coral red 6 LA	17.70

Manufacturing Directions

1. Pass thiamine mononitrate, pyridoxine HCl, citric acid, lactose (item 4), and saccharin sodium through a No. 30-mesh (595-μm or similar) screen.
2. Charge into mixer and dry mix.
3. Dissolve the dyes in purified water.
4. Add the starch (item 9) to this dye solution with stirring.
5. Heat and continue stirring until a thick paste is formed.
6. Cool to room temperature before using.
7. (*Note*: Use 7.5 g of colored starch paste for the vitamins B_1 and B_6 blend and 12.5 g of colored starch paste for the vitamin B_{12} blend.) Add 7.5 g of colored starch paste to powder blend and mix until mass is formed.
8. Pass through a No. 6-mesh (3.36-mm or similar) screen and air dry for 3 to 4 hours.
9. Screen vitamin B_{12} oral powder and lactose (item 12) through a No. 30-mesh (595-μm or similar) screen.
10. Charge into mixer and dry mix.
11. Add 12.5 g colored starch paste to powder blend and mix until mass is formed.
12. Pass through No. 6-mesh (3.36-mm or similar) screen and air dry for 3 to 4 hours.
13. Dry granulations from the two steps separately at 49°C overnight or until LOD is less than 1%.
14. Mill the two dried granulations through a No. 16-mesh (1.2-mm or similar) screen (knives forward, medium speed) and combine.
15. Sift a small quantity of granulation from the steps above over a No. 30-mesh (595-μm or similar) screen and add the orange oil to the fines.
16. Add magnesium stearate, talc powder, and light coral red starch to mixture and pass through a No. 30-mesh (595-μm or similar) screen.
17. Charge base granulation and lubricants into a blender and blend thoroughly.
18. Compress using 11/32-in concave punches.

Thiamine, Pyridoxine, and Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Thiamine hydrochloride	100.00
10.00	2	Pyridoxine hydrochloride	10.00
0.10	3	Cyanocobalamin (gelatin-coated, 1%)	10.00
277.00	4	Ludipress	277.00
3.00	5	Magnesium stearate	3.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with low compressive force.
2. Compress 394 mg in 12-mm biplanar punches.

Thiamine, Pyridoxine, and Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Thiamine mononitrate	100.00
200.00	2	Pyridoxine hydrochloride	200.00
0.10	3	Cyanocobalamin (gelatin-coated, 1%)	10.00
250.00	4	Ludipress	250.00
45.00	5	PEG-6000 (powder)	45.00
5.00	6	Aerosil 200	5.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress 609 mg using 12-mm biplanar punches.

Thiamine, Pyridoxine, and Cyanocobalamin Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
250.00	1	Thiamine mononitrate	250.00
250.00	2	Pyridoxine hydrochloride	250.00
75.00	3	Lactose monohydrate	75.00
25.00	4	Kollidon 30	25.00
QS	5	Isopropanol	QS
1.00	6	Cyanocobalamin (gelatin-coated, 1%)	100.00
25.00	7	Kollidon CL	25.00
2.00	8	Magnesium stearate	2.00
2.00	9	Talc	5.00

Manufacturing Directions

1. Granulate mixture items 1 to 3 with solution of items 4 and 5, dry, pass through a 0.8-mm sieve, mix with items 6 to 9, and press with low compressive force, applying a vibrating hopper.
2. Compress 730 mg using 12-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50.00	1	Thiamine hydrochloride or thiamine mononitrate	50.00
293.00	2	Ludipress	293.00
5.00	3	Magnesium stearate	5.00
2.00	4	Aerosil 200	2.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with medium compressive force.
2. Compress 357 mg, if hydrochloride salt is used, or 347 mg, if mononitrate salt is used, with 12-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50.00	1	Thiamine hydrochloride or thiamine mononitrate	50.00
150.00	2	Lactose monohydrate	150.00
150.00	3	Avicel PH101	150.00
15.00	4	Kollidon CL	15.00
2.00	5	Aerosil 200	2.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with high compressive force.
2. Compress 344 mg, if hydrochloride salt is used, or 373 mg, if mononitrate salt is used, with 12-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Thiamine hydrochloride or thiamine mononitrate	110.00 (or 100.00)
190.00	2	Ludipress	190.00
100.00	3	Lactose monohydrate	100.00
100.00	4	Avicel™ PH101	100.00
9.00	5	Kollidon CL	9.00
3.00	6	Aerosil 200	3.00
2.00	7	Magnesium stearate	2.00

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with medium compressive force.
2. Compress 302 mg, if hydrochloride salt is used, or 320 mg, if mononitrate salt is used, with 8-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Thiamine hydrochloride	100.00
200.00	2	Lactose monohydrate	200.00
10.00	3	Kollidon 30	10.00
60.00	4	Isopropanol	60.00
10.00	5	Kollidon CL	10.00
2.00	6	Magnesium stearate	2.00
1.00	7	Aerosil 200	1.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 3 and 4, dry, and sieve through a 0.8-mm screen, mix with items 5 to 7, and press to tablets.
2. Compress 330 mg using 8-mm biplanar punches.

Thiamine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
300.00	1	Thiamine mononitrate	300.00
100.00	2	Dicalcium phosphate (Di-Tab)	100.00
15.00	3	Kollidon 30	15.00
QS	4	Isopropanol	~50.00
10.00	5	Kollidon CL	10.00
4.00	6	Magnesium stearate	4.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 3 and 4, dry, and sieve through a 0.8-mm screen.
2. Mix with items 5 and 6 and compress 430 mg into tablets using 12-mm biplanar punches.

Tolnaftate and Undecylenate Foot Care Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
150.00	1	Glyceryl stearate and PEG-75 stearate	150.00
20.00	2	Hydrogenated palm/Palm kernel oil PEG-6 esters	20.00
60.00	3	Mineral oil	60.00
0.50	4	Sorbic acid	0.50
0.50	5	Sodium methyl paraben	0.50
509.00	6	Deionized water	509.00
50.00	7	Undecylenic acid	50.00
200.00	8	Zinc undecylenate	200.00
10.00	9	Tolnaftate	10.00

Manufacturing Directions

1. Mix and heat items 1 to 7 to 75°C.
2. Allow to cool with gentle stirring.
3. At 30°C, add items 8 and 9.
4. Homogenize, if necessary.

Tolnaftate Foot Care Microemulsion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
155.00	1	Ethoxydiglycol	155.00
130.00	2	Polyglyceryl-6-dioleate	130.00
450.00	3	PEG-8 caprylic/capric glycerides	450.00
10.00	4	Tolnaftate	10.00
100.00	5	Deionized water	100.00
50.00	6	Apricot kernel oil PEG-6 esters	50.00
100.00	7	Caprylic/Capric triglycerides	100.00
5.00	8	Chlorocresol	5.00

Manufacturing Directions

1. Mix items 1 to 3 and dissolve item 4 in this mixture.
2. Add items 5 to 8 and mix until uniform.

Tolu Balsam Cough Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
11.03	1	Tolu balsam tincture	11.03
2.50	2	Magnesium carbonate (powder)	2.50
15.00	3	Sucrose (granulated sugar)	15.00
QS	4	Purified water	90.00 mL
0.77	5	Methyl paraben	0.77
0.086	6	Propyl paraben	0.86
514.36	7	Sucrose (granulated sugar)	514.36
129.24	8	Glycerin (96%)	129.24
2.00	9	Dextromethorphan hydrobromide	2.00
1.00	10	Ephedrine HCl (powder)	1.00
8.00	11	Ammonium chloride	8.00
0.40	12	Chlorpheniramine maleate	0.40
1.00	13	Phenylephrine HCl	1.00
333.32	14	Glucose (liquid)	333.32
0.35	15	Flavor	0.35
0.15	16	Flavor	0.15
1.01	17	Ipecac (fluid extract)	1.01
8.57	18	Alcohol (ethanol, 190 proof)	8.57
0.037	19	Dye	0.037
QS	20	Hydrochloric acid (reagent-grade bottles)	QS
QS	21	Purified water	212.00 mL

Manufacturing Directions

1. Charge tolu balsam tincture into mixing tank and add magnesium carbonate.
2. Mix well to suspend.
3. Add sugar (item 3) with mixing.
4. Add 90 mL purified water (item 4) and mix thoroughly.
5. Allow to set for 1 hour.
6. Mix periodically while circulating through Shriver filter (or equivalent).
7. Solution must be brilliantly clear.
8. Filter and save for next part.
9. Charge 210.5 mL purified water (item 21) into suitable tank.
10. Add and dissolve parabens with heat (90–95°C) and mixing.
11. Add and dissolve sugar (item 7) with mixing; heat if necessary.
12. Add glycerin, continue agitation, and cool to room temperature.
13. To cooled syrup, add filtrate from step above.
14. Add and dissolve the following ingredients with mixing: dextromethorphan hydrobromide, ephedrine HCl, ammonium chloride, chlorpheniramine maleate, and phenylephrine HCl.
15. Add glucose. Mix well.
16. Add and dissolve flavors and Ipecac fluid extract in 190-proof alcohol.
17. To the tank or in a separate container, add flavors and Ipecac extract to 10 mL of glucose liquid and mix.
18. Add this mixture to the main mixture.
19. Rinse the container with a further 5 mL of liquid glucose and add the rinsing to the mixture.
20. Add the remaining liquid glucose. Mix well.
21. Dissolve in 1.75 mL purified water and add.
22. Check pH (range: 4–5).
23. Use hydrochloric acid to adjust pH to 4 to 5, with 4.5 being optimum (approximately 0.3 mL HCl per liter of syrup).
24. QS to 1 L with purified water.
25. Filter until sparkling clear.
26. Add a suitable filter aid and mix until uniform.
27. Filter into tank for filling.

Triclosan and Zinc Foot Deodorant Powder

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
3.00	1	Triclosan (Irgasan® DP300)	3.00
2.00	2	Zinc undecylenate, USP	2.00
0.20	3	Menthol (crystals), USP	0.20
926.80	4	Talc (powder), USP	926.80
30.00	5	Magnesium stearate	30.00
30.00	6	Cornstarch, NF	30.00
8.00	7	Perfume	8.00

Manufacturing Directions

1. Pass the following ingredients through a 250-μm screen or similar: Irgasan DP300, zinc undecylenate, magnesium stearate, cornstarch, menthol, and approximately 10% of the total amount of talc.
2. Charge materials from first step into a suitable mixer.
3. Mix until uniform.
4. Discharge powder from second step into another suitable mixer.
5. Add and disperse perfume.
6. Mix until uniform.
7. Pass mixture from step above through a 250-μm screen or similar.
8. Charge mixture from step above into a V-mixer or similar and add balance of talc powder.
9. Mix for 30 minutes or until homogeneous.

Triclosan Foot Care Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
50.00	1	Glyceryl stearate (Gelol)	50.00
50.00	2	Propylene glycol stearate	50.00
100.00	3	Octyldodecyl myristate	100.00
50.00	4	Isostearyl isostearate	50.00
20.00	5	Dimethicone (100 cS)	20.00
651.00	6	Deionized water	651.00
50.00	7	Sucrose distearate	50.00
4.00	8	Phenoxyethanol, methyl paraben, ethyl paraben, and propyl paraben	4.00
20.00	9	Propyleneglycol	20.00
3.00	10	Triclosan	3.00
2.00	11	Fragrance	2.00

Manufacturing Directions

1. Heat items 1 to 5 and items 6 to 7 separately to 75°C. Mix the two parts with turbine mixing for 1 minute.
2. Cool with gentle stirring.
3. Add items 9 and 10 and then item 11 with mixing at 30°C to 35°C.

Triprolidine and Pseudoephedrine Hydrochloride Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.25	1	Triprolidine HCl (4.8% excess)	0.26
6.00	2	Pseudoephedrine HCl (3.0% excess)	6.18
600.00	3	Sucrose	600.00
100.00	4	Glycerin (glycerol)	100.00
100.00	5	Sorbitol (70% solution)	100.00
15.00	6	Propylene glycol	15.00
1.00	7	Methyl paraben	1.00
0.30	8	Propyl paraben	0.30
0.50	9	Saccharin sodium	0.50
0.04	10	Quinoline yellow	0.04
0.05	11	Menthol	0.05
0.25	12	Raspberry flavor	0.25
1.15	13	Sodium citrate	1.15
QS	14	Purified water	QS to 1 L

Manufacturing Directions

1. Add 400 g of purified water to the manufacturing vessel and heat to 90°C to 95°C.
2. Add items 7 and 8 while mixing to dissolve at high speed.
3. Add item 3 while mixing at slow speed (temperature: 90–95°C).
4. Mix for 1 hour at high speed.
5. Cool down to 50°C while mixing at slow speed.
6. Add items 9 and 13 to the manufacturing vessel while mixing at high speed.
7. Load items 4 and 5 into the manufacturing vessel using a transfer pump while mixing at high speed.
8. Add 20 g of cold purified water (30°C) in a separate container and dissolve items 1 and 2 by using stirrer.
9. Mix for 10 minutes and add to the manufacturing vessel while mixing at high speed.
10. Add 1 g of purified water in a separate container and manually dissolve item 10.
11. Add color to the manufacturing vessel while mixing at high speed.
12. Dissolve item 11 in item 12, then add item 6.
13. Add this flavor mixture to the manufacturing vessel while mixing at high speed.
14. Bring the volume up to 1 L with item 14 and finally mix for 15 to 20 minutes at high speed.
15. Check and record the pH (limit: 5.8–6.8 at 25°C).
16. If required, adjust pH with 20% citric acid or 20% sodium citrate solution.
17. Filter the syrup at 1.5 bar.
18. Recirculate approximately 20 to 30 mL syrup.

Triprolidine and Pseudoephedrine Hydrochloride Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
2.60	1	Triprolidine HCl (4% excess)	2.70
60.00	2	Pseudoephedrine HCl (5% excess)	63.00
122.40	3	Lactose monohydrate	122.40
25.50	4	Maize starch	28.00
1.00	5	Povidone (PVP K-30)	1.00
4.00	6	Povidone (PVP K-30)	4.00
–	7	Alcohol (ethanol, 95%)	28.00
1.50	8	Magnesium stearate	1.50

Manufacturing Directions

1. Dissolve item 6 in item 7 using a stirrer.
2. Avoid loss of ethanol by evaporation.
3. Pass items 1 to 5 through a 630-μm sieve using sifter.
4. Collect in a stainless steel drum.
5. Load the sieved powders into a mixer.
6. Mix and chop for 5 minutes at low speed.
7. Add PVP solution to the mixer at medium rate while mixing.

8. Start the chopper at low speed when half of the solution is added.
9. Mix and chop at low speed until the satisfactory mass is obtained.
10. Spread the wet granules onto the trays.
11. Keep the trolleys in the open air for approximately 1 hour.
12. Load the trolleys into the oven, and start the air circulation at room temperature for 2 hours.
13. Dry the granules at 55°C with air circulation for 5 hours.
14. Scoop the granules after 2 hours of drying. Move the upper trays down and the lower trays up for uniform drying.
15. Check the moisture content (limit: NMT 1.5%).
16. Pass the dried granules through a 1-mm sieve using a granulator.
17. Collect in a stainless steel drum and load into the blender.
18. Pass item 8 through a 250-μm sieve using a sifter.
19. Collect in a polyethylene bag.
20. Mix 2 g of granules with this mixture and add to the blender.
21. Mix for 1 minute.
22. Unload the lubricated granules in a stainless steel drum.
23. Compress 220 mg in 8.5-mm round, concave punches.

Trolamine Salicylate Cream

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/kg (g)
50.00	1	Glyceryl stearate	5.00
25.00	2	Cetyl alcohol	2.50
30.00	3	Cetyl phosphate and DEA cetyl phosphate	3.00
40.00	4	Stearyl stearoyl stearate	4.00
40.00	5	Cococaprylate/Caprate	4.00
40.00	6	Cetyl palmitate	4.00
5.00	7	Dimethicone	0.50
502.00	8	Deionized water	50.20
10.00	9	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	1.00
5.50	10	Magnesium aluminum silicate	0.55
2.50	11	Xanthan gum	0.25
100.00	12	Deionized water	10.00
100.00	13	Trolamine salicylate (TEA salicylate)	10.00
50.00	14	Propylene glycol	5.00

Manufacturing Directions

1. Heat items 8 and 9 to 85°C, and add items 10 and 11.
2. Mix until well dispersed.
3. Add items 1 to 7 and mix well at 80°C to 85°C.
4. Continue mixing. While cooling to 65°C, add items 12 to 14 and continue mixing and cooling to 35°C.
5. The pH should be 5.5 to 5.6.

Ultrasonic Adhesive Gel

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
5.00	1	Preservative (e.g., parabens)	5.00
754.00	2	Water	754.00
6.00	3	Carbopol 940 (Goodrich)	6.00
20.00	4	Sodium hydroxide solution 10%	20.00
15.00	5	Kollidon 30	15.00
200.00	6	Water	200.00

Manufacturing Directions

1. Prepare solution of item 1 in item 2 by heating to 70°C and add item 3 slowly to obtain a homogeneous suspension.
2. Add items 4 to 6.
3. A clear, colorless adhesive gel is obtained.
4. Addition of sodium chloride changes consistency.

Urea Peroxide Ear Drops

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
65.00	1	Urea peroxide (40% excess)	91.00
15.00	2	Sodium citrate (dihydrate, powder)	15.00
5.00	3	Polysorbate 20 (Tween 20)	5.00
2.50	4	Tartaric acid (12663)	2.50
QS	5	Anhydrous glycerin	QS
QS	6	Nitrogen	QS

Manufacturing Directions

1. Add 500 mL of glycerin into a suitable tank.
2. Start mixing at slow speed and heat the contents to 70°C to 75°C.
3. Flood tank with nitrogen, increase mixing speed, and slowly add sodium citrate.
4. Add tartaric acid.
5. Mix for at least 30 minutes or until dissolved.
6. Maintain the temperature at 70°C to 75°C.
7. When sodium citrate is completely dissolved, cool to 25°C to 30°C with constant mixing.
8. Prepare urea peroxide by breaking up lumps and screening to remove large particles.
9. Wear gloves.
10. Add an additional 250 to 300 mL of glycerin into tank.
11. Add urea peroxide slowly to prevent lumping, while mixing constantly.
12. Mix at high speed after addition.
13. Add Polysorbate 20 with constant mixing and QS to final volume with glycerin.
14. Mix for at least 30 minutes and until solution is clear.
15. Pass solution through an approximately No. 100-mesh (150-μm or similar) screen and collect in clean, dry carboys. (The filter support screen in a millipore holder may be used for filtering. The solution is too viscous to flow through a membrane or any cellulosic filter.)

Valeriana and Passiflora Extract Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
44.00	1	Valeriana extract, powder	44.00
33.00	2	Passiflora extract, powder (with excess)	36.00
120.00	3	Avicel PH101	120.00
11.00	4	Kollidon CL	11.00
3.60	5	Aerosil 200	3.60
7.30	6	Magnesium stearate	7.30

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with low compressive force.
2. Compress 231 mg using 9-mm biconvex punches.

Vitamin A and Vitamin D Infant Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
1500 IU	1	Vitamin A palmitate (1.7 MM IU/g) (50% excess)	1.323
400 IU	2	Vitamin D (40 MM IU/g) (Cholecalciferol) (25% excess)	0.012
10.00	3	Polysorbate 80 (Tween 80)	10.00
0.88	4	Vitamin E (oily; alpha-tocopheryl acetate)	0.88
0.50	5	Edetate disodium (sodium EDTA)	0.50
1.00	6	Ascorbic acid	1.00
0.10	7	Saccharin sodium	0.10
600.00	8	Glycerin (glycerol)	600.00
100.00	9	Sorbitol (70% solution)	100.00
50.00	10	Propylene glycol	50.00
1.00	11	Flavor	1.00
1.50	12	Flavor	1.50
QS	13	Dye	QS
QS	14	Dye	QS
–	15	Purified water	QS to 1 L

Manufacturing Directions

1. This product is a microemulsion and thermolabile preparation. The temperature of solution must not exceed 25°C at the time of processing. Store bulk at a temperature of 15°C to 20°C under nitrogen protection. Period of storage should not exceed 48 hours prior to filling in the bottle.
2. Collect 200 g of purified water in a melting vessel.
3. Heat to 90°C to 95°C for 10 minutes and then cool to 20°C to 25°C.
4. Bubble nitrogen gas into purified water for 20 minutes.
5. Load 100 g of purified water into the manufacturing vessel.
6. Bubble nitrogen gas during all stages of the processing.
7. Add items 5, 6, and 7 one by one to the manufacturing vessel while mixing.
8. Check that all materials are dissolved completely.
9. Add items 8 and 9 and 20 g of item 10 one by one to the manufacturing vessel while mixing at slow speed.
10. Mix for 5 minutes.
11. Avoid aeration.
12. Add item 3 in a stainless steel container.
13. Mix items 1, 2, and 4 one by one using a stirrer.
14. Mix for 1 hour at slow speed.
15. Avoid aeration.
16. Add the oil phase to the aqueous phase in the manufacturing vessel at a rate of 4 mL/min while mixing. Keep on bubbling nitrogen gas throughout the process.
17. Dissolve items 11 and 12 in 30 g of item 10 in a stainless steel container by slow stirring.
18. Add to manufacturing vessel while mixing.
19. Dissolve items 14 and 13 in 40 g of purified water (25–30°C) in a stainless steel container with slow stirring.
20. Add to manufacturing vessel while mixing.
21. Adjust the volume to 1 L with cooled purified water.
22. Check and record the volume and pH (limit: 2.5–4.8).
23. Filter the solution through a prefilter and 0.2-μm membrane filter into the receiving tank.
24. Bubble with nitrogen gas for 15 minutes.
25. Store the solution with a nitrogen blanket.

Vitamin A and Vitamin D_3 Drops

Bill of Materials			
Scale (mg/g)	Item	Material Name	Quantity/L (g)
30,000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	1.90
3000 IU	2	Vitamin D_3 (40 MM IU/g)	7.50 mg
12.00	3	Cremophor (RH, 40%)	12.00
0.30	4	BHT	0.30
10.00	5	Lutrol E 400	10.00
0.80	6	Paraben	0.80
0.20	7	Sorbic acid	0.20
QS	8	Water	QS to 1 L

Manufacturing Directions

1. Heat mixture of items 1 to 5 and solution of items 6 to 8 to approximately 65°C and add this slowly to the well-stirred mixture of items 1 to 5.
2. Clear or slightly opalescent yellow liquid is obtained.

Vitamin A and Vitamin D_3 Oral Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (mg)
1000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	60.00
100 IU	2	Vitamin D_3 (40 MM IU/g)	0.30
0.002	3	BHT	0.20
3.00	4	Cremophor EL or Cremophor (RH, 40%)	3.00 g
QS	5	Preservative	QS
QS	6	Flavor	QS
QS	7	Water	QS to 1 L

Manufacturing Directions

1. Heat mixture of items 1 to 4 to approximately 65°C, stir well, and slowly add the hot solution of item 5 (65°C).
2. Cool to room temperature and add item 6 to obtain a clear, yellow liquid.

Vitamin A and Vitamin D_3 Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
30,000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	19.00
10,000 IU	2	Vitamin D_3 (40 MM IU/g)	0.25
70.00 mg	3	Cremophor (RH, 40%)	7.00
QS	4	Sugar syrup (50%)	QS to 1 L

Manufacturing Directions

1. Heat mixture of items 1 to 3 to approximately 45°C, stir well, and slowly add item 4 to obtain a clear, yellow liquid (pH 6.2).

Vitamin A and Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
5000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	3.33
50.00	2	Vitamin E acetate	60.00
150.00	3	Cremophor (RH, 40%)	150.00
150.00	4	Ethanol (96%)	150.00
QS	5	Water	QS to 1 L

Manufacturing Directions

1. Heat mixture of items 1 to 3 to approximately 65°C, stir well, and slowly add the mixture of items 4 and 5.
2. Color is yellow. Clarity is clear (turbity units, 25 FTU).
3. It must be determined whether or not the ethanol concentration has a sufficient preservative efficiency.
4. The addition of BHT as an antioxidant is recommended.

Vitamin A and Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L
25,000 IU	1	Vitamin A palmitate (1.7 Mio IU/g)	1.50
50.00	2	Vitamin E acetate	5.00
210.00	3	Cremophor (RH, 40%)[a]	21.00
QS	4	Preservative	QS
QS	5	Water	71.50

[a]The quantity is reduced by 1 g if 1 g of D,L-alpha-tocopherol is also added in the formulation.

Manufacturing Directions

1. Mix the vitamins with Cremophor (and D,L-alpha-tocopherol, if used) at 60°C.
2. Add solution of preservatives (at 37°C) slowly, with stirring to produce clear, yellow, viscous liquids.

Vitamin A and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
33,000 IU	1	Vitamin A acetate (dry powder, 500,000 IU/g)	69.00
70.00	2	Vitamin E acetate (dry powder)	70.00
146.00	3	Mannitol (granulated) with 10% of Kollidon 30	146.00
17.00	4	Kollidon CL	17.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with high compressive force.
2. Compress 300 mg in 12-mm biplanar punches.

Vitamin A Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100,000 IU	1	Vitamin A acetate (dry powder, 325,000 IU/g)	350.00
350.00	2	Mannitol	350.00
25.00	3	Kollidon VA 64	25.00
5.00	4	Magnesium stearate	5.00
3.00	5	Aerosil 200	3.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with medium compressive force.
2. Compress 750 mg in 12-mm biplanar punches.

Vitamin A Concentrate (Water-Miscible)

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
100,000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	6.50
2.00	2	BHT	0.20
210.00	3	Cremophor (RH, 40%)	21.00
QS	4	Preservative	QS
QS	5	Water	QS to 1 L

Manufacturing Directions

1. Heat the mixture of items 1 to 3 to approximately 65°C. Stir well.
2. Add slowly the warm solution of items 4 and 5 (65°C) to obtain a clear, yellow liquid that is miscible with water.

Vitamin A Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/1000 Tablets (g)
50,000 IU	1	Vitamin A palmitate (1.7 Mio IU/g)	3.00
110.00	2	Cremophor (RH, 40%)	11.00
1.00	3	BHT	0.10
QS	4	Water	85.90

Manufacturing Directions

1. Heat the mixture of items 1 to 3 to approximately 65°C. Stir well.
2. Add slowly the hot water (65°C) to obtain a clear or slightly opalescent yellow solution of low viscosity.
3. Lutrol E 400 can be added at a level of 5% (compensated for by item 4).

Vitamin A Suppositories

Bill of Materials			
Scale (mg/supository)	Item	Material Name	Qty/1000 Suppositories (g)
150,000 IU	1	Vitamin A palmitate (1.7 MM IU/g)	88.23
1.00	2	BHT	10.00
400.00	3	Cremophor (RH, 40%)	400.00
800.00	4	Lutrol E 1500	800.00
500.00	5	Lutrol E 4000	505.00

Manufacturing Directions

1. Dissolve BHT in warm vitamin A.
2. Add Cremophor and mix with the molten Lutrol E grades.
3. Fill into molds of suppositories to obtain a weight of 2 g.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50,000 IU	1	Vitamin A acetate (dry powder, 500,000 IU/g)	110.00
100.00	2	Avicel PH102	100.00
10.00	3	Kollidon VA 64	10.00
5.00	4	Kollidon CL	5.00
1.00	5	Aerosil 200	1.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with low compressive force.
2. Compress 231 mg using 9-mm biconvex punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
5000	1	Vitamin A acetate (dry powder, 500,000 IU/g)	110.00
189.00	2	Ludipress	189.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress 306 mg in 8-mm punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50,000	1	Vitamin A acetate (dry powder, 500,000 IU/g)	120.00
120.00	2	Ludipress	120.00
10.00	3	Avicel PH101	10.00
1.00	4	Magnesium stearate	1.00
1.00	5	Aerosil 200	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress 277 mg in 8-mm punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50,000	1	Vitamin A acetate (dry powder, 500,000 IU/g)	110.00
154.00	2	Avicel PH101	154.00
10.00	3	Kollidon VA 64	10.00
4.00	4	Kollidon CL	4.00
1.00	5	Aerosil 200	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press with low compressive force.
2. Compress 250 mg in 8-mm punches.

Vitamin A Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
25,000 IU	1	Vitamin A acetate (dry powder, 500,000 IU/g)	55.00
572.00	2	Dicalcium phosphate (granulated) (Di-Tab) with 3% of Kollidon 30	572.00
28.00	3	Polyethylene glycol, powder	28.00
19.40	4	Kollidon CL	19.40
5.60	5	Aerosil 200	5.60

Manufacturing Directions

1. Granulate the dicalcium phosphate with Kollidon 30, dissolved in isopropanol or water, and pass through a 0.5- to 12-mm screen sieve using a vibrating hopper.
2. Mix the obtained dried granules with the other components, sieve, and press with high compressive force.
3. Compress 680 mg in biplanar punches.

Vitamin A, Vitamin B_6, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
40,000 IU	1	Vitamin A acetate (dry powder, 500,000 IU/g)	80.00
40.00	2	Pyridoxine hydrochloride	40.00
35.00	3	Vitamin E acetate (dry powder, SD 50)	75.00
395.00	4	Ludipress	395.00
4.00	5	Magnesium stearate	4.00
5.00	6	Aerosil 200	5.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high compressive force.
2. Compress 583 mg in 12-mm biplanar punches.

Vitamin A, Vitamin C, and Vitamin D_3 Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
2000/200 IU	1	Vitamin A and vitamin D_3 (dry powder, 500,000 and 50,000 IU/g, respectively)	4.00
30.00	2	Ascorbic acid (powder)	33.00
300.00	3	Sucrose (crystalline)	300.00
300.00	4	Sorbitol (crystalline)	300.00
300.00	5	Mannitol	300.00
300.00	6	Ludipress	300.00
5.00	7	Stearic acid	5.00
0.10	8	Saccharin sodium	0.10
30.00	9	Cyclamate sodium	30.00
30.00	10	Flavor mixture (Firmenich)	30.00
20.00	11	PEG-6000, powder	20.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high compressive force.
2. Compress 1290 mg in 16-mm biplanar punches.

Vitamin A, Vitamin C, and Vitamin E Tablets (1200 IU, 60 mg, 30 mg)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets
1200 IU	1	Vitamin A acetate (dry powder, 500,000 IU/g)	2.40
60.00	2	Ascorbic acid (powder)	60.00
30.00	3	Vitamin E acetate (dry powder, 50%)	60.00
105.00	4	Lactose monohydrate	105.00
30.00	5	Avicel PH101	30.00
20.00	6	Kollidon 25	20.00
5.00	7	Talc	5.00
1.00	8	Aerosil 200	1.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium compression force.
2. Compress 285 mg in 8-mm biplanar punches.

Vitamin B Complex, Amino Acids, and Magnesium Effervescent Granules (Sugar-Free)

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
2.00	1	Thiamine hydrochloride	2.00
2.00	2	Pyridoxine hydrochloride	2.00
5.00	3	Cyanocobalamin (dry powder, 0.1%)	5.00
20.00	4	L-Glutamine	20.00
10.00	5	Inositol	10.00
10.00	6	Potassium L-aspartate	10.00
500.00	7	D,L-Carnitine hydrochloride	500.00
350.00	8	Magnesium L-aspartate	350.00
600.00	9	Anhydrous citric acid	600.00
500.00	10	Sodium bicarbonate	500.00
QS	11	Flavors	QS
50.00	12	Kollidon VA 64	50.00
80.00	13	Isopropanol	80.00

Manufacturing Directions

1. Mix items 1 to 6, add the mixture of items 7 to 12, granulate the mixture of these two combinations with item 13, pass through a 0.8-mm sieve, dry well, and mix.
2. Fill 2.1 g of the granules into sachets.

Vitamin B Complex + Amino Acid + Magnesium Effervescent Granules (Sugar-free, 1 RDA of vitamins + 500 mg carnitine + 20 mg glutamine)

Formulation

I. Thiamine hydrochloride, 2 g; pyridoxine hydrochloride, 2 g; cyanocobalamin dry powder 0.1%, 5 g; L-glutamine, 20 g; inositol, 10 g; potassium L-aspartate, 10 g.
II. DL-Carnitine hydrochloride, 500 g; magnesium L-aspartate, 350 g; citric acid, anhydrous, 600 g; sodium bicarbonate, 500 g; flavors, QS; Kollidon VA 64, 50 g.
III. Isopropanol, 80 g.

Manufacturing Directions

1. Mix the components I, add the mixture II, granulate mixture I+II with the liquid III, pass through a 0.8-mm sieve, dry well, and mix with III.
2. Fill 2.1 g of the granules in sachets.

Vitamin B Complex and Carnitine Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
95.00	1	Thiamine mononitrate	95.00
20.00	2	Riboflavin	20.00
100.00	3	Nicotinamide	100.00
50.00	4	Calcium D-pantothenate	50.00
2.00	5	Folic acid	2.00
0.20	6	Biotin	0.20
0.005	7	Cyanocobalamin (gelatin coated, 1%)	0.50
50.00	8	Carnitine hydrochloride	50.00
100.00	9	Inositol	100.00
2.00	10	Adenosine phosphate	2.00
15.70	11	Kollidon 30	15.70
70.00	12	Isopropanol	70.00
26.00	13	Kollidon CL	26.00
122.00	14	Lactose monohydrate	122.00
14.00	15	PEG-6000, powder	14.00

Manufacturing Directions

1. Granulate mixture of items 1 to 10 with solution of items 11 and 12.
2. Dry, pass through a 0.8-mm sieve, mix with items 13 and 15, and press with low compressive force.
3. Compress 708 mg using 13-mm biplanar punches.

Vitamin B Complex and Folic Acid Dragées

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
4.35	1	Calcium D-pantothenate (granulate, 67%)	6.50
2.60	2	Thiamine mononitrate (10.4%)	25.00
20.00	3	Magnesium oxide (light)	20.00
45.75	4	D-Mannitol (powder)	45.75
100.00	5	DL-Methionine	100.00
2.30	6	Riboflavin	2.30
6.30	7	Nicotinamide	6.30
2.40	8	Pyridoxine HCl	2.40
4.00	9	Magnesium stearate	4.00
0.1150	10	D-Biotin	0.1150
0.46	11	Folic acid	0.46
100.00	12	Choline tartarate	100.00
28.00	13	Silicic acid (precipitated)	28.00
0.87 μg	14	Vitamin B_{12} (as 0.1% water soluble form)	0.871
3.15	15	Vitamin E (50%)	6.30
30.00	16	Sodium carboxymethyl starch	30.00
116.66	17	Isopropyl alcohol	116.66
22.00	18	Povidone (PVK K-90) (Luviskol)	22.00

Manufacturing Directions

1. Incorporate in mixer PVP K-90 and isopropyl alcohol and make a solution with continuous stirring.
2. Place in mixer choline tartarate, DL-methionine, D-mannitol powder, magnesium oxide (previously sieved), silicic acid, and sodium carboxymethyl starch and mix for 15 minutes.
3. Add the solution of isopropyl alcohol and alcohol in first step for 10 minutes until moist mass is obtained.
4. Granulate the moist mass through a centrifugal granulator with a 10-mm screen.
5. Spread the granules on paper-lined trays and dry overnight in a drying oven at 50°C.
6. Crush the granules through a 1.5-mm sieve.
7. Vitamin granulate: Tumble D-biotin, vitamin B_{12}, folic acid, riboflavin, and pyridoxine hydrochloride in mixer for 5 minutes.
8. Combine in the mixer the nicotinamide, vitamin E, thiamine mononitrate/gelatin/mannitol granulate, D-mannitol powder, and sodium carboxymethyl starch, then add the vitamin mixture and mix for 10 minutes.
9. Pass through a 1-mm sieve if lumpy.
10. In a mixer, make a separate solution of PVP K-90 and isopropyl alcohol.
11. Place in the mixer the solution of isopropyl alcohol and PVP, then knead until an evenly moist homogeneous mass is obtained.
12. Add calcium D-pantothenate granules and mix for 3 to 5 minutes.
13. Pass the granules through a centrifugal granulator with a 10-mm screen and spread on paper-lined trays.
14. Keep overnight in a drying oven at 50°C. The RH of the granules should be 10% to 20%.
15. Crush the dried granules through an oscillator with a 1.5-mm sieve.
16. Put the granulate mixture in the mixing drum—the choline tartarate and the two lots of vitamin granules.
17. Mix and then add the magnesium stearate.
18. Check to be sure that the RH of the mixture is 10% to 20%.
19. Compress and apply a sealer coat (lacquer), sugar coat, and finishing coating.

Vitamin B Complex and Iron Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
910.00	1	Sorbitol solution	910.00
0.019	2	Propyl paraben	0.019
0.17	3	Methyl paraben	0.17
1.50	4	Niacinamide (white powder)	1.50
0.30	5	Riboflavin	0.30
103.60	6	Propylene glycol	103.60
126.40	7	Glycerin	126.40
26.13	8	Iron sulfate (granular)	26.132
0.037	9	Dye	37.50 mg
0.25	10	Pyridoxine hydrochloride	0.25
1.20	11	Saccharin sodium (dihydrate powder)	1.20
22.00	12	Sodium cyclamate (powder)	22.00
30.00	13	Ascorbic acid (white powder)	30.00
0.80	14	Sodium bicarbonate (powder)	0.80
0.36	15	Thiamine hydrochloride (powder, regular)	0.36
0.625	16	D-Pantothenyl alcohol (dexpanthenol)	0.62
0.002	17	Vitamin B_{12} (cyanocobalamin)	2.00 mg
0.007	18	Flavor	0.70 mL
QS	19	Deionized purified water	QS to 1 L
QS	20	HyFlo filter aid	QS
QS	21	Hydrochloric acid	QS
QS	22	Sodium hydroxide	QS

Manufacturing Directions

1. Manufacture under complete carbon dioxide (CO_2) protection.
2. Load 780 g (portion of item 1) of sorbitol solution into a jacketed stainless steel tank. The remaining sorbitol will be used later.
3. Add parabens (unless added previously), niacinamide, and riboflavin to the sorbitol or glucose solution.
4. Heat solution to 85°C to 90°C and mix until the ingredients are dissolved.
5. Remove heat.
6. While mixing, cool the main solution to 50°C to 60°C.
7. Hold at this temperature while bubbling CO_2 into it.
8. CO_2 protection must be continued for the remainder of the manufacturing procedure.
9. Heat 50 mL of purified water to boiling and bubble CO_2 into it while cooling to 55°C.
10. Add and dissolve, with mixing, iron sulfate with 30 mL of purified water at 55°C.
11. Use CO_2 protection.
12. Warm the solution to 50°C to 55°C while mixing to dissolve, then slowly add the solution, with good mixing, to the solution above.
13. The above addition should be made as soon as possible to prevent oxidation.
14. Add the pyridoxine, saccharin sodium, and sodium cyclamate and mix until dissolved.
15. Cool the solution to 30°C.
16. Add the ascorbic acid, with good stirring, to 78 g of reserved sorbitol; make a slurry.
17. Use a container that has plenty of headspace.
18. Then add the sodium bicarbonate slowly in small portions to the ascorbic acid slurry, with stirring, until all of the powder has been added and most of the foaming has stopped.
19. Add this slurry slowly to the solution from the step above with vigorous mixing until a uniform solution results.
20. Rinse the mixing container with 22 g of the reserved sorbitol and add to the product with stirring.
21. Add and dissolve thiamine hydrochloride with mixing.
22. If necessary, warm the D-pantothenyl alcohol until liquefied and add it to the 0.5-mL CO_2-saturated purified water.
23. Use an additional 0.5 mL of CO_2-saturated purified water to thoroughly rinse the container of D-pantothenyl alcohol and add this to the D-pantothenyl alcohol solution.
24. Mix the D-pantothenyl alcohol solution thoroughly until it is homogeneously dispersed.
25. Add the D-pantothenyl alcohol solution to the main solution with mixing.
26. Use an additional 0.5 mL of CO_2-saturated purified water to rinse out the container in which the D-pantothenyl alcohol solution is made and add to the product with mixing.

27. Dissolve the vitamin B_{12} in 0.5 mL of purified water to make a clear solution and add this to the product with good mixing.
28. Dissolve the guarana flavor in the 10 g of propylene glycol, reserved from earlier step, with good stirring.
29. Add this solution to the product with good mixing.
30. Check pH (range: 3.00–3.30).
31. Adjust, if necessary, with a solution of 10% sodium hydroxide or 10% hydrochloric acid depending on the test results.
32. Adjust the volume of the product with the remaining 30 g of the sorbitol solution and, if necessary, purified water to 1 L.
33. Mix for 1 hour.
34. Allow to stand overnight to eliminate entrapped CO_2 gas.
35. Readjust volume to 1 L with purified water.
36. Mix for 1 hour.
37. Filter by adding HyFlo filter aid and mixing it, followed by passing through a filter press.
38. Do not allow temperature to exceed 30°C.
39. Bubble CO_2 gas into clear filtrate for 5 minutes, then seal tank, and hold product under CO_2 protection.

Vitamin B Complex and Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
33.00	1	Thiamine mononitrate	33.00
4.00	2	Riboflavin	4.00
10.00	3	Pyridoxine hydrochloride	10.00
66.00	4	Nicotinamide	66.00
17.00	5	Calcium D-pantothenate	17.00
350.00	6	Tartaric acid (powder)	350.00
450.00	7	Sodium bicarbonate	450.00
750.00	8	Sucrose, crystalline	750.00
30.00	9	Kollidon 30	30.00
QS	10	Isopropanol	QS
500.00	11	Ascorbic acid (crystalline)	500.00
3.00 g	12	Riboflavin	3.00
10.00	13	Cyanocobalamin (gelatin-coated, 0.1%)	10.00
10.00	14	Orange flavor	10.00
2.00	15	Saccharin sodium	2.00
5.00	16	Cyclamate sodium	5.00
50.00	17	PEG-6000 (powder)	50.00

Manufacturing Directions

1. Granulate mixture of items 1 to 9 with solvent item 10, dry, pass through a 0.8-mm sieve, mix with items 13 to 17, and press with high compressive force at a maximum relative atmospheric humidity of 30%.
2. Compress 2315 mg in 20-mm biplanar punches.

Vitamin B Complex and Vitamin C Instant Granules

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
3.60	1	Thiamine hydrochloride	3.60
5.70	2	Riboflavin phosphate sodium	5.70
45.00	3	Nicotinamide	45.00
4.50	4	Pyridoxine hydrochloride	4.50
15.0	5	Cyanocobalamin (gelatin-coated, 0.1%)	15.00
150.0	6	Ascorbic acid (powder)	150.00
723.00	7	Sucrose	723.00
51.00	8	Kollidon 30	51.00
QS	9	Ethanol	180 mL

Manufacturing Directions

1. Mix items 1 to 7, granulate with solution of items 8 and 9, dry, and pass through a 0.8-mm sieve.
2. Fill 1 g of the granules in sachets (or 10 g in 100 mL flakes as dry syrup) to produce yellow, homogeneous granules dispersible in cold water.
3. Approximately 1 g of the granules (= 1 sachet) corresponds to two daily vitamin B and vitamin C requirements of adults.
4. Because of the high loss of riboflavin phosphate sodium, it should be substituted by riboflavin.

Vitamin B Complex and Vitamin C Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.60	1	Thiamine hydrochloride	0.60
0.55	2	Riboflavin phosphate sodium	0.55
2.50	3	Nicotinamide	2.50
1.20	4	Dexpanthenol	1.20
0.55	5	Pyridoxine hydrochloride	0.55
9.00	6	Ascorbic acid (crystalline)	9.00
0.25	7	Orange flavor	0.25
0.05	8	EDTA sodium	0.05
0.50	9	Propyl gallate	0.50
2.00	10	Sorbic acid	2.00
5.00	11	Kollidon 25	5.00
10.00	12	Sorbitol (crystalline)	10.00
9.00	13	Glycerol	9.00
10.00	14	1,2-Propylenglycol (pharma)	10.00
5.00	15	Water	5.00
QS	16	Sugar syrup (64% sucrose in water)	QS to 1 kg

Manufacturing Directions

1. Mix solution of items 1 to 5 with sugar syrup, adjust the clear solution to approximately pH 4.2, and use nitrogen as an inert gas in the final packaging; 10 g provides 2 to 3 RDA.

Vitamin B Complex and Vitamin C Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.15	1	Thiamine hydrochloride	0.15
0.15	2	Riboflavin phosphate sodium	0.15
0.70	3	Nicotinamide	0.70
0.035	4	Dexpanthenol	0.035
0.150.00	5	Pyridoxine hydrochloride	0.15
2.25	6	Ascorbic acid (crystalline)	2.25
0.28	7	Orange aroma	0.28
0.56	8	EDTA sodium	0.56
186.50	9	Propylene glycol (pharma) + water (2:1)	186.50
0.15	10	Paraben	0.15
84.30	11	Sorbitol (crystalline)	84.30
562.50	12	Sucrose (crystalline)	562.50
42.00	13	Water	42.00

Manufacturing Directions

1. Dissolve items 1 to 8 in item 2.
2. Prepare a solution of items 10 to 13 by heating.
3. Cool and mix with solution of the balance of the formulation.
4. Adjust to a pH of 4.2 to 4.5.
5. Adjust volume with water. Use more, if necessary.
6. Use nitrogen as an inert gas during packaging.

Vitamin B Complex and Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
5.00	1	Thiamine mononitrate	5.00
5.00 g	2	Riboflavin	5.00
5.00	3	Pyridoxine hydrochloride	5.00
0.50	4	Folic acid	0.50
30.00	5	Niacin	30.00
0.10	6	Biotin	0.10
10.00	7	Calcium D-pantothenate	10.00
150.00	8	Ascorbic acid (crystalline/powder)	150.00
172.40	9	Ludipress	172.40
20.00	10	Kollidon VA 64	20.00
2.00	11	Magnesium stearate	2.00

Manufacturing Directions

1. Mix all ingredients and pass through a 0.8-mm sieve and mix.
2. Use medium to low compressive force to compress 400 mg in 10-mm biplanar punches.

Vitamin B Complex and Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
15.00	1	Thiamine hydrochloride	15.00
2.00	2	Riboflavin	2.00
5.00	3	Pyridoxine hydrochloride	5.00
25.00	4	Choline bitartrate	25.00
10.00	5	Nicotinamide	10.00
100.00	6	Ascorbic acid (crystalline/powder)	100.00
220.00	7	Ludipress	220.00
8.00	8	Stearic acid	8.00

Manufacturing Directions

1. Mix all ingredients and pass through a 0.8-mm sieve and mix.
2. Use medium to low compressive force to compress 411 mg in 12-mm biplanar punches.
3. The thiamine mononitrate formulation is more stable compared with the thiamine hydrochloride formulation (above).

Vitamin B Complex, Choline, and Bile Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
60.00	1	Acid dehydrochloric (powder)	60.00
100.00	2	Choline dihydrogen citrate	100.00
20.00	3	Niacinamide (white powder)	20.00
100.00	4	Inositol	100.00
2.50	5	Riboflavin (2% excess)	2.55
0.50	6	Pyridoxine hydrochloride	0.50
30.00	7	Povidone (K value, 29–32)	30.00
100.00	8	Racemethionine (crystals)	100.00
60.00	9	Ox bile extract (powder, No. 30 mesh) (Bilein)	60.00
–	10	Alcohol dehydrated (200 proof)	26.00
3.00 μg	11	Cyanocobalamin (oral powder in gelatin, 1000 μg/g)	3.30
3.00	12	Thiamine hydrochloride (powder, regular)	3.60
8.40	13	Magnesium stearate (impalpable powder)	8.40
8.40	14	Stearic acid (fine powder)	8.40

Manufacturing Directions

1. Mill dehydrochloric acid, choline dihydrogen citrate, nicotinamide, inositol, and methionine through a 600-μm screen.
2. Charge milled mixture from first step with riboflavin, pyridoxine hydrochloride, povidone, and ox bile extract in mass mixer.
3. Add alcohol QS (approximately 26 g or 32.7 mL) slowly to the mass.
4. Mass for approximately 45 minutes in mixer.
5. Scrape all material from the mass mixer as much as possible.
6. Rinse mass mixer between runs.
7. Granulate through a comminuting or similar mill or a 4.76-mm screen.
8. Dry at 49°C to less than 1% LOD.
9. Sift through an 840-μm screen in a shaker and grind coarsely through a comminuting mill (knives forward, medium speed).
10. Charge one-half of the base granulation through a 1.68-mm screen into a blender, if necessary.
11. Mix cyanocobalamin oral powder with an equal volume of base granulation and charge into a blender through a 1.68-mm screen.
12. Blend thiamine hydrochloride, magnesium stearate, and stearic acid.
13. Then hand-screen mixture through a 600-μm screen.
14. Load into a blender through a 1.68-mm screen with the remainder of the base granulation and blend for 20 minutes.
15. Compress and coat tablets using an appropriate formulation to render required color and sealing of tablet.

Vitamin B Complex Syrup

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
0.60	1	Thiamine hydrochloride	0.60
0.55	2	Riboflavin 5-phosphate sodium	0.55
2.50	3	Nicotinamide	2.50
1.20	4	Dexpanthenol	1.20
0.55	5	Pyridoxine hydrochloride	0.55
2.00	6	Sorbic acid	2.00
0.05	7	EDTA sodium	0.05
2.25	8	Vanillin	2.25
465.00	9	Sucrose	465.00
25.00	10	Kollidon 25	25.00
90.00	11	Glycerol	90.00
100.00	12	Propylene glycol (pharma)	100.00
310.00	13	Water	310.00

Manufacturing Directions

1. Dissolve the sucrose in the heat mixture of glycerol, propylene glycol, and water.
2. Cool to room temperature and dissolve the other components to obtain a clear solution.

Vitamin B Complex Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
0.66	1	Dexpanthenol	0.66
4.40	2	Nicotinamide	4.40
0.22	3	Pyridoxine hydrochloride	0.22
0.60	4	Riboflavin- 5-phosphate sodium	0.60
1.50	5	Thiamine hydrochloride	1.50
350.00	6	Sorbitol (70% solution)	350.00
11.20	7	Propylene glycol	11.20
0.84	8	Methyl paraben	0.84
0.168	9	Propyl paraben	0.168
550.00	10	Maltitol solution (Lycasin 80/55)	550.00
0.15	11	Edetate disodium (sodium EDTA)	0.15
3.72	12	Citric acid (monohydrate)	3.72
3.72	13	Sodium citrate	3.72
2.50	14	Sodium benzoate	2.50
0.50	15	Saccharin sodium	0.50
150.00	16	Glycerin (glycerol)	150.00
1.50	17	Flavor	1.50
1.00	18	Flavor	1.00
–	19	Purified water	QS to 1 L

Manufacturing Directions

1. Load items 6, 10, and 16 in a manufacturing vessel and mix for 5 minutes.
2. Dissolve items 8 and 9 in item 7 in a stainless steel container.
3. Put the entire container in hot water (60–70°C) and stir to dissolve.
4. Add the clear solution to the mixer.
5. Dissolve items 11 and 12 in 40 g of purified water in a stainless steel container.
6. Add the clear solution to the mixer.
7. Dissolve items 13, 14, and 15 in 50 g of purified water in a stainless steel container.
8. Add the clear solution to mixer and mix for 5 minutes.
9. Dissolve item 1 in 10 g of purified water in a stainless steel container.
10. Add the clear solution to mixer.
11. Dissolve items 3 and 5 in 10 g of purified water in a stainless steel container.
12. Add the clear solution to mixer.
13. Dissolve items 2 and 4 in 30 g of purified water in a stainless steel container.
14. Add the clear yellow solution to mixer and mix for 5 minutes.
15. Add items 17 and 18 to mixer.
16. Bring the volume up to 1 L with purified water and finally mix for 15 to 20 minutes.
17. Check and record the pH (limit: 4.4–4.8 at 25°C).
18. If required, adjust pH with 20% citric acid or 20% sodium citrate solution.
19. Filter the syrup at 1.5 bar.
20. Recirculate approximately 200 to 300 mL syrup.
21. Transfer the filtered syrup to the storage vessel, flushing with nitrogen gas.
22. Store the syrup under a nitrogen blanket for NMT 2 days prior to filling.

Vitamin B Complex Syrup (without B_{12})

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
570.00	1	Sucrose[a]	570.00
70.00	2	Glycerin (glycerol)	70.00
3.72	3	Citric acid (monohydrate)	3.72
1.00	4	Edetate disodium (sodium EDTA)	1.00
0.90	5	Calcium pantothenate (10% excess)	1.00
5.70	6	Sodium citrate	5.70
0.84	7	Methyl paraben	0.84
0.168	8	Propyl paraben	0.168
1.90	9	Benzoic acid	1.90
1.14	10	Strawberry flavor manefils	1.14
9.60	11	Alcohol (ethanol, 95%)	9.60
1.50	12	Thiamine hydrochloride (50% excess)	1.50
0.20	13	Pyridoxine hydrochloride (10% excess)	0.22
4.00	14	Nicotinamide (10% excess)	4.40
0.30	15	Riboflavin sodium phosphate (50% excess)	0.60
QS	16	Purified water	QS to 1 L

[a]513 mg for thiamine mononitrate and 504 mg for thiamine hydrochloride.

Manufacturing Directions

1. Flush with nitrogen gas (purity 99.95%).
2. Add 400 g of purified water to the manufacturing vessel and heat to 90°C to 95°C.
3. Add item 1 while mixing at low speed.
4. After addition of item 1, mix for 30 to 35 minutes at high speed (temperature: 90–95°C).
5. Cool to 40°C while mixing at low speed.
6. Disperse 1 g of filter aid in 10 g of cooled purified water (25–30°C) in a stainless steel container to prepare a slurry.
7. Add the slurry to the syrup in syrup vessel.
8. Mix for 15 minutes at high speed.
9. Filter the syrup at 1.5 bar.
10. Recirculate approximately 40 to 60 mL syrup.
11. Transfer the filtered syrup to the storage vessel.
12. Recharge the filtered syrup to the manufacturing vessel.
13. Start mixing.
14. Add item 2 to the syrup vessel while mixing at high speed.
15. Add item 3 to the syrup vessel while mixing to dissolve at high speed.
16. Dissolve item 4 in 6 g of cooled purified water (25–30°C) and add to the syrup vessel while mixing at high speed.
17. Dissolve item 5 in 6 g of cooled purified water and add to the syrup vessel while mixing at high speed for 30 minutes.
18. Dissolve item 6 in 10 g of cooled purified water (25–30°C) and add to the syrup vessel while mixing at high speed.
19. Dissolve items 7 to 10 in item 11 in a stainless steel container and add to the syrup vessel while mixing at high speed for 15 minutes.
20. Dissolve items 12 and 13 in 6 g of cooled purified water (25–30°C) in a separate stainless steel container and add to the syrup vessel while mixing at high speed.
21. Rinse the container with 1 g of cooled, purified water (25–30°C) and add the rinsing to the syrup vessel while mixing at high speed.
22. Flush the vessel with nitrogen gas (purity 99.95%) for 15 minutes.
23. Dissolve item 14 in 9 g of cooled purified water in a separate stainless steel container and add to the syrup vessel while mixing at high speed.
24. Rinse the container with 1 g of cooled purified water (25–30°C) and add the rinsing to the syrup vessel while mixing at high speed.
25. Dissolve item 15 in 4 g of cooled, purified water (25–30°C) in a separate stainless steel container and add to the syrup vessel while mixing at high speed.
26. Rinse the container with 1 g of cooled, purified water and add the rinsing to the syrup vessel while mixing at high speed.
27. Bring the volume up to 1 L with cooled, purified water (25–30°C) and finally mix for 15 minutes at high speed.
28. Check and record the pH (limit: 4.3–4.7 at 25°C).
29. If required, adjust pH with 10% solution of citric acid or sodium citrate.
30. Flush the syrup with nitrogen gas (purity 99.95%) for 15 minutes.
31. Close the tank.
32. Hold the syrup for 12 hours.
33. Filter the syrup at 1.5 bar.
34. Recirculate approximately 40 to 60 mL syrup.
35. Transfer the filtered syrup to the storage vessel.

Vitamin B Complex Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
25.00	1	Thiamine mononitrate or hydrochloride	25.00
25.00	2	Riboflavin	25.00
80.00	3	Nicotinamide	80.00
40.00	4	Calcium D-pantothenate	40.00
16.00	5	Pyridoxine hydrochloride	16.00
0.16	6	Cyanocobalamin (gelatin coated, 0.1%)	16.00
282.00	7	Avicel PH101	282.00
16.00	8	Kollidon 30	16.00
3.00	9	Aerosil 200	3.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve and mix.
2. Compress in 12-mm biplanar punches with medium to high compressive force.
3. The mononitrate formulation is preferred for stability reasons.

Vitamin B Complex Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
2.30	1	Thiamine mononitrate	2.30
2.60	2	Riboflavin	2.60
2.30	3	Nicotinamide	2.30
2.20	4	Calcium D-pantothenate	2.20
2.70	5	Pyridoxine hydrochloride	2.70
0.024	6	Cyanocobalamin (gelatin coated, 0.1%)	2.40
280.00	7	Ludipress	280.00
14.00	8	Flavor (Firmenich)	14.00
0.050	9	Saccharin sodium	0.05
4.00	10	Cyclamate sodium	4.00
5.00	11	Magnesium stearate	5.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and 8-mm biplanar punches.
2. Compress 314 mg using low compression force.
3. According to the European Commission, this formulation is classified as dietary food.

Vitamin B Complex Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
15.00	1	Microcrystalline cellulose (Avicel PH102)	15.00
0.20	2	Colloidal silicon dioxide (Aerosil 200)	0.20
3.00	3	Calcium pantothenate	3.00
9.33	4	Powdered cellulose	9.33
35.60	5	Lactose (spray dried)	35.60
0.91	6	Magnesium stearate	0.91
20.00	7	Nicotinamide	20.00
2.10	8	Pyridoxine hydrochloride	2.10
2.00	9	Riboflavin base	2.00
0.80	10	Talc (fine powder)	0.80
2.10	11	Thiamine mononitrate	2.10

Manufacturing Directions

1. Riboflavin base is a fine powder that tends to form globules while mixing.
2. Disperse the base with Aerosil and lactose carefully.
3. Mix items 9 and 2 and 6.67 g of item 5 in the drum of a drum mixer for 10 minutes.
4. Pass the mix 2 times through a 500-μm sieve using a sifter.
5. Pass items 3, 8, and 11 and 6.67 g of item 5 through a granulator fitted with a 1.0-mm sieve.
6. Pass items 1, 4, and 7 and 22.27 g of item 5 through a granulator fitted with a 1.0-mm sieve.
7. Pass items 6 and 10 through a sifter fitted with a 500-μm sieve.
8. Load sieved material from previous step to the blender.
9. Load sieved material to the blender.
10. Blend the powders for 15 minutes.
11. Load lubricant powders into the blender and mix for an additional 5 minutes.
12. Compress 91 mg at low RH (55–60%).
13. Coat tablets with a sealing coat, color coat, and polishing coat.

Vitamin B Complex, Vitamin A, Vitamin C, and Vitamin D Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
60.00	1	Sucrose	600.00
51.00	2	Methyl paraben	1.00
0.20	3	Propyl paraben	0.20
1.00	4	Edetate disodium (sodium EDTA)	1.00
10.00	5	Ascorbic acid (50% excess)	15.00
0.80	6	Sodium hydroxide	0.80
4.00	7	Nicotinamide (5% excess)	4.20
0.40	8	Riboflavin sodium phosphate (8% excess)	0.43
1.00	9	Thiamine hydrochloride (50% excess)	1.50
1.20	10	Pyridoxine hydrochloride (10% excess)	1.32
0.50	11	Monosodium glutamate (sodium glutamate)	0.50
1.26 μg	12	Cyanocobalamin (50% excess)	0.0018
150.00	13	Propylene glycol	150.00
1000.0 IU	14	Vitamin A palmitate (1.75 MM IU/g) (54% excess)	0.88
100.0 IU	15	Cholecalciferol (40 MM IU/g) (52% excess)	0.0038
13.20	16	Polysorbate 80 (Tween 80)	13.20
2.50	17	Poloxyl 20 cetostearyl ether (Cetomacrogol 1000)	2.50
0.30	18	Lemon oil terpeneless	0.30
0.84	19	Strawberry oil (composed)	0.84
QS	20	Purified water	QS to 1 L

Manufacturing Directions

1. This product is an aqueous solution of water-soluble vitamins with oily vitamin A palmitate and cholecalciferol solubilized in water using the surfactant system of Tween 80 and Cetomacrogol.
2. This syrup is a solubilized oil surfactant system and is affected by heat and rate of mixing.
3. The temperature of the solution must not exceed 30°C at the time of final mixing.
4. The final mixing must be continuous, without any interruption.
5. For the preparation of oily phase, the container must be dry.
6. Before start of batch, cool approximately 80 mL of purified water and flush with nitrogen gas (purity, 99.95%).
7. Use this water for making solutions and for adjusting the volume.
8. Add 420 g of purified water to the manufacturing vessel and heat to 90°C to 95°C.
9. Add items 2 and 3 while mixing to dissolve.
10. Add item 1 while mixing at slow speed.
11. After addition of item 1, mix for 30 to 35 minutes at high speed and a temperature of 90°C to 95°C.
12. Cool to 25°C to 30°C while mixing at low speed.
13. Bubble nitrogen gas for 10 minutes.
14. Add item 4 to the syrup while mixing at high speed to dissolve.
15. Add item 5 to the syrup while mixing at high speed to dissolve.
16. Add 4.00 g of purified water (25°C) in a separate container and dissolve item 6 by using a stirrer.
17. Transfer the cooled item 6 solution to the syrup tank while mixing at high speed.
18. Mix for 15 minutes.
19. Check the pH of the syrup (limit: 3.75–3.85).
20. Add items 7 to 11 one by one to the syrup in the manufacturing vessel while mixing at high speed to dissolve.
21. Mix for 10 minutes.
22. Add 6 g of cold purified water (25°C) in a separate container and dissolve item 12.
23. Add to the manufacturing vessel while mixing at high speed.
24. Rinse the container with cooled purified water (approximately 2 mL) and transfer the rinsing to the syrup-manufacturing vessel. Mix well at high speed.
25. Add item 13 to the manufacturing vessel while mixing at high speed.
26. Warm item 14 to 70°C in a separate stainless steel container in a water bath.
27. Warm item 16 to 70°C and mix well with item 14 under nitrogen atmosphere.
28. Add item 15 while mixing.
29. Melt item 17 in a stainless steel container and add with stirring to mix well.
30. Cool to 30°C while mixing under nitrogen atmosphere.
31. Add items 18 and 19 to the oily phase solution and mix for 15 minutes at high speed.
32. Check and record the volume of the oily phase.

33. Start mixing and continue mixing (mixing must be continuous).
34. Start the addition of the oily phase solution in a thin stream (do not stop mixing during addition of oily phase).
35. After the addition is complete, mix for an additional 15 minutes at high speed.
36. Rinse the oily phase vessel with a sufficient quantity of syrup from the syrup vessel.
37. Transfer the rinsing to the syrup vessel.
38. Bring the volume up to 1 L with cooled purified water (25°C) and finally mix for 20 minutes at high speed.
39. Check and record the pH (limit: 3.75–3.85 at 25°C).
40. Filter the syrup at 1.5 bar.
41. Recirculate approximately 40 to 60 mL syrup.

Vitamin B Complex, Vitamin A, Vitamin C, and Vitamin D Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
2.00	1	Thiamine mononitrate (20% excess)	2.40
1.00	2	Riboflavin (10% excess)	1.10
74.50	3	Lactose (spray dried)	74.50
15.00	4	Nicotinamide	15.00
300 IU	5	Vitamin D_3 (dry powder, 100,000 IU/g)	3.60
3000 IU	6	Vitamin A palmitate (250,000 IU/g)	18.00
36.00	7	Cellulose (microcrystalline) (Avicel PH102)	36.00
20.00	8	Ascorbic acid (90%) (33% excess)	26.60
1.00	9	Silicon dioxide (colloidal) (Aerosil 200)	1.00
1.80	10	Magnesium stearate	1.80

Manufacturing Directions

1. Mix items 1 and 2 and 13.33 g of item 3 in a drum using a drum mixer for 10 minutes.
2. Pass the mix through a 250-µm sieve using a sifter.
3. Collect in a stainless steel drum and load into the blender.
4. Pass items 4 to 7 and 61.17 g of item 3 through a granulator fitted with a 1-mm sieve.
5. Collect in a stainless steel drum and load into the blender.
6. Pass item 8 through a Fitz mill fitted with sieve number 24230.
7. Collect in a stainless steel drum and load into the blender.
8. Mix for 10 minutes.
9. Pass item 9 through a 500-µm sieve using a sifter.
10. Collect in a polyethylene bag.
11. Pass item 10 through a 250-µm sieve using a sifter.
12. Collect in the same polyethylene bag.
13. Mix and add 0.53 to 1.33 g powder from the step above.
14. Mix gently.
15. Add to the blender.
16. Mix for 3 minutes.
17. Unload lubricated granules in stainless steel drums.
18. Compress 180 mg in 7-mm round concave punches.
19. Apply a sealing coat, a color coat, and finishing coat (see appendix).

Vitamin B Complex, Vitamin A, Vitamin C, Vitamin D, and Calcium Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
675.00	1	Glycerin (96%)	675.00
16.66	2	Niacinamide (white powder)	16.66
2.73	3	Riboflavin-5′-phosphate sodium (3% excess)	2.82
0.50	4	Methyl paraben	0.50
1.00	5	Acid benzoic	1.00
105.00	6	Saccharin sodium (powder)	105.00
73.36	7	Calcium chloride (granules, dihydrate)	73.36
28.78	8	Ferrous gluconate	28.78
2.25	9	Thiamine hydrochloride (powder, regular) (35% excess)	3.375
1.00	10	Pyridoxine hydrochloride	1.00
83.33	11	Ascorbic acid (white powder) (35% excess)	112.50
0.25	12	Oil orange terpeneless	0.25
0.081	13	Alcohol (ethanol; 190 proof, nonbeverage)	0.081
80.00	14	Polysorbate 80	80.00
0.16	15	Butylated hydroxyanisole (BHA)	0.16
0.66	16	Viosterol in corn oil (syn., oleovitamin D; 1000 mD/g) (25% excess)	0.83
0.056	17	Vitamin A palmitate (1,500,000 IU/g)	0.056
10.00	18	Caramel (acid proof)	10.00
QS	19	Deionized purified water	QS to 1 L

Manufacturing Directions

1. Product must not stand more than 1 week before filling.
2. Avoid unnecessary exposure of product to light, air, and heat.
3. Manufacture and store product under complete CO_2 protection.
4. Avoid vigorous mixing.
5. Charge glycerin and 210 mL purified water into a stainless steel jacketed tank.
6. Add, with mixing, in the following order: niacinamide, riboflavin-5′-phosphate sodium, methyl paraben USP, benzoic acid, and saccharin sodium.
7. Continue mixing, heat to 95°C to 100°C, and hold to completely dissolve the ingredients.
8. Add in calcium chloride portions and stir until complete solution is obtained.
9. Continue mixing and cool to 70°C to 75°C.
10. Add ferrous gluconate with mixing and dissolve at 70°C to 75°C.
11. Check for the absence of undissolved material.
12. Check volume, if necessary. Replace lost purified water by heating with additional previously boiled purified water, QS to 750 mL.
13. Cool with mixing to room temperature (25–30°C) while bubbling CO_2 gas through.
14. Continue the CO_2 gas bubbling for balance of the process.
15. Add and dissolve each ingredient in this order: thiamine hydrochloride, pyridoxine hydrochloride, and ascorbic acid.
16. Dissolve oil orange in ethyl alcohol and add to mixture with stirring.
17. Heat Polysorbate 80 to 50°C to 60°C and hold for approximately 10 minutes with slow mixing.
18. Add and dissolve butylated hydroxyanisole.
19. Mix slowly and saturate with CO_2 while cooling to 25°C to 30°C.
20. Add and dissolve viosterol in corn oil and vitamin A palmitate, mixing well and continuing CO_2 gas bubbling.
21. Add polysorbate solution to main batch and mix thoroughly.
22. Rinse container with a portion of the main batch and add.
23. Heat 50 mL purified water to 35°C to 40°C while bubbling CO_2 gas through.
24. Add the caramel color.
25. Mix well until uniform consistency is obtained.
26. Add to main batch.
27. Rinse container with a small quantity of purified water that has been previously saturated with CO_2 gas.
28. Add to the main batch.
29. Add purified water that has been previously saturated with CO_2 gas, QS to 1 L.
30. Filter, without using a filter aid. Cycle to achieve clarity.
31. Maintain carbon dioxide cover.

Vitamin B Complex, Vitamin A, Vitamin C, Vitamin D, and Mineral Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
61.00	1	Ascorbic acid (coated), EC	61.00
5.50	2	Calcium pantothenate	5.50
8.00 μg	3	Cyanocobalamin	0.008
4.00	4	Copper sulfate, $5H_2O$	4.00
1.70	5	Magnesium oxide (heavy)	1.70
10.00	6	Nicotinamide	10.00
0.575	7	Pyridoxine hydrochloride	0.575
0.16	8	Potassium iodide	0.16
2.30	9	Riboflavin	2.30
3.25	10	Thiamine mononitrate	3.25
24.00	11	Vitamin A palmitate (250,000 IU/g)	24.00
4.80	12	Vitamin D_3 powder (100,000 IU/g)	4.80
2.20	13	Zinc sulfate, $7H_2O$	2.20
19.265	14	Lactose monohydrate	19.265
25.00	15	Cellulose (microcrystalline) (Avicel PH102)	25.00
3.00	16	Povidone (PVP K-90)	3.00
6.50	17	Cellulose (microcrystalline) (Avicel PH102)	6.50
7.00	18	Crospovidone (Kollidon CL)	7.00
1.00	19	Colloidal silicon dioxide (Aerosil 200)	1.00
0.75	20	Magnesium stearate	0.75
3.00	21	Microcrystalline cellulose (powder)	3.00
–	22	Alcohol (absolute)	18.46

Manufacturing Directions

1. Dissolve item 16 in item 22 using a stirrer.
2. Dissolve item 3 while stirring to obtain a clear solution.
3. Press items 2, 6, 7, 9, 10, 14, and 15 through a 500-μm stainless steel sieve in a sifter.
4. Load into mixer and mix for 5 minutes at high speed.
5. Knead the dry powder with binding solution while mixing at high speed for 3 minutes.
6. After the addition is complete, scrape the sides and blades.
7. Mix for an additional 2 minutes using a mixer and chopper at high speed. Check the end point of granulation.
8. (The end point occurs when the granulation consists of few or no lumps.) If required, add an additional quantity of item 22 and record this extra quantity of item 22.
9. Unload the wet granules in stainless steel trays for drying.
10. Transfer the trays to an oven.
11. Keep the door partially open.
12. Switch on the oven, with air circulation, heater switched off, for 2 hours to evaporate alcohol.
13. Close the door of the oven.
14. Dry the granules at 55°C for 12 hours.
15. After 4 hours of drying, scrape the semidried granules to break up the lumps to promote uniform drying.
16. Check the LOD (limit: 0.8–1.2%).
17. If required, dry further at 55°C for 2 hours.
18. Check the LOD.
19. Grind the dried granules through a 1.25-mm sieve using a granulator set at medium speed.
20. Load granules into the blender.
21. Mix items 4 and 13 and 3.08 g of item 17 in a polyethylene bag.
22. Mill through a Fitz mill using sieve number 1530-0030 (knives forward, medium speed).
23. Collect in stainless steel drum.
24. Add to blender.
25. Sift items 1, 11, and 12 through a 630-μm sieve.
26. Add to blender.
27. Sift items 5, 8, 18, 19, and 21 and 3.42 g of item 17 through a 500-μm sieve.
28. Add to blender.
29. Mix for 5 minutes.
30. Sift item 20 through a 250-μm sieve.
31. Mix a portion of the powder mix (approximately 3.85 g) with sieved item 20.
32. Add to the blender.
33. Mix for 1 minute.
34. Compress 185 mg per tablet using 7-mm round, concave punches.
35. Coat using a subcoat, a color coat, and a finishing coat (see appendix).

Vitamin B Complex, Vitamin A, Vitamin C, Vitamin D, and Vitamin E Pediatric Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
8333 IU	1	Vitamin A palmitate (1.7 M IU/g) (50% excess)	7.35
666 IU	2	Vitamin D (40 M IU/g) (Cholecalciferol)	0.021
75.00	3	Polysorbate 80 (Tween 80)	75.00
0.005	4	Lemon oil terpeneless	0.50
0.88	5	Vitamin E (oily) (alpha-tocopheryl acetate)	0.88
0.50	6	Edetate disodium (sodium EDTA)	0.50
83.33	7	Ascorbic acid (30% excess)	108.33
1.00	8	Saccharin sodium	1.00
2.50	9	Thiamine hydrochloride (50% excess)	3.75
16.66	10	Nicotinamide (5% excess)	17.50
0.833	11	Pyridoxine hydrochloride (5.6% excess)	0.88
2.00	12	Riboflavin sodium phosphate (7.9% excess as riboflavin)	2.16
700.00	13	Glycerin (glycerol)	700.00
250.00	14	Purified water	250.00

Manufacturing Directions

1. This product is a microemulsion and is a thermolabile preparation.
2. The temperature of the solution must not exceed 25°C at the time of processing.
3. Add 200 g of purified water to the manufacturing vessel.
4. Bubble nitrogen gas during all stages of the process.
5. Charge items 6 to 12 one by one into the manufacturing vessel while mixing.
6. Check that all materials are dissolved completely.
7. Load item 13 into the manufacturing vessel while mixing at slow speed.
8. Mix for 5 minutes.
9. Add item 3 in a separate stainless steel container.
10. Mix items 1, 2, 4, and 5 one by one using stirrer.
11. Mix for 1 hour at slow speed.
12. Add oil phase preparation to the aqueous phase at a rate of 4 mL/min while mixing at slow speed and continue nitrogen gas bubbling throughout the process.
13. Rinse the oil phase container with 50 g of nitrogen-bubbled and cooled purified water and transfer the rinsing to the manufacturing vessel.
14. Adjust the volume to 1 L using nitrogen-bubbled purified water.
15. Mix for 15 minutes at slow speed.
16. Check and record the volume and pH (limit: pH 2.8–4.2).
17. Filter the solution through a Sartorius prefilter and 0.2-μm membrane filter into receiving tank.
18. Bubble with nitrogen gas for 15 minutes.

Vitamin B Complex, Vitamin C, and Calcium Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
7.00	1	Thiamine mononitrate	7.00
5.00	2	Riboflavin	5.00
25.00	3	Nicotinamide	25.00
20.00	4	Pyridoxine hydrochloride	20.00
12.00	5	Calcium D-pantothenate	12.00
75.00	6	Calcium carbonate	75.00
164.00	7	Calcium glycerophosphate	164.00
400.00	8	Sodium bicarbonate	400.00
300.00	9	Tartaric acid (powder)	300.00
400.00	10	Sucrose (crystalline)	400.00
350.00	11	Sucrose (powder)	350.00
50.00	12	Kollidon 30	50.00
10.00	13	Kollidon 30	10.00
QS	14	Isopropanol	QS
550.00	15	Ascorbic acid (powder)	550.00
2.00	16	Riboflavin	2.00
5.00	17	Cyanocobalamin (gelatin-coated, 0.1%)	5.00
40.00	18	PEG-6000 (powder)	40.00
50.00	19	Kollidon CL	50.00

Manufacturing Directions

1. Granulate mixture of items 1 to 12 with solution of item 19.
2. Granulate items 13 to 18 separately, dry at 60°C with vacuum, mix with item 1, blend.
3. Compress 2.5 g using 20-mm planar punches at medium to high compression force.

Vitamin B Complex, Vitamin C, and Ferrous Sulfate Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
300.00	1	Ferrous sulfate	300.00
15.00	2	Kollidon 30	15.00
6.00	3	Kollidon 30	6.00
QS	4	2-Propanol	QS
45.00	5	Thiamine mononitrate	45.00
10.00	6	Riboflavin	10.00
82.00	7	Pyridoxine hydrochloride	82.00
69.00	8	Nicotinamide	69.00
470.00	9	Ascorbic acid (powder)	470.00
690.00	10	Ludipress	690.00
50.00	11	PEG-6000 (powder)	50.00
9.00	12	Aerosil 200	9.00

Manufacturing Directions

1. Granulate the mixture of items 1 to 2 with solution of items 5 to 12.
2. Pass through a 0.8-mm sieve.
3. Mix with items 3 and 4.
4. Compress with high compressive force 25 to 30 kN. Compress 1750 mg in 20-mm biplanar punches.

Vitamin B Complex, Vitamin C, and Iron Syrup

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
QS	1	Glucose (liquid), NF	QS to 1 L
225.00	2	Purified water, USP	225.00
0.30	3	Methyl paraben	0.30
1.00	4	Acid benzoic, USP	1.00
5.00	5	Alcohol (ethanol; 190 proof, nonbeverage), USP	5.00
10.00	6	Nicotinamide niacinamide (white powder), USP	10.00
10.00	7	Riboflavin; use riboflavin 5-phosphate sodium	1.64
2.00	8	Pyridoxine hydrochloride, USP	2.00
20.00	9	Ascorbic acid (white powder), USP	28.00
0.03	10	Dye	0.03
0.02	11	Dye	0.02
2.00	12	Thiamine hydrochloride (powder, regular), USP	2.40
2.00	13	D-Pantothenyl alcohol	2.50
2.00 μg	14	Vitamin B_{12} (cyanocobalamin, USP)	3.40 mg
200.00	15	Sucrose, NF	200.00
0.028 mL	16	Flavor	2.80 mL
QS	17	Hydrochloric acid	2.00 mL
QS	18	Carbon dioxide gas	QS

Manufacturing Directions

1. This preparation is susceptible to oxidation and must be protected from air and sunlight at all times.
2. Carbon dioxide must be used extensively to prevent oxygen from reacting with the materials.
3. All purified water must be boiled prior to use for 10 minutes and cooled under CO_2 protection.
4. Charge 100 mL of purified water into a suitably sized stainless steel tank.
5. Add the riboflavin, nicotinamide, benzoic acid, and paraben.
6. Rinse the tank down with 10 mL purified water, seal, and heat with mixing to 95°C.
7. Continue mixing and heating for 15 minutes, until solution is complete.
8. Commence cooling with continuous mixing.
9. When the solution has cooled to 50°C to 70°C, add and dissolve the sugar.
10. Commence CO_2 protection when the temperature reaches 40°C.
11. Slurry the ascorbic acid in 75 or 110 mL of CO_2-saturated purified water (use the smaller quantity only if using a total of 225 mL water) and add to bulk solution when temperature has reached 25°C to 35°C.
12. Rinse the ascorbic acid vessel with 10 mL purified water and add rinsing to bulk.
13. Mix for at least 30 minutes.
14. Dissolve thiamine and pyridoxine in 20 mL CO_2-saturated purified water and add to bulk solution at 25°C to 35°C.
15. Add 10 mL CO_2-saturated purified water to the D-pantothenyl alcohol and warm on a water bath until solution is complete.
16. Add vitamin B_{12} and mix until dissolved.
17. Add and dissolve dyes.
18. Add this solution to the bulk solution and mix thoroughly.
19. Mix flavor with 95% of alcohol and add to the bulk solution.
20. Rinse the container with the remaining alcohol and add to the bulk with vigorous agitation.
21. Check pH (range: 3.0–3.3).
22. Use hydrochloric acid to adjust, if necessary.
23. Adjust the final volume with liquid glucose.
24. Filter through suitable medium until clear and bright.

Vitamin B Complex, Vitamin C, and Iron Syrup

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
QS	1	Sorbitol solution, USP	QS to 1 L
QS	2	Purified water, USP	225.00
0.20	3	Methyl paraben	0.20
0.20	4	Propyl paraben, NF	0.02
2.00	5	Nicotinamide niacinamide (white powder), USP	10.00
10.00	6	Riboflavin; use riboflavin 5-phosphate sodium	1.64
10.00	7	Iron sulfate (ferrous sulfate; granular), USP	10.00
3.60	8	Saccharin sodium (powder), USP	3.60
2.00	9	Pyridoxine hydrochloride, USP	2.00
25.00	10	Ascorbic acid (white powder), USP	28.00
0.03	11	Dye	0.030
0.02	12	Dye	0.020
2.00	13	Thiamine hydrochloride (powder, regular), USP	2.40
2.00	14	D-Pantothenyl alcohol	2.50
2.0 μg	15	Vitamin B_{12} cyanocobalamin, USP	3.40 mg
1.00	16	Flavor	1.00
10.00	17	Propylene glycol, USP	10.00
QS	18	Hydrochloric acid	2.00 mL
—	19	HyFlo filter aid	1.00
QS	20	Carbon dioxide gas	QS

Manufacturing Directions

1. This preparation is susceptible to oxidation and must be protected from air and sunlight at all times.
2. Carbon dioxide must be used extensively to prevent oxygen from reacting with the materials.
3. All purified water must be boiled prior to use for 10 minutes and cooled under CO_2 protection.
4. Charge 950 g of sorbitol solution into a jacketed stainless steel tank and heat to 95°C to 100°C.
5. Heat 250 mL of purified water to boiling for 10 minutes and bubble CO_2 into it while cooling to room temperature.
6. Add, with stirring, the parabens, niacinamide, and riboflavin 5 phosphate sodium.
7. Rinse the container with 5 mL of water.
8. Stir well.
9. Mix until solution is obtained and check the clarity.
10. Remove the source of heat from the vessel.
11. Thoroughly deoxygenate the liquid by bubbling CO_2 through the liquid and allow to cool to 50°C to 60°C.
12. Heat 15 mL of water to 70°C, saturate with CO_2, and dissolve saccharin sodium (item 8) and pyridoxine hydrochloride in 5 mL of water. Add to the main bulk.
13. Rinse the container with 2.5 mL of water.
14. Cool the solution to 30°C with CO_2 protection.
15. Dissolve ascorbic acid in 120 mL of water.
16. Rinse the container with 5 mL of water.
17. Dissolve dyes in 3 mL of water.
18. Rinse the container with 2 mL of water.
19. Mix dye solution with ascorbic acid solution.
20. Add this to the main bulk with stirring.
21. Dissolve thiamine in 30 mL of water and add to the main bulk.
22. Rinse the container with 2.5 mL of water.
23. Add 10 mL of water to the D-pantothenyl and warm up on a water bath until in solution.
24. Add this mixture to the main bulk.
25. Rinse the container with 2.5 mL of water.
26. Dissolve vitamin B_{12} in 12.5 mL of water and add to the main bulk.
27. Rinse the container with 2.5 mL of water.
28. Mix flavor with 7.5 g of propylene glycol until mixture is homogeneous and add to the main bulk.
29. Rinse the container with 2.5 g of propylene glycol and add to the main bulk with vigorous agitation.
30. Check pH (range: 3.0–3.3).
31. Use hydrochloric acid to adjust, if necessary.
32. Adjust the volume of the product with sorbitol solution and mix for 30 minutes to ensure homogeneity.
33. Add the HyFlo filter aid and mix.
34. Filter the liquid through a filter press previously washed in purified water.
35. Transfer the clear filtrate into a clean, closed vessel.
36. Mix for 15 minutes while bubbling CO_2 gas.

Vitamin B Complex, Vitamin C, and Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Niacinamide, (white powder), USP	100.00
750.00	2	Ascorbic acid; use sodium ascorbate (microcrystalline), USP	843.65
20.00	3	Calcium pantothenate, USP	30.00
10.00	4	Riboflavin, USP	10.00
5.00	5	Pyridoxine hydrochloride, USP	5.25
40.00	6	Povidone, USP	40.00
68.00	7	Anhydrous isopropyl alcohol	68.00
15.00	8	Thiamine mononitrate (powder), USP	15.75
24.79	9	Vitamin E, USP, D,L-alpha-tocopoheryl acid succinate	33.71
150.00 μg	10	Folic acid (powder), USP	0.18
5.00	11	Magnesium stearate	5.00
40.00	12	Cellulose (microcrystalline), NF	40.00
4.00 μg	13	Vitamin B_{12}; use cyanocobalamin powder in gelatin (1000 μg/g)	4.20

Manufacturing Directions

1. Avoid unnecessary exposure to light and moisture.
2. Mill the nicotinamide and the sodium ascorbate through a 600-μm screen fitted to a Fitz mill or similar (impact forward, high speed).
3. Load into a suitable mass mixer.
4. Load calcium pantothenate, riboflavin, and pyridoxine hydrochloride into the mass mixer.
5. Dry blend for 5 minutes.
6. Dissolve povidone in alcohol (approximately 84 mL) in a separate container.
7. While mixing the blended powders, add the povidone solution.
8. Continue to mix until a satisfactory granule mass is obtained.
9. If required, use additional alcohol.
10. Granulate through a Fitz mill, or similar, using a 5/8-in band (15.88-mm aperture or similar) or a 4.76-mm screen with knives forward at slow speed.
11. Dry the granulation at 49°C to less than 1.5% LOD.
12. Sift the dry granulation through a 1.19-mm screen.
13. Pass remaining coarse granules through a No. 2 band (1.59-mm aperture or similar) using a Fitz mill or similar (knives forward, medium speed).
14. Blend together the thiamine mononitrate, vitamin E, folic acid, magnesium stearate, and a portion of the microcrystalline cellulose.
15. Mill blended powders through a 600-μm screen (impact forward, high speed).
16. Care must be taken to prevent losses.
17. Load half of the base granulation, the balance of the microcrystalline cellulose and the powder blend into a suitable blender.
18. Blend for 5 minutes.
19. Add balance of base granulation and blend for 15 minutes.
20. Do not mill cyanocobalamin.
21. Blend together by hand the cyanocobalamin with a portion of the blended powders.
22. Return to the blender and blend for 15 minutes.
23. Compress using ovaloid-shaped punches.
24. Seal tablets with a subcoat and then apply color coat and finishing coating.

Vitamin C and Calcium Carbonate Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
300.00	1	Calcium; use calcium carbonate	315.00
450.00	2	Sodium bicarbonate/tartaric acid (powder)	450.00
600.00	3	Kollidon 30	600.00
35.00	4	Kollidon 30	35.00
200.00	5	Isopropanol	200.00
400.00	6	Sucrose (crystalline)	400.00
500.00	7	Ascorbic acid (crystalline, with excess)	550.00
120.00	8	Kollidon CL	120.00
60.00	9	PEG-6000 (powder)	60.00

Manufacturing Directions

1. Granulate mixture of items 1 to 3 with a solution of items 4 and 5, mix with item 6, and dry.
2. Add items 7 to 9 and press with high compressive force at a maximum atmospheric RH of 30%.
3. Compress 2500 mg in 20-mm biplanar punches.

Vitamin C and Vitamin E Lozenges

Bill of Materials			
Scale (mg/lozenge)	Item	Material Name	Qty/1000 Lozenges (g)
100.00	1	Ascorbic acid (crystalline)	100.00
50.00	2	Vitamin E acetate (dry powder, SD 50)	100.00
400.00 g	3	Dextrose	400.00
4.00 g	4	Kollidon 90 F	4.00
25.00 g	5	Isopropanol	25.00
6.00 g	6	PEG-6000 (powder)	6.00

Manufacturing Directions

1. Granulate mixture of items 1 to 4 with isopropanol, dry, pass through a 0.8-mm sieve, mix with item 6, and press with high compression force.
2. Compress 600 mg using 12-mm biplanar punches.

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Ascorbic acid: 222.20 mg ascorbic acid and 312.50 mg sodium ascorbate microcrystalline	500.00
850.00	2	Sorbitol (granular)	850.00
100.00	3	Lactose (120 mesh)	100.00
3.30	4	FD&C yellow dye No. 5 lake	3.30
82.90	5	Cellulose (microcrystalline), NF (Avicel PH101)	82.90
11.60	6	Silica gel	11.60
8.29	7	Flavor	8.29
0.50	8	Flavor	0.50
8.29	9	Sodium cyclamate	8.29
33.20	10	Magnesium stearate	33.20

Manufacturing Directions

1. Pass the ascorbic acid, sodium ascorbate, sorbitol, lactose, FD&C yellow dye, microcrystalline cellulose, silica gel, flavors, and sodium cyclamate through a 420-μm screen.
2. Using a comminuting mill, pass the coarse granules through a 420-μm screen (knives forward, medium speed).
3. Transfer milled materials to a suitable blender and blend for 5 minutes.
4. Screen the magnesium stearate by hand through an 840-μm screen and transfer to blender.
5. Mix for 1 minute.
6. Compress using 18-mm standard concave punches.

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
422.00	1	Ascorbic acid (powder)	422.00
283.00	2	Microcrystalline cellulose	283.00
130.00	3	Sucrose (powder)	130.00
80.00	4	Sucrose (crystalline)	80.00
24.00	5	Kollidon VA 64	24.00
24.00	6	Cyclamate sodium	24.00
20.00	7	PEG-6000 (powder)	20.00
12.00	8	Orange flavor and strawberry flavor	12.00
2.00	9	Aerosil 200	2.00
1.00	10	Saccharin sodium	1.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm sieve, and press into tablets with medium to high compression force.
2. Compress 250 mg (for 100-mg strength), 1250 mg (for 500-mg strength), or 2500 mg (for 500-mg strength).

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Ascorbic acid (crystalline)	500.00
1100.00	2	Sorbitol (crystalline)	1100.00
200.00	3	Sucrose (crystalline)	200.00
200.00	4	Sucrose (powder)	200.00
300.00	5	Dextrose	30.00
100.00	6	PEG-6000 (powder)	100.00
10.00	7	Magnesium stearate	10.00
10.00	8	Aerosil 200	10.00
1.00	9	Saccharin sodium	1.00
10.00	10	Cyclamate sodium	10.00
30.00	11	Orange flavor	30.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium to high compression force.
2. Compress 2080 mg using 20-mm biplanar punches.

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Ascorbic acid (crystalline)	100.00
450.00	2	Sodium ascorbate (crystalline)	450.00
264.00	3	Sorbitol (crystalline)	264.00
200.00	4	Sucrose (crystalline)	200.00
200.00	5	Sucrose (powder)	200.00
300.00	6	Dextrose	300.00
60.00	7	PEG-6000 (powder)	60.00
3.00	8	Magnesium stearate	3.00
4.00	9	Aerosil 200	4.00
1.00	10	Saccharin sodium	1.00
10.00	11	Cyclamate sodium	10.00
20.00	12	Orange flavor	20.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium to high compression force.
2. Compress 1295 mg using 16-mm biplanar punches.

Vitamin C Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
6.70	1	Anhydrous silica (colloidal) (Aerosil 200)	6.70
40.00	2	Cellulose (microcrystalline) (Avicel PH101)	40.00
6.50	3	Aspartame	6.50
170.00	4	Ascorbic acid (coated), EC	170.00
10.50	5	Orange flavor (dry)	10.50
13.00	6	Carmellose sodium (sodium CMC 7 MFD)	13.00
2.80	7	Orange dye	2.80
470.00	8	Dextrates, NF	470.00
19.50	9	Magnesium stearate	19.50
13.00	10	Stearic acid (fine powder)	13.00
160.00	11	Sorbitol (powder)	160.00
388.00	12	Sodium ascorbate (granular)	388.00

Manufacturing Directions

1. Processing should be done in a controlled temperature and humidity area (limit: RH, 40–50%; temperature, 20–25°C).
2. Mix items 2 and 7 in a polyethylene bag for 1 to 2 minutes.
3. Sift twice through a 250-μm sieve.
4. Collect in a polyethylene bag and check the uniformity of dispersion.
5. If required, sift again.
6. Mix items 3, 5, and 6 in a polyethylene bag for 1 to 2 minutes.
7. Sift once through a 250-μm sieve.
8. Add to the first step and mix for 1 to 2 minutes.
9. Sift items 4, 8, 11, and 12 once through a 1000-μm sieve and collect in a stainless steel drum.
10. Add the sieved materials from the above steps to the stainless steel drum.
11. Mix in a drum blender for 2 to 3 minutes.
12. Mix items 1, 9, and 10 in a polyethylene bag for 1 to 2 minutes.
13. Sift twice through a 500-μm sieve.
14. Add 25 to 30 g of granules to the lubricant mixture.
15. Mix for 1 to 2 minutes.
16. Add this mixture to the granules.
17. Mix in a drum blender for 1 minute.
18. Check the moisture content (limit: moisture content NMT 3.5%).
19. Check temperature and humidity before beginning compression (limit: RH, 40–50%; temperature, 20–25°C).
20. Compress 1300 mg per tablet using 16-mm punches.
21. Fill appropriate amounts for lower strength (e.g., 100-mg tablets in 10-mm punches).

Vitamin C Chewable Tablets with Dextrose

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Ascorbic acid (crystalline); use ascorbic acid (coated, 97.5%), EC	110.00
500.00	2	Dextrose	500.00
4.00	3	Kollidon 90 F	4.00
30.00–50.00	4	Water and/or isopropanol	30.00–50.00
6.00	5	PEG-6000 (powder)	6.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 4 and 5 (in a fluidized bed), sieve, add item 3, and press with high compression force.
2. Compress 620 mg in 12-mm biplanar punches.
3. If no fluidized bed is available, use of water as a granulation solvent should be avoided.
4. The use of coated ascorbic acid does not increase the stability.

Vitamin C Chewable Tablets with Fructose

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
120.00	1	Ascorbic acid (powder)	120.00
500.00	2	Fructose	500.00
200.00	3	Ludipress	200.00
100.00	4	Avicel PH101	100.00
15.00	5	Kollidon VA 64	15.00
4.00	6	Aerosil 200	4.00
35.00	7	PEG-6000 (powder)	35.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high compression force.
2. Compress 970 mg in 12-mm biplanar punches.

Vitamin C Chewable Tablets with Sucrose

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Ascorbic acid	500.00
850.00	2	Sucrose, crystalline	850.00
575.00	3	Avicel™ PH101	575.00
60.00	4	Kollidon VA 64	60.00
15.00	5	Magnesium stearate	15.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with medium compression force.
2. Compress 2000 mg in 20-mm biplanar punches.

Vitamin C Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Quantity/L (g)
100.00	1	Ascorbic acid (white powder), USP	100.00
979.00	2	Propylene glycol, USP	979.00

Manufacturing Directions

1. Keep under CO_2 protection at all times. Avoid contact with iron. Use stainless steel or glass-lined equipment only.
2. Load 868 g propylene glycol into a glass-lined or suitable stainless steel jacketed tank.
3. While mixing, heat to 70°C to 80°C.
4. Bubble CO_2 gas into the propylene glycol from the bottom of the tank.
5. Add and dissolve the ascorbic acid into the propylene glycol with a minimum of stirring under CO_2 protection.
6. When the ascorbic acid is in solution, immediately cool to approximately 25°C while continuing to mix.
7. Also, while cooling, change adding CO_2 from the bottom of the tank to adding it at the top of the tank.
8. QS to 1 L, using propylene glycol, and mix for at least 10 minutes.
9. Use a prefilter pad and a lint-free filter paper. Recirculate the product through the filter press until sparkling clear.

Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
1000.00	1	Vitamin C (as ascorbic acid)	1000.00
800.00	2	Tartaric acid (fine crystals)	800.00
1000.00	3	Sodium bicarbonate	1000.00
0.50	4	Riboflavin	0.50
20.00	5	Saccharin sodium	20.00
20.00	6	Sodium chloride (milled)	20.00
50.00	7	Lime flavor	50.00
1709.50	8	Sugar (fine crystals)	1709.50
QS	9	Alcohol	QS

Manufacturing Directions

1. All operations must be carried out at a RH of less than 40% at 25°C.
2. Active substance granulates: If saccharin sodium is lumpy, sieve it by means of a centrifugal granulator (1 mm) or a 3-mm band sieve.
3. Suck into the mixer the entire amount of sugar, ascorbic acid, tartaric acid, and saccharin sodium (previously sieved, if required), together with first part sieved sodium bicarbonate (open filter, closed bypass; jacket temperature of 40°C); backflash filter twice, evacuate to approximately 800 mbar, and close filter.
4. Mix with mixer for approximately 10 minutes (jacket temperature 40°C) at a speed of 50 rpm.
5. Turn off the mixer and evacuate to 10 mbar (open filter, closed bypass; jacket temperature of 40°C).
6. Separately dissolve or suspend riboflavin in alcohol.
7. Suck this granulating liquid into the evacuated vessel at a mixer speed of 30 rpm (closed filter, closed bypass; jacket temperature of 40°C).
8. With jacket heating turned off, granulate up to a product temperature of 60°C at a mixer speed of 110 rpm (time required is approximately 20–25 minutes).
9. At a jacket temperature of 56°C and a mixer rotation speed of approximately 15 rpm, dry for 2 to 5 minutes (closed filter, open bypass).
10. When dust develops in the course of further drying, close the bypass and open the filter.
11. At a mixer speed of 20 rpm and interval setting (2 min/15 s), continue the drying at a jacket temperature of approximately 58°C and vacuum of 10 mbar until a total drying time of 10 to 20 minutes is reached.
12. Sieve the active substance granulate by sucking it by means of vacuum at a jacket temperature of approximately 59°C and a mixer speed of 20 rpm through a Buehler universal mill (1.5-mm screen) directly into a suitable container.
13. Preferable RH of the active substance is less than 10%.
14. Sieve milled sodium chloride and lime flavor through a round hand sieve (1 mm) with a diameter of approximately 38 cm. Add to sieved sodium carbonate (second part) in a mixing drum and mix (e.g., tumble mix, 19 rpm for 10 minutes).
15. Combine this dry mix (sucked by vacuum) with the active substance granulate.
16. Finally, add the remaining sieved and lump-free sodium bicarbonate (third part).
17. Mix the mixture that is ready for compression for 45 minutes.
18. The preferable RH of the mixture is less than 20%.
19. In a suitable rotary tablet press, compress effervescent tablets with a weight of 4600 mg and a hardness of 8 kpi.

Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Ascorbic acid (powder)	112.00
200.00	2	Sorbitol (instant)	200.00
1000.00	3	Anhydrous citric acid	1000.00
587.00	4	Sodium bicarbonate	587.00
65.00	5	PEG-6000 (powder)	65.00
10.00	6	Lemon flavor	10.00
25.00	7	Cyclamate sodium	25.00
1.00	8	Saccharin sodium	1.00

Manufacturing Directions

1. Dry the sodium bicarbonate for 1 hour at 100°C, mix with the other components, pass all through a 0.8-mm sieve, and press with high compression force at a maximum atmospheric RH of 30%.
2. Compress 2050 mg in 20-mm biplanar punches.

Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
1000.00	1	Ascorbic acid (crystalline)	1000.00
800.00	2	Sorbitol (crystalline)	800.00
150.00	3	Anhydrous citric acid	150.00
660.00	4	Sodium bicarbonate	660.00
80.00	5	PEG-6000 (powder)	80.00
QS	6	Lemon flavor	QS
QS	7	Cyclamate sodium	QS
QS	8	Saccharin sodium	QS

Manufacturing Directions

1. Dry the sodium bicarbonate for 1 hour at 100°C, mix with the other components, pass all through a 0.8-mm sieve, and press with high compression force at a maximum atmospheric RH of 30%.
2. Compress 2690 mg in 20-mm biplanar punches.

Vitamin C Effervescent Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
500.00	1	Sodium hydrogen carbonate	500.00
430.00	2	Tartaric acid	430.00
8.00	3	Kollidon 25	8.00
0.20	4	2-Propanol	200.00 mg
550.00	5	Ascorbic acid (crystalline)	550.00
660.00	6	Sucrose	660.00
67.00	7	PEG-6000 (powder)	67.00
67.00	8	Dextrose (powder)	67.00
10.00	9	Orange flavor	10.00
1.00	10	Saccharin sodium	1.00

Manufacturing Directions

1. Granulate mixture of items 1 and 2 with solution of items 2 and 3, pass through a 0.5-mm sieve, and dry at 60°C.
2. Dry mixture of items 5 and 6 at 60°C.
3. Mix together with the previous granules and with items 7 to 10.
4. At a maximum atmospheric RH of 30%, press to effervescent tablets.
5. Compress 2300 mg in 20-mm biplanar punches.

Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Ascorbic acid (coated)	104.00
2.40	2	Anhydrous colloidal silica (Aerosil 200)	2.40
60.00	3	Cellulose (microcrystalline) (Avicel PH102)	60.00
0.13	4	FD&C yellow dye No.10 lake	0.13
37.00	5	Lactose (spray dried)	37.00
3.20	6	Glyceryl behenate (glyceryl monostearate)	3.20
2.40	7	Stearic acid (fine powder)	2.40
1.00	8	Magnesium stearate	1.00

Manufacturing Directions

1. Processing should be done under controlled temperature and humidity (limit: RH, 40–50%; temperature, 20–25°C).
2. Mix items 5 and 4 in a polyethylene bag for 1 to 2 minutes.
3. Sift twice through a 630-μm sieve.
4. Collect in a polyethylene bag.
5. Check the uniformity of dispersion.
6. If required, sift again.
7. Sift item 3.
8. Sift mixture from first step and item 2 through a 630-μm sieve.
9. Load into a drum blender.
10. Sift item 4 through a 630-μm sieve.
11. Load into the mix in the drum blender.
12. Mix items 6, 7, and 8 in a polyethylene bag for 1 to 2 minutes.
13. Sift through a 250-μm sieve.
14. Collect in a polyethylene bag.
15. Add 13.33 g to 20.00 g of granules to the lubricant mixture.
16. Mix for 1 to 2 minutes.
17. Add this to the mix in a stainless steel drum blender.
18. Mix in a drum blender for 2 minutes.
19. Check the temperature and humidity before beginning compression (limit: RH, 40–45%; temperature, 20–25°C).
20. Compress 210 mg in 8-mm round concave punches.

Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Ascorbic acid (powder)	100.00
232.00	2	Ludipress	232.00
1.00	3	Magnesium stearate	1.00

Manufacturing Directions

1. Mix all components, sieve, and press into 335-mg tablets.
2. Compression force affects disintegration time.

Vitamin C Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
200.00	1	Ascorbic acid (powder)	200.00
231.00–256.00	2	Ludipress	231.00–256.00
25.00	3	Kollidon VA 64	25.00
15.00	4	Kollidon CL	15.00
1.20	5	Aerosil 200	1.20
2.50	6	Magnesium stearate	2.50

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm screen, and press with medium compression force (18 kN).
2. Compress 499 mg in 12-mm biplanar punches.

Vitamin E and Benzocaine Solution

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Vitamin E acetate	50.00
20.00	2	Benzocaine	20.00
50.00	3	Lutrol F 127	50.00
250.00	4	Cremophor (RH, 40%)	250.00
2.00	5	Sorbic acid	2.00
628.00	6	Water	628.00

Manufacturing Directions

1. Dissolve sorbic acid and benzocaine in water at 60°C, slowly add the heated mixture of vitamin E acetate and Cremophor at an RH of 40% and temperature of 60°C to 65°C.
2. Cool the clear solution to approximately 5°C and dissolve Lutrol F 127 to obtain a clear, colorless viscous liquid.

Vitamin E Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
100.00	1	Vitamin E acetate (SD 50)	200.00
493.00	2	Ludipress	493.00
390.00	3	Sorbitol (crystalline)	390.00
100.00	4	Mannitol	100.00
400.00	5	Dicalcium phosphate (granulated with 5% Kollidon 30)	400.00
7.00	6	Aerosil 200	7.00
3.00	7	Magnesium stearate	3.00

Manufacturing Directions

1. Mix all components, pass through a 0.8-mm screen, and press with high compression force.
2. Compress 711 mg in 12-mm biplanar punches.

Vitamin E Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
150.00	1	Vitamin E acetate (dry powder, 50%)	300.00
300.00	2	Sorbitol	300.00
6.00	3	Aerosil 200	6.00
0.20	4	Saccharin sodium	0.20
6.00	5	Magnesium stearate	6.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high compression force.
2. Compress 620 mg in 12-mm biplanar punches.

Vitamin E Chewable Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
400.00	1	Vitamin E acetate (dry powder, SD 50)	800.00
790.00	2	Ludipress	790.00
20.00	3	Aerosil 200	20.00
QS	4	Flavors	QS

Manufacturing Directions

1. Pass all components through a 0.5-mm sieve, mix, and press with high compression force.
2. Compress 1665-mg tablets in 20-mm biplanar punches.

Vitamin E Concentrate (Water-Miscible)

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
105.00	1	Vitamin E acetate	105.00
250.00	2	Cremophor (RH, 40%)	250.00
QS	3	Preservative	QS
QS	4	Water	QS to 1 L

Manufacturing Directions

1. Heat the mixture of items 1 and 2 and solution of item 3 in item 4 separately to approximately 65°C.
2. Slowly add to the well-stirred solution to obtain a clear, colorless liquid that is miscible with water.

Vitamin E Drops

Bill of Materials			
Scale (mg/mL)	Item	Material Name	Qty/L (g)
50.00	1	Vitamin E acetate	50.00
160.00	2	Cremophor (RH, 40%)	160.00
QS	3	Preservative	QS
QS	4	Water	QS to 1 L

Manufacturing Directions

1. Heat mixture of items 1 and 2 and solution of item 3 in 4 to approximately 65°C.
2. Add them slowly to obtain a clear or lightly opalescent, colorless liquid.

Vitamin E Gel Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
100.00	1	Vitamin E acetate	100.00
150.00	2	Propylene glycol (pharma)	150.00
200.00	3	Lutrol F 127	200.00
550.00	4	Water	550.00

Manufacturing Directions

1. Mix vitamin E acetate with propylene glycol and add the water.
2. After cooling to approximately 6°C, slowly dissolve Lutrol F 127 in the well-stirred mixture.
3. Maintain cool until the air bubbles escape to obtain a turbid white gel at temperatures from 20°C to 50°C with viscosity at 25°C of approximately 120,000 mPa.

Vitamin E Softgel Capsules

Bill of Materials			
Scale (mg/Capsule)	Item	Material Name	Qty/1000 Capsules (g)
400.00	1	Vitamin E preparation, USP	400.00
25.00	2	Soybean oil, USP	25.00
QS	3	Gelatin mass (clear)	QS

Manufacturing Directions

1. Weigh items 1 and 2 and transfer into a suitable stainless steel container; mix for a minimum of 1 hour, screen, transfer into tanks through a No. 80 to No. 100 mesh of stainless steel.
2. Encapsulate 425 mg of mixture into size 7.5 oval capsules using clear gelatin mass.

Vitamin E Solution with Ethanol

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/L (g)
0.10	1	Vitamin E acetate	0.10
4.00–5.00	2	Cremophor, EL	4.00–5.00
570.00	3	Water	570.00
380.00	4	Ethanol (96%)	380.00

Manufacturing Directions

1. Heat mixture of item 1 and 2 to approximately 60°C. Stir well.
2. Add slowly the warm solvent mixture of items 3 and 4 to obtain a clear, colorless liquid of low viscosity.

Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50.00	1	Vitamin E acetate (dry powder, SD 50)	100.00
140.00	2	Mannitol	140.00
140.00	3	Tablettose®	140.00
15.00	4	Kollidon VA 64	15.00
2.00	5	Magnesium stearate	2.00
10.00	6	Aerosil 200	10.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high compression force.
2. Compress 410 mg in 12-mm biplanar punches.

Vitamin E Tablets

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
50.00	1	Vitamin E acetate (dry powder, SD 50)	100.00
300.00	2	Sorbitol (crystalline)	300.00
3.00	3	Magnesium stearate	3.00
3.00	4	Aerosil 200	3.00

Manufacturing Directions

1. Pass all components through a 0.8-mm sieve, mix, and press with high compression force.
2. Compress 413 mg in 12-mm biplanar punches.

Zinc Oxide Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
7.00	1	Magnesium aluminum silicate	7.00
641.00	2	Water	641.00
7.00	3	Unimulse C	7.00
30.00	4	Propylene glycol	30.00
30.00	5	Eucalyptus oil	30.00
30.00	6	Lanolin oil	30.00
50.00	7	Dimethicone (350 cS)	50.00
50.00	8	Benzoate alcohol (C12–C15)	50.00
100.00	9	Polysorbate 80	100.00
50.00	10	Zinc oxide	50.00
10.00	11	Cornstarch	10.00
QS	12	Preservatives	QS

Manufacturing Directions

1. Slowly add item 1 to the water, agitating with maximum shear until smooth.
2. Add items 3 and 4, mixing each time until uniform.
3. Mix items 5 to 10 until uniform and mix with other portions until uniform.
4. Add items 11 and 12 and mix until smooth.

Zinc Oxide Ointment

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
120.00	1	Cetearyl alcohol and PEG-40 castor oil and sodium cetearyl sulfate	120.00
180.00	2	Petrolatum	180.00
60.00	3	Oleoyl oleate	60.00
60.00	4	Mineral oil (light)	60.00
100.00	5	Zinc oxide	100.00
QS	6	Water	QS
10.00	7	Propylene glycol, diazolidinyl urea, methyl paraben, and propyl paraben	10.00

Manufacturing Directions

1. Mix and heat items 1 to 5 to 70°C to 75°C.
2. Mix and heat items 6 and 7 to 70°C to 75°C.
3. While stirring, add second mixture to first mixture.
4. Begin cooling and continue stirring until batch reaches 30°C, then homogenize.

Zinc Pyrithione Shampoo

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/1000 Tablets (g)
547.50	1	Deionized water	547.50
7.50	2	Hydroxyethylcellulose	7.50
347.00	3	TEA-lauryl sulfate	347.00
43.00	4	PEG-20 lanolin alcohol ether	43.00
20.00	5	Glycol stearate	20.00
15.00	6	Cocamide MEA	15.00
10.00	7	Zinc pyrithione (48%)	20.00
QS	8	Fragrance, preservative	QS

Manufacturing Directions

1. Add item 2 to the water and mix.
2. In a separate vessel, combine items 3 to 5, heat to 80°C, and mix.
3. Cool to 50°C.
4. Add items 6 and 7 and mix.
5. Add this mixture to mixture of item 2.
6. Cool to 40°C and add item 8.

Zinc Undecylenate Cream

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
7.50	1	Magnesium aluminum silicate	7.50
487.50	2	Deionized water	487.50
100.00	3	Sorbitol 70%	100.00
10.00	4	Polysorbate 80	10.00
200.00	5	Zinc undecylenate	200.00
50.00	6	Caprylic acid	50.00
30.00	7	C12–C15 benzoate alcohol	30.00
15.00	8	Polysorbate 80	15.00
20.00	9	C18–C36 acid	20.00
80.00	10	Glyceryl stearate and PEG-100 stearate	80.00
QS	11	Preservatives	QS

Manufacturing Directions

1. Slowly add item 1 in the water, mixing with maximum available shear until smooth.
2. Add items 2 to 5 in order, mixing each until uniform.
3. Avoid incorporating air. Heat with stirring to 70°C to 75°C.
4. Heat items 6 to 10 separately to 70°C to 75°C and add to the above mixture with mixing while cooling. Fill at 45°C to 50°C.

Zirconium Oxide Lotion

Bill of Materials			
Scale (mg/g)	Item	Material Name	Qty/kg (g)
15.00	1	Magnesium aluminum silicate	15.00
3.00	2	Carboxymethyl cellulose sodium (medium viscosity)	3.00
796.50	3	Water	796.50
40.00	4	Zirconium oxide	40.00
50.00	5	Propylene glycol	50.00
80.00	6	Isopropyl alcohol	80.00
15.00	7	Benzocaine	15.00
0.50	8	Menthol	0.50
QS	9	Preservative	QS

Manufacturing Directions

1. Dry blend items 1 and 2 and slowly add them to the water while agitating with maximum shear until smooth.
2. Add items 4 and 5 and then items 6 to 9. Mix.

Part III

Tablet Coating Formulations

Pharmaceutical Coating Manufacturing Formulations

INTRODUCTION

Solid dosage forms are frequently coated for varied purposes, which include the following:

- Mask taste and smell
- Offer protection from the environment
- Provide protection from gastric acid (enteric coating)
- Make dose easy to swallow
- Provide identification
- Add esthetic appeal
- Hide surface defects

Many types of coatings are available.

I. Sugarcoating: Compressed tablets are coated with colored or uncolored sugar layer that is water soluble and quickly dissolves after swallowing. The sugarcoat protects the enclosed drug from the environment and provides a barrier to objectionable taste or odor. The sugarcoat also enhances the appearance of the compressed tablet and permits imprinting manufacturing's information. Sugarcoating provides a combination of insulation, taste masking, smoothing the tablet core, and coloring and modified release. The disadvantages of sugarcoating are the time and expertise required in the coating process thereby increasing size, weight, and shipping costs. Sugar-coating process involves five separate operations:
   a. Sealing/Waterproofing: Prior to applying any sugar/water syrup, the tablet cores must be sealed, thoroughly dried, and free of all residual solvents. The seal coat provides a moisture barrier and hardness to the surface of the tablet to minimize attritional effects. Core tablets having rapid disintegration rates conceivably could start the disintegration process during the initial phase of sugarcoating. The sealants are generally water-insoluble polymers/film formers applied from an organic solvent solution. The quantities of material applied as a sealing coat will depend primarily on the tablet porosity, since highly porous tablets will tend to soak up the first application of solution, thus preventing it from spreading uniformly across the surface of every tablet in the batch. Hence, one or more further application of resin solution may be required to ensure that the tablet cores are sealed effectively. Common materials used as a sealant include shellac, zinc, cellulose acetate phthalate (CAP), polyvinylacetate phthalate, hydroxypropyl cellulose (HPC), hydroxypropylmethylcellulose (HPMC), and so on.
   b. Subcoating: Subcoating is the actual start of the sugar-coating process and provides the rapid buildup necessary to round up the tablet edge. It also acts as the foundation for the smoothing and color coats. Generally two methods are used for subcoating. Dusting with powder and then drying follows one where the application of gum-based solution and the routine repeated until the desired shape is achieved. The other method is where a suspension of dry powder in gum/sucrose solution is applied followed by drying the tablets. Thus, subcoating is a sandwich of alternate layer of gum and powder. It is necessary to remove the bulk of the water after each application of coating syrup.
   c. Grossing/Smoothing: The grossing/smoothing process is specifically for smoothing and filing the irregularity on the surface generated during subcoating. It also increases the tablet size to a predetermined dimension. If the subcoating is rough with high amount of irregularities then the use of grossing syrup containing suspended solids will provide more rapid buildup and better filling qualities. Smoothing usually can be accomplished by the application of a simple syrup solution (approximately 60–70% sugar solid). This syrup generally contains pigments, starch, gelatin, acacia, or opacifier, if required. Small quantities of color suspension can be applied to impart a tint of the desired color when there are irregularities in coating.
   d. Color coating: This stage is often critical in the successful completion of a sugar-coating process and involves the multiple application of syrup solution (60–70% sugar solid) containing the requisite coloring matter. Mainly soluble dyes were used in the sugarcoating to achieve the desired color, since the soluble dye will migrate to the surface during drying. But nowadays the insoluble certified lakes have virtually replaced the soluble dyes in pharmaceutical tablet coating. The most efficient process for color coating involves the use of a predispersed opacified lake suspension.
   e. Polishing: Sugar-coated tablets need to be polished to achieve a final elegance. Polishing is achieved by applying the mixture of waxes like beeswax, carnauba wax, candelilla wax, or hard paraffin wax to tablets in polishing pan.

II. Film coating: Film coating is the deposition of a thin film of polymer surrounding the tablet core. Conventional pan equipments may be used but nowadays more sophisticated equipments are employed to have a high degree of automation and coating time. The polymer is solubilized into solvent. Other additives like plasticizers and pigments are added. Resulting solution is sprayed onto a rotated tablet bed. The drying conditions cause removal of the solvent, giving thin deposition of coating material around each tablet core. Usually spray process is employed in preparation of film-coated tablets. Accela Cota is the prototype of perforated cylindrical drum providing high drying air capacity. Fluidized bed equipment has made considerable impact where tablets

are moving in a stream of air passing through the perforated bottom of a cylindrical column. With a smaller cylindrical insert, the stream of cores is rising in the center of the device together with a spray mist applied in the middle of the bottom. For fluidized bed coating, very hard tablets (hardness > 20 N) have to be used. The fundamental requirements are independent of the actual type of equipments being used and include adequate means of atomizing the spray liquid for application to the tablet core, adequate mixing and agitation of tablet bed, sufficient heat input in the form of drying air to provide the latent heat of evaporation of the solvent. This is particularly important with aqueous-based spraying and good exhaust facilities to remove dust and solvent laden air. The materials used in film coating include:

a. Film formers:
   i. HPMC: It is available in different viscosity grades. It is a polymer of choice for air suspension and pan spray coating systems because of solubility characteristic in gastric fluid, organic, and aqueous solvent system. Advantages include the following: it does not affect tablet disintegration and drug availability; it is cheap, flexible, highly resistant to heat, light, and moisture; it has no taste and odor; color and other additives can be easily incorporated. The disadvantage is that when it is used alone, the polymer has tendency to bridge or fill the debossed tablet surfaces. So a mixture of HPMC and other polymers/ plasticizers is used.
   ii. Methylhydroxyethylcellulose (MHEC): It is available in wide variety of viscosity grades. It is not frequently used as HPMC because soluble in fewer organic solvents.
   iii. Ethyl cellulose (EC): Depending on the degree of ethoxy substitution, different viscosity grades are available. It is completely insoluble in water and gastric fluids. Hence it is used in combination with water-soluble additives like HPMC and not alone. Unplasticized EC films are brittle and require film modifiers to obtain an acceptable film formulation. Aqua coat is aqueous polymeric dispersion utilizing EC. These pseudolatex systems contain high solids, low-viscosity compositions that have coating properties quite different from regular EC solution.
   iv. HPC: It is soluble in water less than 40°C (insoluble more than 45°C), gastric fluid, and many polar organic solvents. HPC is extremely tacky as it dries from solution system. It is used for subcoat and not for color or glass coat. It gives a flexible film.
   v. Povidone: Degree of polymerization decides molecular weight of material. It is available in four viscosity grades, that is, K-15, K-30, K-60, and K-90. Average molecular weight of these grades is 10,000, 40,000, 160,000, and 360,000 respectively. K-30 is widely used as tablet binder and in tablet coating. It has excellent solubility in wide variety of organic solvents, water, gastric and intestinal fluids. Povidone can be crosslinked with other materials to produce films with enteric properties. It is used to improve dispersion of colorants in coating solution.
   vi. Sodium carboxy methyl cellulose: It is available in medium, high, and extra high viscosity grades. It is easily dispersed in water to form colloidal solutions but it is insoluble in most organic solvents and hence not a material of choice for coating solution based on organic solvents. Films prepared by it are brittle but adhere well to tablets. Partially dried films are tacky. So coating compositions must be modified with additives.
   vii. Polyethylene glycols (PEG): Lower molecular weights PEG (200–600) are liquid at room temperature and are used as plasticizers. High molecular weights PEG (900–8000 series) are white, waxy solids at room temperature. Combination of PEG waxes with CAP gives films that are soluble in gastric fluids.
   viii. Acrylate polymers: It is marketed under the name of Eudragit®. Eudragit®E is a cationic copolymer. Only Eudragit E is freely soluble in gastric fluid up to pH 5 and expandable and permeable above pH 5. This material is available as organic solution (12.5% in isopropanol/acetone), solid material, or 30% aqueous dispersion. Eudragit®RL & RS are copolymers with low content of quaternary ammonium groups. These are available only as organic solutions and solid materials. They produce films for delayed action (pH dependent).
b. Solvents: Mostly solvents are used either alone or in combination with water, ethanol, methanol, isopropanol, chloroform, acetone, methylene chloride, and so on. Water is more used because no environmental and economic considerations are needed. For drugs that readily hydrolyze in presence of water, nonaqueous solvents are used.
c. Plasticizers: As the solvent is removed, most polymeric materials tend to pack together in three-dimensional honeycomb arrangement. Both internal and external plasticizing techniques are used to modify quality of film. Combination of plasticizer may be used to get desired effect. Concentration of plasticizer is expressed in relation to the polymer being plasticized. Recommended levels of plasticizers range from 1% to 50% by weight of the film former. Commonly used plasticizers are castor oil, PG, glycerin, lower molecular weight (200–400 series), PEG, surfactants, and so on. For aqueous coating PEG and PG are more used, while castor oil and spans are primarily used for organic solvent-based coating solution. External plasticizer should be soluble in the solvent system used for dissolving the film former and plasticizer. The plasticizer and the film former must be at least partially soluble or miscible in each other.
d. Colorants: Colorants can be used in solution form or in suspension form. To achieve proper distribution of suspended colorants in the coating solution requires the use of the powdered colorants (<10 μm). Most common colorants in the United States are certified FD&C or D&C colorants. These are synthetic dyes or lakes. Lakes are choice for sugar or film coating as they give reproducible results. Concentration of colorants in the coating solutions depends on the color shade desired, the type of dye, and the concentration of opaquant extenders. If very light shade is

desired, concentration of less than 0.01% may be adequate. On the other hand, if a dark color is desired, a concentration of more than 2% may be required. The inorganic materials (e.g., iron oxide) and the natural coloring materials (e.g., anthocyanins, carotenoids) are also used to prepare coating solution. Magenta red dye is nonabsorbable in the biologic system and resistant to degradation in the gastrointestinal track. Opadry® (opaque color concentrate for film coating) and Opadry (complete film coating concentrate) are promoted as achieving less lot-to-lot color variation.

e. Opaquant extenders: These are very fine inorganic powder used to provide more pastel colors and increase film coverage. These inorganic materials provide white coat or mask color of the tablet core. Colorants are expensive and higher concentration is required. These inorganic materials are cheap. In presence of these inorganic materials, amount of colorants required decreases. Most commonly used materials are titanium dioxide, silicate (talc and aluminum silicates), carbonates (magnesium carbonates), oxides (magnesium oxide), and hydroxides (aluminum hydroxides). Pigments were investigated in the production of opaque films and it was found that they have good hiding power and film-coated tablets have highlighted intagliations.

f. Other components: Flavors, sweeteners, surfactants, antioxidants, antimicrobials may be incorporated into the coating solution.

III. Enteric coating: The one layer is applied as one homogenous layer, which can be white, opaque, or colored. Benefit is only one application needed. The two-layer system where the enteric formulation is applied first, followed by colored film. Both layers can be of enteric polymer or only the basic layer contains enteric polymer while the top layer is fast disintegrating and water-soluble polymer. Polymers used for enteric coating include the following:

a. Cellulose acetate phthalate (CAP): It is widely used in industry. Aquateric is reconstituted colloidal dispersion of latex particles. It is composed of solid or semisolid polymer spheres of CAP ranging in size from 0.05 to 3 μm. Cellulose acetate trimellitate (CAT) developed as an ammoniated aqueous formulation showed faster dissolution than a similar formulation of CAP. Disadvantages include the following: it dissolves above pH 6 only, delays absorption of drugs, it is hygroscopic and permeable to moisture in comparison with other enteric polymer, it is susceptible to hydrolytic removal of phthalic and acetic acid changing film properties. CAP films are brittle and usually used with other hydrophobic film forming materials.

b. Acrylate polymers: Eudragit®L and Eudragit®S are two forms of commercially available enteric acrylic resins. Both of them produce films resistant to gastric fluid. Eudragit®L and S are soluble in intestinal fluid at pH 6 and 7 respectively. Eudragit L is available as an organic solution (isopropanol), solid or aqueous dispersion. Eudragit S is available only as an organic solution (isopropanol) and solid.

c. Hydroxypropylmethylcellulose phthalate (HPMCP): HPMCP 50, 55, and 55-s (also called HP-50, HP-55, and HP-55-s) are widely used. HP-55 is recommended for general enteric preparation while HP-50 and HP-55-s for special cases. These polymers dissolve at a pH 5 to 5.5.

d. Polyvinyl acetate phthalate: It is similar to HP-55 in stability and pH dependent solubility.

e. Enteric coating can be combined with polysaccharides, which are enzyme degraded in colon, for example, cyclodextrin and galactomannan.

IV. Controlled-release coating: Polymers like modified acrylates, water-insoluble cellulose (EC) are used for control-release coating.

V. Compressed coating: This type of coating requires a specialization tablet machine. Compression coating is not widely used but it has advantages in some cases in which the tablet core cannot tolerate organic solvent or water and yet needs to be coated for taste masking or to provide delayed or enteric properties to the finished product and also to avoid incompatibility by separating incompatible ingredients.

VI. Electrostatic coating: Electrostatic coating is an efficient method of applying coating to conductive substrates. A strong electrostatic charge is applied to the substrate. The coating material containing conductive ionic species of opposite charge is sprayed onto the charged substrate. Complete and uniform coating of corners and adaptability of this method to such relatively nonconductive substrate as pharmaceutical is limited.

VII. Dip coating: Coating is applied to the tablet cores by dipping them into the coating liquid. The wet tablets are dried in a conventional manner in coating pan. Alternative dipping and drying steps may be repeated several times to obtain the desired coating. This process lacks the speed, versatility, and reliability of spray-coating techniques. Specialized equipment has been developed to dip-coat tablets, but no commercial pharmaceutical application has been obtained.

VIII. Vacuum film coating: Vacuum film coating is a new coating procedure that employs a specially designed baffled pan. The pan is hot, water jacketed, and it can be sealed to achieve a vacuum system. The tablets are placed in the sealed pan and the air in the pan is displaced by nitrogen before the desired vacuum level is obtained. The coating solution is then applied with airless spray system. The heated pan causes the evaporation and the vapor is removed by the vacuum system. Because there is no high-velocity heated air, the energy requirement is low and coating efficiency is high. Organic solvent can be effectively used with this coating system with minimum environmental or safety concerns.

Formulations for tablet coating are often proprietary to various manufacturers as these address several formulation needs as described above. The suppliers of coating ingredients are often open to sharing the coating technology and companies are highly encouraged to make use of them, more particularly where the coating materials have an open DMF available for regulatory filings. The following companies are a very good source of information:

Eudragit (http://www.pharma-polymers.com/pharmapolymers/en/eudragit/)

Colorcon® (http://www.colorcon.com/products/coatings)

Methocel/Ethocel (http://www.dow.com/dowexcipients/applications/tablet_coating.htm)

The advantage of using these prepackaged formulations is consistency in color matching, as well as other considerations regarding ease of use.

The most significant aspect remains the choice of colors, which often determines the method of manufacturing the coating solutions. With a limited choice of dyes and lakes available for selection, manufacturers often use a combination of several colors and dyes along with agents such as talc for opaqueness to obtain the desired color and protection.

Given below is a current listing of approved colors in various regulatory regions.

Approved Drug Colorants for Internal Use in Japan-1[a]

Name	CAS Number	Color Index Number	Precedent Limit	Compendia
Black iron oxide	12227-89-3	77499	1.539 mg	JPE
Caramel			1500 mg	JPE
Carbon black	1333-86-4	77268:1	0.096 mg	JPE
Carmine	1390-65-4	75470	1.8 mg	JPE
Beta-carotene	7235-40-7	40800	0.1%	JPE
Copper chlorophyll			1.8 mg	Japan Pharmaceutical Codex
Glycyrrhiza extract			300 mg	JP
Gold leaf	7440-57-5		14 mg	JPE
Light anhydrous silicic acid	7631-86-9		2.6 g	JP
Medicinal carbon	16291-96-6		150 mg	JP
2-Octyldodecyl myristate	22766-83-2		100 mg	JPE
Orange essence			15 mg	JPE
Powdered green tea			100 mg	JPE
Red ferric oxide	1309-37-1	77491	95.4 mg	JPE
Riboflavin	83-88-5		0.8 mg	JP
Riboflavin butyrate			0.4 mg	JP
Riboflavin sodium phosphate			2 mg	JP
Rose oil	8007-01-0		0.1 mg	NF
Rye green leaf extract			2 mg	JPE
Sodium copper chlorophyllin			75 mg	Japan Pharmaceutical Codex
Sodium hydroxide	1310-73-2		224 mg	JP
Talc	14807-96-6		3384 mg	JP
Titanium oxide	13463-67-7	77891	384 mg	JP
Yellow ferric oxide	1310-14-1	77492	5.67 mg	JPE

[a]These colorants appear in the application column in the Japanese Pharmaceutical Excipients Directory 2007 (Japanese Version) as coloring agents. Precedent limits are quoted from the Japanese Pharmaceutical Excipients Directory 2007 (Japanese version). Each limit represents the maximum daily intake that a patient should consume from the use of a particular dosage form.

Approved Drug Colorants for Internal Use in Japan-2[a]

Name	Alternate Name	Color Index Number	CAS Number	Precedent Limit
Amaranth[b]	Red #2, Acid Red 27	16185	915-67-3	c
Erythrosine[b]	Red #3, Acid Red 51	45430	16423-68-0	c
New Coccine (Ponceau4R)[b]	Red #102, Acid Red 18	16255	2611-82-7	c
Phloxine B	Red #104(1), Acid Red 92	45410	18472-87-2	c
Rose Bengal	Red #105(1), Acid Red 94	45440	632-69-9	c
Acid Red	Red #106, Acid Red 52	45100		c
Tartrazine[b]	Yellow #4, Acid Yellow 23	19140	1934-21-0	c
Sunset Yellow FCF[b]	Yellow #5	15985	2783-94-0	c
Fast Green FCF	Green #3	42053	2353-45-9	c
Brilliant Blue FCF[b]	Blue #1	42090	3844-45-9	c
Indigo Carmine[b]	Blue #2, Acid Blue 74	73015	860-22-0	c

[a]Based on colors approved by the MHW's "Ministerial Ordinance to establish Tar colors which can be used in Pharmaceuticals"; No. 30; August 31, 1966. Aluminum lakes of these colors are also authorized.

[b]These colorants make the list of the application column in the Japanese Pharmaceutical Excipients Directory 2007 (Japanese Version) as coloring agents.

[c]Not more than 0.1% by weight of color (lake or dye) can be used in a dosage form. If one colorant was combined with other colorants, total weight of these colorants must be less than 0.1% of the final product.

Approved Drug Colorants for Use in Canada[a]

I. Colorants approved for internal and external drug use

Color	Alternate Name	Color Index Number	CAS Number
Acid fuchsin D	D&C red #33	17200	3567-66-6
Alizarin cyanine green F	D&C green #5	61570	4403-90-1
Allura red AC	FD&C red #40	16035	25956-17-6
Amaranth	Delisted FD&C red #2	16185	915-67-3
Anthocyanin (Derived from juice expressed from fresh edible fruits or vegetables)			
Beta-APO-8´ Carotenal	–	40820	1107-26-2
Brilliant blue FCF sodium salt	FD&C blue #0	42090	3844-45-8
Brilliant blue FCF ammonium salt	D&C blue #4	42090	6371-85-2
Canthaxanthin	–	40850	514-78-3
Caramel	–	–	–
Carbon black	–	77266	1333-86-4
Carmine	–	75470	1260-17-9
Carmoisine	Azorubine	14720	3567-69-9
Beta-carotene	–	40800	7235-40-7
Chlorophyll	–	75810	479-61-8
Eosin YS acid form	D&C red #21	45380:2	15086-94-9
Eosin YS sodium salt	D&C red #22	45380	17372-87-1
Erythrosine	FD&C red #3	45430	16423-68-0
Fast green FCF	FD&C green #3	42053	2353-45-9
Flaming red	D&C red #36	12085	2814-77-9
Helindone pink CN	D&C red #30	73360	2379-74-0
Indigo	D&C blue #6	73000	482-89-3
Indigotine	FD&C blue #2`	73015	860-22-0
Iron oxides	Iron oxide red	77491	1309-37-1
	Iron oxide yellow	77492	51274-00-1
	Iron oxide black	77499	12227-89-3
Lithol rubin B sodium salt	D&C red #6	15850	5858-81-1
Lithol rubin B calcium salt	D&C red #7	15850:1	5281-04-9
Phloxine B sodium salt	D&C red #28	45410	18472-87-2
Phloxine B acid form	D&C red #27	45410:1	13473-26-2
Ponceau 4R	–	16255	2611-82-7
Ponceau SX	FD&C red #4	14700	4548-53-2
Quinoline yellow WS	D&C yellow #10	47005	8004-92-0
Riboflavin	–	–	83-88-5
Sunset yellow FCF	FD&C yellow #6	15985	2783-94-0
Tartrazine	FD&C yellow #5	19140	1934-21-0
Titanium dioxide	–	77891	13463-67-7

[a]Based on the Canadian Department of Health's Food and Drug Regulations on Coloring Agents; Part C.01.040.2; Aug. 30, 1995 [16].

II. Colorants approved for external drug use

Color	Alternate Name	Color Index Number	CAS Number
Acid violet	Ext. D&C violet #2	60730	–
Alizurol purple SS	D&C violet #2	60725	81-48-1
Annatto	–	75120	–
Bismuth oxychloride	–	77163	–
Chromium hydroxide green	Pigment green 18	77289	–
Dibromofluorescein (Solvent red 72)	D&C orange #5	45370:1	–
Deep maroon	D&C red #34	15880:1	6417-83-0
Ferric ferrocyanide	–	77510	–
Guanine	–	75170	–
Orange II	D&C orange #4	15510	633-96-5
Manganese violet	–	77742	–
Mica	–	77019	–
Pyranine concentrated	D&C green #8	59040	6358-69-6
Quinizarin green SS	D&C green #6	61565	128-80-3
Toney red	D&C red #17	26100	85-86-9
Uranine acid form	D&C yellow #7	45350:1	7/5/2321
Uranine sodium salt	D&C yellow #8	45350	518-47-8
Zinc oxide	–	77947	–

Approved Drug Colourants Listed by the European Union[a]

Colour	E Number	Colour Index Number	Alternate Names
Allura red AC	E129	16035	FD&C red #40
Aluminum	E173	77000	–
Amaranth	E123	16185	Delisted FD&C red #2
Anthocyanins	E163	–	–
Beet root red	E162	–	Betanin
Beta APO-8´-carotenal	E160e	40820	–
Beta APO-8´-carotenoic			–
Acidethyl ester	E160f	40825	
Brilliant black BN	E151	28440	Black PN
Brilliant blue FCF	E133	42090	FD&C blue #1
Brown HT	E155	20285	–
Calcium carbonate	E170	77220	–
Canthaxanthin	E161g	40850	–
Caramel	E150a	–	–
Caramel,-caustic sulphite	E150b	–	–
Caramel,-ammpnia	E150c	–	–
Caramel, sulphite ammonia	E150d	–	–
Carbon vegetable black	E153	77268:1	Carbo medicinalis vegetalis
Carmine	E120	75470	Carmine 40, carminic acid
Carmoisine	E122	14720	Azorubine
Carotene		75130	Alpha, beta & gamma carotene
i. Mixed carotenes	E160a(i)	75130	–
ii. Beta-carotene	E160a(ii)	40800	–
Chlorophylls/Chlorophyllins		–	–
i. Chlorophylls	E140(i)	75810	–
ii. Chlorophyllins	E140(ii)	75815	–
Chlorophylls/Chlorophyllins			
Copper complexes		75815	–
i. Copper complexes	E141(i)		
of chlorophylls		–	–
ii. Copper complexes	E141(ii)		
of chlorophyllins		–	–
Cochineal	E120	75470	Carminic acid
Erythrosine	E127	45430	FD&C red #3
Gold	E175	77480	–
Green S	E142	44090	Acid brilliant green BS
Indigotine	E132	73015	FD&C blue #2, indigo carmine
Iron oxides & hydroxides	E172	77491	Iron oxide red
		77492	Iron oxide yellow
		77499	Iron oxide black
Lutein	E161b	–	–
Lycopene	E160d	–	–
Paprika extract	E160c	–	Capsanthin, capsorubin
Patent blue V	E131	42051	Acid blue 3
Ponceau 4R	E124	16255	Cochineal red A
Quinoline yellow[b]	E104	47005	China yellow
Riboflavin		–	–
i. Riboflavin	E101(i)	–	–
ii. Riboflavin-5'-phosphate	E101(ii)	–	–
Sunset yellow FCF	E110	15985	FD&C yellow #6, orange yellow S
Tartrazine	E102	19140	FD&C yellow #5
Titanium dioxide	E171	77891	–
Turmeric	E100	75300	Curcumin

[a]This list is derived from Annex 1 of Directive 94/36/EC, colours permitted for use in foodstuffs. EMEA Guideline EMEA/CHMP/QWP/396951/2006 states that colourants mentioned in this annex are permitted for use in medicinal products.

[b]This is not D&C yellow #10. Although the C.I. numbers are the same, the dyes differ in composition. Quinoline yellow is primarily the disulfonated quinoline dye, whereas D&C yellow #10 is the monosulfonated color. Quinoline yellow is not accepted for use in the United States; conversely, D&C yellow #10 cannot be used in the EU.

Note: Aluminum lakes prepared from colours mentioned in this list are also permitted.

Color Additives Exempt from Certification Permitted for Use in the United States[a]

Color	Color Index Number	CAS Number	21 CFR References			
			Food	Drug	Cosmetic	Medical Devices
Algae meal (dried)	–	–	73.275	–	–	–
Algae meal (haematococcus)	–	–	73.185	–	–	–
Alumina	77002	1332-73-6	–	73.1010	–	–
Aluminum powder	77000	7429-90-5	–	73.1645	73.2645	–
Annatto extract	75120	8015-67-6	73.30	73.1030	73.2030	–
Astaxanthin	–	–	73.35	–	–	–
Beta- Apo-8'-carotenal	40820	1107-26-2	73.90	–	–	–
Beta carotene	40800	7235-40-7	73.95	73.1095	73.2095	–
Beet powder	–	57917-55-2	73.40	–	–	–
Bismuth citrate	–	–	–	–	73.2110	–
Bismuth oxychloride	77163	7787-59-9	–	73.1162	73.2162	–
Bronze powder	77440	7440-50-8	–	73.1646	73.2646	–
		7740-66-6				
Calcium carbonate	77220	471-34-1	–	73.1070	–	–
Canthaxanthin	40850	514-78-3	73.75	73.1075	–	–
Caramel	–	–	73.85	73.1085	73.2085	–
Carbazole violet	51319	6358-30-1	–	–	–	73.3107
Carmine	75470	1390-65-4	73.100	73.1100	73.2087	–
Carrot oil	–	–	73.300	–	–	–
Chlorophyllin copper complex	75810	–	–	73.1125	73.2125	73.3110
Chromium-cobalt-aluminum oxide	77343	68187-11-1	–	73.1015	–	73.3110a
Chromium hydroxide green	77289	12182-82-0	–	73.1326	73.2326	–
Chromium oxide greens	77288	1308-38-9	–	73.1327	73.2327	73.3111
C.I. vat orange 1	59105	–	–	–	–	73.3112
Cochineal extract	75470	1260-17-9	73.100	73.1100	–	–
Corn endosperm oil	–	–	73.315	–	–	–
Copper powder	77400	7440-50-6	–	73.1647	73.2647	–
1,4-Bis [(2-hydroxyethyl) amino]-9,10-anthracenedione bis(2-propenoic) ester copolymers	–	10956-07-1	–	–	–	73.3100
1,4-Bis [(2-methylphenyl)amino]-9,10-anthracenedione	–	6737-68-4	–	–	–	73.3105
1,4-Bis[4-(2-methacryloxyethyl) phenylamino]-9,10-anthraquinone Copolymers	–	121888-69-5	–	–	–	73.3106
2-[[2,5-Diethoxy-4-[(4-methylphenyl) thiol]phenyl]azo]-1,3,5-benzenetriol	–	–	–	–	–	73.3115
16,23-Dihydrodinaptho[2,3-a:2´,3´-i] napth[2´,3´:6,7]indolo[2, 3-c]carbazole-5,10,15,17,22,24-hexone	70800	2475-33-4	–	–	–	73.3117
N,N´-(9,10-Dihydro-9,10-dioxo-1,5-anthracenediyl) bis-benzamide	61725	82-18-8	–	–	–	73.3118
7,16-Dichloro-6,15-dihydro-5,9,14,18-anthrazinetetrone	69825	130-20-1	–	–	–	73.3119
16,17-Dimethoxydinaphtho[1,2,3-cd:3´,2´,1´-lm] perylene-5,10 dione	59825	128-58-5	–	–	–	73.3120
4-[2,4-(Dimethylphenyl)azo]-2,4-dihydro-5-methyl-2-phenyl-3*H*-pyrazol-3-one	–	6407-78-9	–	–	–	73.3122
Dihydroxy acetone	–	62147-49-3	–	73.1150	73.2150	–
Disodium EDTA copper	–	–	–	–	73.2120	–
6-Ethoxy-2-(6-ethoxy-3-oxobenzo [*b*]thien-2-(3*H*)-ylidene)benzo[*b*] thiophen-3-(2*H*)-one	73335	3263-31-8	–	–	–	73.3123
Ferric ammonium citrate	–	1185-57-5	–	73.1025	–	–
Ferric ammonium ferrocyanide	77510	25869-00-5	–	73.1298	73.2298	–
Ferric ferrocyanide	77510	14038-43-8	–	73.1299	73.2299	–
Ferrous gluconate	–	299-29-6	73.160	–	–	–
Ferrous lactate	–	5905-52-2	73.165	–	–	–
Fruit juice	–	–	73.250	–	–	–

Color Additives Exempt from Certification Permitted for Use in the United States[a] (*Continued*)

Color	Color Index Number	CAS Number	21 CFR References			
			Food	Drug	Cosmetic	Medical Devices
Grape color extract	–	–	73.169	–	–	–
Grape skin extract	–	–	73.170	–	–	–
Guaiazulene	–	489-84-9	–	–	73.2180	–
Guanine	75170	68-94-0 73-40-5	–	73.1329	73.2329	–
Henna	75480	83-72-7	–	–	73.2190	–
Iron oxides, synthetic	77491(Red) 77492(Yellow) 77499(Black)	1309-37-1 51274-00-1 12227-89-3	73.200	73.1200	73.2250	73.3125
Lead acetate	–	6080-56-4	–	–	73.2396	–
Logwood extract	75290	8005-33-2	–	73.1410	–	–
Manganese violet	77742	10101-66-3	–	–	73.2775	–
Mica	77019	12001-26-2	–	73.1496	73.2496	–
Mica-based pearlescent pigment	–	–	73.350	73.1350	–	73.3128
Paprika	–	–	73.340	–	–	–
Paprika oleoresin	–	8023-77-6	73.345	–	–	–
Phaffia yeast	–	–	73.355	–	–	–
Potassium sodium copper chlorophyllin	75180	–	–	73.1125	73.2125	–
Phthalocyanine green	74260	1328-53-6	–	–	–	73.3124
Poly(hydroxyethyl methacrylate)-dye copolymers	–	–	–	–	–	73.3121
Pyrogallol	76515	87-66-1	–	73.1375	–	–
Pyrophyllite	44004	8047-76-5	–	73.1400	73.2400	–
Riboflavin	–	83-88-5	73.450	–	–	–
Saffron	75100	42553-65-1 27876-94-4	73.500	–	–	–
Silver	77820	7440-22-4	–	–	73.2500	–
Sodium copper chlorophyllin	75815	28302-36-5	73.125	–	–	–
Tagetes meal & extract	75125	–	73.295	–	–	–
Talc	77019	14807-96-6	–	73.1550	–	–
Toasted cotton seed meal	–	–	73.140	–	–	–
Titanium dioxide	77891	13463-67-7	73.575	73.1575	73.2575	73.3126
Tomato lycopene extract and concentrate			73.585	–	–	–
Turmeric	75300	458-37-7	73.600	–	–	–
Turmeric oleoresin	75300	458-37-7	73.615	–	–	–
Ultramarine blue	77007	57455-37-5	73.50	–	73.2725	–
Ultramarine green	77013	–	–	–	73.2725	–
Ultramarine pink	77007	127-96-9	–	–	73.2725	–
Ultramarine red	77007	127-96-9	–	–	73.2725	–
Ultramarine violet	77007	127-96-9	–	–	73.2725	–
Vegetable juice	–	–	73.260	–	–	–
Vinyl alcohol/methyl methacrylate dye reaction products	–	–	–	–	–	73.3127
Zinc oxide	77947	1314-13-2	–	73.1991	73.2991	–
Luminescent zinc sulfide	–	–	–	–	73.2995	–

[a]Based on 21 CFR 2007. Restrictions may exist limiting the use of some of these colors to specific applications (i.e., external drug use only, etc.). Additionally, there may be quantitative limits for the use of some colors. The specific 21 CFR reference for each color should be reviewed to determine potential restriction status.

Provisionally Listed Color Additives Subject to U.S. Certification[a]

Color	Common Name	Color Index Number	CAS Number	21 CFR References		
				Food	Drug	Cosmetic
FD&C lakes	Lakes	See Individual Color	See Individual Color	82.51	82.51	82.51
D&C lakes	Lakes	See Individual Color	See Individual Color	–	82.1051	82.1051
Ext. D&C lakes	Lakes	See Individual Color	See Individual Color	–	82.2051	82.2051
FD&C blue #1 lake	Brilliant blue FCF	42090:2	68921-42-6	82.101	82.101	82.101
FD&C blue #2 lake	Indigotine	73015:1	16521-38-3	82.102	82.102	82.102
D&C blue #4 lake	Alphazurine FG	42090	6371-85-3	–	82.1104	82.1104
FD&C green #3 lake	Fast green FCF	42053	2353-45-9	82.203	82.203	82.203
D&C green #5 lake	Alizarin cyanine green F	61575	4403-90-1	–	82.1205	82.1205
D&C green #6 lake	Quinizarine green SS	61565	128-80-3	–	82.1206	82.1206
D&C orange #4 lake	Orange II	15510:2	633-96-5	–	82.1254	82.1254
D&C orange #5 lake	Dibromofluorescein	45370:2	596-03-2	–	82.1255	82.1255
D&C orange #10 lake	Diiodofluorescein	45425:2	38577-97-8	–	82.1260	82.1260
D&C orange #11 lake	Erythrosine yellowish Na	45425:2	38577-97-8	–	82.1261	81.1261
FD&C red #4 lake	Ponceau SX	14700	4548-53-2	82.304	82.304	82.304
D&C red #6 lake	Lithol rubin B	15850:2	17852-98-1	–	82.1306	82.1306
D&C red #7 lake	Lithol rubin B Ca	15850:1	5281-04-9	–	82.1307	82.1307
D&C red #17 lake	Toney lake	26100	85-86-9	–	82.1317	82.1317
D&C red #21 lake	Tetrabromofluorescein	45380:3	15086-94-9	–	82.1321	82.1321
D&C red #22 lake	Eosine	45380:3	17372-87-1	–	82.1322	82.1322
D&C red #27 lake	Tetrachlorotetra-Bromofluorescein	45410:2	13473-26-2	–	82.1327	82.1327
D&C red #28 lake	Phloxine B	45410:2	18472-87-02	–	82.1328	82.1328
D&C red #30 lake	Helindone pink CN	73360	2379-74-0	–	82.1330	82.1330
D&C red #31 lake	Brilliant lake red R	15800:1	6371-76-2	–	82.1331	82.1331
D&C red #33 lake	Acid fuchsine	17200	3567-66-6	–	82.1333	82.1333
D&C red #34 lake	Lake bordeaux B	15880:1	6417-83-0	–	82.1334	82.1334
D&C red #36 lake	Flaming red	12085	2814-77-9	–	82.1336	82.1336
D&C violet #2 lake	Alizurol purple SS	60725	81-48-1	–	82.1602	82.1602
FD&C yellow #5 lake	Tartrazine	19140:1	12225-21-7	82.705	82.705	82.705
FD&C yellow #6 lake	Sunset yellow FCF	15985:1	15790-07-5	82.706	82.706	82.706
D&C yellow #7 lake	Fluorescein	45350:1	2321-07-5	–	82.1707	82.1707
Ext. D&C yellow #7 lake	Napthol yellow S	10316	846-70-8	–	82.2707a	82.2707a
D&C yellow #8 lake	Uranine	45350	518-47-8	–	82.1708	82.1708
D&C yellow #10 Lake	Quinoline yellow WS	47005:1	68814-04-0	–	82.1710	82.1710

[a]Based on 21 CFR 2007. Restrictions may exist limiting the use of some of these colors to specific applications (i.e., external drug use only, etc.). Additionally there may be quantitative limits for the use of some colors. The specific 21 CFR reference for each color should be reviewed to determine potential restriction status.

List of Permanently Listed Color Additives Subject to U.S. Certification[a]

Color	Common Name	Color Index Number	CAS Number	21 CFR References			
				Food	Drug	Cosmetic	Medical Devices
D&C black #2	Carbon black	77266	1333-86-4	–	–	74.2052	–
D&C black #3	Bone black	77267	8021-99-6	–	–	74.2053	–
FD&C blue #1	Brilliant blue FCF	42090	2650-18-2	74.101	74.1101	74.2101	–
FD&C blue #2	Indigotine	73015	860-22-0	74.102	74.1102	–	74.3102
D&C blue #4	Alphazurine FG	42090	6371-85-3	–	74.1104	74.2104	–
D&C blue #6	Indigo	73000	482-89-3	–	–	–	74.3106
D&C blue #9	Indanthrene blue	69825	130-20-1	–	74.1109	–	–
D&C brown #1	Resorcin brown	20170	1320-07-6	–	–	74.2151	–
FD&C green #3	Fast green FCF	42053	2353-45-9	74.203	74.1203	74.2203	–
D&C green #5	Alizarin cyanine green F	61570	4403-90-1	–	74.1205	74.2205	–
D&C green #6	Quinizarine green SS	61565	128-80-3	–	74.1206	74.2206	74.3206
D&C green #8	Pyranine concentrated	59040	63-58-69-6	–	74.1208	74.2208	–
Orange B	–	19235	–	74.250	–	–	–
D&C orange #4	Orange II	15510	633-96-5	–	74.1254	74.2254	–
D&C orange #5	Dibromofluorescein	45370:1	596-03-2	–	74.1255	74.2255	
D&C orange #10	Diiodofluorescein	45425:1	38577-97-8	–	74.1260	74.2260	–
D&C orange #11	Erythrosine yellowish Na	45425	38577-97-8	–	74.1261	74.2261	
[Phthalocyaninato (2-)] copper	Copper phthalocyanine	74160	147-14-8	–	–	–	74.3045
FD&C red #3	Erythrosine	45430	16423-68-0	74.303	74.1303	–	–
FD&C red #4	Ponceau SX	14700	4548-53-2	–	74.1304	74.2304	–
D&C red #6	Lithol rubin B	15850	5858-81-1	–	74.1306	74.2306	–
D&C red #7	Lithol rubin B Ca	15850:1	4/9/5281	–	74.1307	74.2307	–
D&C red #17	Toney red	26100	85-86-9	–	74.1317	74.2317	74.3230
D&C red #21	Tetrabromo fluorescein	45380:2	15086-94-9	–	74.1321	74.2321	–
D&C red #22	Eosine	45380	17372-87-1	–	74.1322	74.2322	–
D&C red #27	Tetrachlorotetra-bromofluorescein	45410:1	13473-26-2	–	74.1327	74.2327	–
D&C red #28	Phloxine B	45410	18472-87-2	–	74.1328	74.2328	–
D&C red #30	Helindone pink CN	73360	2379-74-0	–	74.1330	74.2330	–
D&C red #31	Brilliant lake red R	15800:1	6371-76-2	–	74.1331	74.2331	–
D&C red #33	Acid fuchsine	17200	3567-66-6	–	74.1333	74.2333	–
D&C red #34	Lake bordeaux B	15880:1	6417-83-0	–	74.1334	74.2334	–
D&C red #36	Flaming red	12085	2814-77-9	–	74.1336	74.2336	–
D&C red #39	Alba red	13058	6371-55-7	–	74.1339	–	–
FD&C red #40	Allura red AC	16035	25956-17-6	74.340	74.1340	74.2340	–
FD&C red #40 lake	Allura red AC	16035:1	68583-95-9	74.340	74.1340	74.2340	–
Citrus red #2	–	12156	6358-53-8	74.302	–	–	–
D&C violet #2	Alizurol purple SS	60725	81-48-1	–	74.1602	74.2602	74.3602
Ext. D&C violet #2	Alizarin violet	60730	4430-18-6	–	–	74.2602a	–
FD&C yellow #5	Tartrazine	19140	1934-21-0	74.705	74.1705	74.2705	–
FD&C yellow #6	Sunset yellow FCF	15985	2783-94-0	74.706	74.1706	74.2706	–
D&C yellow #7	Fluorescein	45350:1	7/5/2321	–	74.1707	74.2707	–
Ext. D&C yellow #7	Napthol yellow S	10316	846-70-8	–	74.1707a	74.2707a	–
D&C yellow #8	Uranine	45350	518-47-8	–	74.1708	74.2708	–
D&C yellow #10	Quinoline yellow WS	47005	8004-92-0	–	74.1710	74.2710	74.3710
D&C yellow #11	Quinoline yellow SS	47000	8003-22-3	–	74.1711	74.2711	–

[a]Based on 21 CFR 2007. Restrictions may exist limiting the use of some of these colors to specific applications (i.e., external drug use only, etc.). Additionally, there may be quantitative limits for the use of some colors. The specific 21 CFR reference for each color should be reviewed to determine potential restriction status.

Another choice confronting manufacturers is whether to use an aqueous coating or an organic coating system; both have their advantages and disadvantages. Whereas organic coatings provide greater protection against moisture uptake during the coating process (important for moisture-sensitive ingredients) and are easier to apply because of the fast evaporation of solvents, problems encountered with these coatings include environmental control of organic solvents going into the atmosphere, the need to perform solvent residue tests, and the need to have explosion-proof facilities; thus, aqueous coating systems are often preferred.

I. CELLULOSE-BASED

Cellulose acetate phthalate (CAP)
Caution: Check with regulatory authorities about approved states of all dyes before using them.

II. HYDROXYPROPYL METHYL CELLULOSE (METHOCEL, HPMC) AQUEOUS COATINGS

Methocel-based coatings in an aqueous base are the most popular coating options; two methods of making solutions are possible.
If a lake is used, then alcohol is also included (see, for example, Holberry Red).

A. Brite Rose

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
6.00	1	Hydroxypropyl methylcellulose 2910 (15 cps)	60.00
2.00	2	PEG-400 (low color)	20.00
2.00	3	PEG-8000	20.00
0.25	4	FD&C red dye No. 30 lake	2.50
2.00	5	Titanium dioxide (special coating grade)	20.00
QS	6	Deionized purified water	QS to 1 L

Manufacturing Directions

1. Charge 250 mL of water into a suitable container and heat to 60°C to 70°C.
2. With gentle stirring, disperse the HPMC onto the hot water. When the cellulose has wetted, quickly add 250 mL of cold water.
3. Stir until the dispersion is homogenous, although the solution of cellulose may not be complete.
4. Dissolve PEG-8000 in 50 mL of water, then add to step above.
5. Add PEG-400 to basic solution above.
6. Load a suitable size ball jar with the FD&C red dye No. 30 and titanium dioxide.
7. Add sufficient water to cover the pigment and balls.
8. Mill overnight or for 12 hours.
9. Other pigment reduction methods may be used to yield a particle size not greater than 1 μm.
10. Add milled pigments to the base solution from the step above and bring the volume up with cold water.
11. Use within 7 days.

B. Cherry Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00
2.00	2	PEG-400 (low color)	20.00
2.00	3	PEG-8000	20.00
1.80	4	FD&C red dye No. 3 lake	18.00
0.10	5	FD&C red dye No. 2 (Amaranth)	1.00
2.10	6	Titanium dioxide (special coating grade)	21.00
QS	7	Deionized purified water, USP	QS to 1 L

C. Geranium Rose

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00
2.00	2	PEG-400 (low color), NF	20.00
2.00	3	PEG-8000	20.00
0.24	4	FD&C red dye No. 3 lake	2.00
QS	5	Deionized purified water, USP	QS to 1 L

D. Gloss

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
3.33	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	33.33
1.66	2	PEG-400 (low color), NF	16.66
QS	3	Deionized purified water, USP	QS to 1 L

E. Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00
2.00	2	PEG-400 (low color), NF	20.00
2.00	3	PEG-8000	20.00
2.50	4	FD&C red dye No. 3 lake	25.00
0.50	5	Titanium dioxide	5.00
QS	6	Deionized purified water, USP	QS to 1 L

F. Moderate Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00
2.00	2	PEG-400 (low color), NF	20.00
2.00	3	PEG-8000	20.00
0.50	4	FD&C yellow dye No. 3 aluminum lake	5.00
2.50	5	Ponceau red dye 4R lake	25.00
1.00	6	Titanium dioxide (special coating grade), USP	10.00
QS	7	Deionized purified water, USP	QS to 1 L

G. Clear

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00
0.10	2	Sorbic acid	1.00
2.00	3	Alcohol (200 proof), SD 3A	20.00 mL
2.00	4	PEG-400 (low color)[a]	20.00
2.00	5	PEG-8000 (optional)	20.00
QS	6	Deionized purified water	QS to 1 L

[a]Increase amount to 6.00 if item 5 is not used.

Manufacturing Directions

1. Charge approximately 500 mL of water into a suitable vessel.
2. Heat water to 65°C to 70°C.
3. Add the PEG-8000 to the hot water and dissolve (if used).
4. While maintaining gentle agitation, sprinkle the HPMC onto the surface of the hot water solution.
5. Position stirring head to avoid excessive entrainment of air.
6. When the cellulose has been dispersed, add the PEG-400.
7. Continue to stir until dispersion is homogeneous, although solution of cellulose may not be complete.
8. Stop stirring and allow solution to stand until entrained air is removed.
9. Dissolve sorbic acid in alcohol and ensure that the solution is complete.
10. When the solution from the step above is clear, add 250 mL of cold water, mix well, and add sorbic acid solution.
11. Mix, then bring up to volume with cold water.
12. Store coating solution in well-filled, well-sealed containers.
13. Use within 3 months.

H. Green

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00
0.10	2	Sorbic acid	1.00
2.00 v/v	3	Alcohol (200 proof), SD 3A	20.00 mL
2.00	4	PEG-400 (low color)	20.00
2.00	5	PEG-8000	20.00
1.00	6	Titanium dioxide (coating grade)	10.00
0.01	7	Dye yellow E104 aluminum lake	0.10
0.0032	8	FD&C blue dye No. 1 lake (11–13%)	0.032
QS	9	Deionized purified water	QS to 1 L

I. Holberry Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00
0.10	2	Sorbic acid	1.00
2.00 v/v	3	Alcohol (200 proof), SD 3A	20.00 mL
2.00	4	PEG-400 (low color)	20.00
2.00	5	PEG-8000	20.00
1.00	6	Titanium dioxide (coating grade)	10.00
1.50	7	FD&C red dye No. 40 lake (29%)	15.00
0.50	8	FD&C blue dye No. 3 lake	5.00
QS	9	Deionized purified water	QS to 1 L

J. Sun Orange

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
6.00	1	Hydroxypropyl methyl cellulose 2910 (15 cps)	60.00
0.17	2	Sorbic acid, NF	1.70
2.00 v/v	3	Alcohol (200 proof), SD 3A	20.00 mL
2.00	4	PEG-400 (low color), NF	20.00
2.00	5	PEG-8000	20.00
2.38	6	Titanium dioxide (coating grade), USP	23.80
2.47	7	FD&C yellow dye No. 5	24.70
0.16	8	FD&C yellow dye No. 6	1.60
QS	9	Deionized purified water, USP	QS to 1 L

K. Opadry Yellow

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Qty/1000 Caplets (g)
10.00	1	Hydroxypropyl methyl cellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	PEG-4000	1.60
1.20	4	Titanium dioxide	1.20
0.30	5	FD&C blue dye No. 1 lake	0.30
0.50	6	FD&C blue dye No. 2 (dispersed)	0.50
0.75	7	Opadry-OY-S 29019 (clear)	0.75
QS	8	Purified water	225.00

Manufacturing Directions

1. The formula for this coating solution is prepared to obtain a weight gain of 10 mg per caplet (around 600 mg in weight).
2. Disperse item 1 in 175 g of purified water (70–80°C) while stirring.
3. Hold overnight for complete dispersion.
4. Disperse items 2 and 3 in 25 g of purified water (25–30°C).
5. Hold overnight for complete hydration.
6. Add mixture from previous step.
7. Homogenize using a homogenizer (gap setting: 1.5 mm).
8. Homogenize items 4, 5, and 6 in 50 g of hypromellose dispersion from step above twice, using a homogenizer (gap setting: 1.5 mm).
9. Pass the dispersion twice through a 90-μm sieve.
10. (*Note*: This is a critical step. Follow instructions closely to prevent foreign particles and spots.) Preparation of polishing solution: Disperse item 7 in 25 g of purified water with slow stirring.
11. Make a vortex by slow stirring and add the powder in such a way as to avoid foam formation.

L. Opadry Yellow

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
10.00	1	Hydroxypropyl methyl cellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	PEG-4000	1.60
1.34	4	Titanium dioxide	1.34
0.046	5	Sunset yellow E110, FCF	0.046
1.34	6	FD&C yellow dye No. 10 lake	1.34
0.75	7	Opadry-OY-S 29019 (clear)	0.75
QS	8	Purified water	225.00

M. Opadry Red

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Qty/1000 Caplets (g)
10.00	1	Hydroxypropyl methyl cellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	PEG-4000	1.60
1.34	4	Titanium dioxide	1.34
0.15	5	Iron oxide red	0.15
0.75	6	Opadry-OY-S (clear)	0.75
QS	7	Purified water	225.00

N. Opadry Green

Bill of Materials			
Scale (mg/caplet)	Item	Material Name	Qty/1000 Caplets (g)
10.00	1	Hydroxypropyl methyl cellulose (hypromellose)	10.00
4.00	2	Talc (fine powder)	4.00
1.60	3	PEG-4000	1.60
2.125	4	Titanium dioxide	2.125
0.053	5	FD&C blue dye No. 1 lake	0.053
0.15	6	FD&C yellow dye No. 10 lake	0.15
0.75	7	Opadry-OY-S (clear)	0.75
QS	8	Purified water	225.00

Manufacturing Directions

1. Disperse item 1 in 175 g of purified water (70–80°C) while stirring.
2. Keep overnight for complete dispersion.
3. Disperse items 2 and 3 in 25 g of purified water (25–30°C).
4. Keep overnight for complete hydration.
5. Add together and homogenize using homogenizer (gap setting: 1.5 mm).
6. Homogenize items 4, 5, and 6 in 50 g of hypromellose dispersion twice, using homogenizer (gap setting: 1.5 mm).
7. Pass the dispersion twice through a 90-μm sieve.
8. (*Note*: This is a critical step. Follow instructions closely to prevent foreign particles and spots.) Disperse item 7 in 25 g of purified water while stirring slowly.
9. Make a vortex by slow stirring and add the powder in such a way as to avoid foam formation.
10. Follow the parameters for coating in Accela Cota.
11. Stir the dispersion at slow speed (6–10 rpm) continuously.
12. Spray the polishing solution under the same conditions as above, adjusting the spray rate to 180 g/min.
13. Check the caplet surface every 5 minutes for sticking.
14. If sticking tends to appear, stop the coating immediately.
15. When the spraying is over, roll the tablets in a pan for 10 minutes with cold air blowing onto the caplets.
16. Unload the film-coated caplets into stainless steel containers lined with polyethylene bags.
17. Appearance is a light green, film-coated caplet that is smooth, with no sticking or chipping on the caplet surface.
18. Weight gain per caplet is NLT 10 mg/tablet.

Caplet load	620 g
Pan speed	4 rpm
Drying air temperature	70–75°C
Exhaust temperature	50–55°C
Fluid pressure	15–20 psi
Valve on spray gun	One revolution open
Atomizing pressure	55 psi
Nozzle orifice	1 mm
Nozzle distance to bed	250–280 mm
Difference of air pressure	−1.0 to −1.5 cm
Spray rate	200–225 g/min
Coating time	3.0–3.5 h

O. White Coating

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
22.75	1	Hypromellose	22.75
4.54	2	Polyethylene glycol	4.54
12.50	3	Talc (fine powder)	12.50
10.00	4	Titanium dioxide	10.00
1.30	5	FD&C yellow No. 10 lake	1.30
–	6	Purified water	~24.00
–	7	Ethanol (95%)	~21.00

III. HPMC OPAQUE ORGANIC COATING

A. Brite Green

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
1.00	1	Titanium dioxide	10.00
50.00 v/v	2	Alcohol (200 proof), SD 3A	~397.00
1.69	3	PEG-400 (low color), NF	16.90
0.02	4	FD&C yellow dye No. 5	0.20
0.0068	5	FD&C blue dye No. 1	0.068
4.00	6	Hydroxypropyl methyl cellulose 2910 (15 cps)	40.00
QS	7	Methylene chloride	~625.00

Manufacturing Directions

1. Charge titanium dioxide and QS with alcohol into a ball mill.
2. Mill the material for 16 hours.
3. Charge 465 mL alcohol into a suitable mixing tank.
4. Start agitation.
5. Slowly add PEG-400 to mixing tank.
6. Mix for 5 minutes.
7. Add FD&C yellow dye to the mixing tank with continued agitation.
8. Rinse bottle with alcohol tapped from mixing tank.
9. Return rinse to mixing tank.
10. Add FD&C blue dye to the mixing tank and rinse.
11. Mix for 2 hours.
12. Tap approximately 10 mL of solution from mixing tank after 0.5, 1, and 1.5 hours of mixing.
13. Put solution back into mixing tank. (*Note*: Tapping solution ensures that dye is not tapped into lower valve and/or pipeline.) Rinse the ball mill with two rinses of 11.6 mL alcohol.
14. Reseal the ball mill and allow it to run 2 to 5 minutes between rinses.
15. Empty content of the ball mill and rinses into mixing tank.
16. Slow sprinkle HPMC into mixing tank with constant agitation.
17. Agitate for an additional 15 minutes. (*Note*: Prevent the development of lumps by slowly sprinkling HPMC into the alcohol.) After mixing for 10 minutes, tap approximately 10 mL from the mixing tank and put back into tank to recirculate.
18. Add sufficient methylene chloride (approximately 474 mL) to bring up to volume.
19. Continue agitation for 2 hours.
20. After 0.5, 1, and 1.5 hours, tap approximately 10 mL of solution from mixing tank and put back into mixing tank to recirculate.
21. (*Note*: No residue should be present in the solution when tapped at 1.5 hours; if some is present, then continue agitation and tap every 15 minutes until no residue is observed.) (*Caution*: Avoid contact with methylene chloride and vapors. They may have toxic effects when swallowed or inhaled.) (*Note*: Nitrogen pressure may be used to assist bottle filling.) Strain mixing-tank contents through two-ply cheesecloth, or similar, into suitable approved containers (one-half the total number of bottles). (*Note*: Lumps may obstruct spray nozzle.)

B. Red Mahogany

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
0.40	1	Titanium dioxide	4.00
45.00 v/v	2	Alcohol (200 proof), SD 3A	~375.30
0.40	3	Vanillin (crystals)	4.00
1.00	4	Propylene glycol	10.00
1.50	5	FD&C red dye No. 40 lake (29%)	15.00
1.00	6	Dye brown lake blend	10.00
4.00	7	Hydroxypropyl methyl cellulose 2910 (15 cps)	40.00
QS	8	Methylene chloride	~530.40

C. Sun Orange

Bill of Materials			
Scale (%)	Item	Material Name	Qty/L (g)
3.00 (w/v)	1	Titanium dioxide	30.00
50.00 (v/v)	2	Alcohol (200 proof), SD 3A	~397.00
2.11 (w/v)	3	Propylene glycol	21.10
3.11 (w/v)	4	FD&C yellow dye No. 5	31.10
0.20 (w/v)	5	FD&C yellow dye No. 6	2.00
4.00 (w/v)	6	Hydroxypropyl methyl cellulose 2910 (15 cps)	40.00
QS	7	Methylene chloride	~625.00

D. Dark Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
1.00	1	Titanium dioxide	10.00
20.00 v/v	2	Alcohol (200 proof), SD 3A	~200.00 mL
2.00	3	PEG-400 (low color)	20.00
0.02	4	Ponceau 4R dye (red)	20.00
0.0068	5	FD&C blue dye No. 1	0.068
2.95	6	Hydroxypropyl methyl cellulose 2910 (15 cps)	29.50
QS	7	Methylene chloride	QS to 1 L

E. Deep Yellow

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
2.00	1	Titanium dioxide	20.00
50.00	2	Alcohol (200 proof), SD 3A	~397.00
2.00	3	PEG-400 (low color)	20.00
2.00	4	FD&C yellow dye No. 5 lake	20.00
2.95	5	Hydroxypropyl methyl cellulose 2910 (15 cps)	29.50
QS	6	Methylene chloride	QS to 1 L

F. Pale Yellow

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
1.50	1	Titanium dioxide	15.00
50.00	2	Alcohol (200 proof), SD 3A	~397.00
2.00	3	PEG-400 (low color), NF	20.00
0.50	4	FD&C yellow dye No. 10 aluminum lake (14–17%)	5.00
2.95	5	Hydroxypropyl methyl cellulose 2910 (15 cps)	29.50
QS	6	Methylene chloride	QS to 1 L

G. Scarlet Red

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
2.00	1	Titanium dioxide	20.00
20.00	2	Alcohol (200 proof), SD 3A	~200.00
2.00	3	PEG-400 (low color), NF	20.00
2.00	4	FD&C yellow dye No. 7 lake	20.00
1.00	5	FD&C yellow dye No. 5 lake	10.00
2.95	6	Hydroxypropyl methyl cellulose 2910 (15 cps)	29.50
QS	7	Methylene chloride	QS to 1 L

IV. HPMC/HPC (KLUCEL®) COATING

A. White

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
2.00	1	Titanium dioxide	20.00
0.50	2	Hydroxypropyl cellulose, NC	5.00
45.00	3	Alcohol (200 proof), SD 3A	~450.00
2.00	4	Propylene glycol	20.00
4.50	5	Hydroxypropyl methyl cellulose 2910 (15 cps)	45.00
QS	6	Methylene chloride	QS to 1 L

Manufacturing Directions

1. Place the titanium dioxide and sufficient methylene chloride into suitably sized ball jars to cover the balls.
2. Mill for not less than 16 hours.
3. While mixing the alcohol, add and disperse the HPMC, HPC, and propylene glycol, followed by 250 mL of methylene chloride.
4. Continue mixing until the solution is complete.
5. While mixing the solution from the second step, empty into it the contents of the ball jar, rinse the balls and jar with methylene chloride, add the rinsing to the batch and mix.
6. Bring the batch up to volume with methylene chloride and mix well until homogeneous.
7. Strain the batch through muslin into suitable approved bottles.
8. Seal and store.

V. HPMC/EC COATING

A. Reddish Orange Opaque

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
1.16	1	Titanium dioxide	11.60
45.00	2	Alcohol (dehydrated; 200 proof)	~450.00
0.20	3	Vanillin (crystals), NF	2.00
0.50	4	Albumen powder (white hen egg)	5.00
2.00	5	PEG-400 (low color), NF	20.00
1.30	6	FD&C red dye No. 3	13.00
0.05	7	FD&C red dye No. 2 (Amaranth), USP	0.50
0.20	8	FD&C yellow dye No. 6	2.00
2.95	9	Hydroxypropyl methyl cellulose 2910, USP (15 cps)	29.50
QS	10	Methylene chloride	QS to 1 L

Manufacturing Directions

1. Load the vanillin, albumen, titanium dioxide, FD&C red dyes No. 2 and 3, and FD&C yellow dye No. 6 into a suitable size ball jar.
2. Add sufficient methylene chloride to cover the pigments and balls.
3. Mill for 24 hours.
4. Measure 400 mL of alcohol into a suitable stainless steel container.
5. Sprinkle the HPMC/EC onto the surface of the alcohol while stirring vigorously.
6. When the HPMC/EC has been wetted, quickly add 300 mL methylene chloride while stirring vigorously.
7. Add the PEG-400 to the solution from above and rinse the container with the remaining alcohol. Add the rinsings to the bulk.
8. Empty the contents of the ball jar from the first step into the coating solution from previous step, while stirring vigorously.
9. Rinse the ball jar with methylene chloride. Add the rinsings to the bulk.
10. Bring up to volume with methylene chloride.

B. Subcoating Solution

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
45.00	1	Alcohol (190 proof), USP	450.00 mL
0.50	2	Hydroxypropyl cellulose, NF	5.00
4.50	3	Hydroxypropyl methyl cellulose 2910, USP (15 cps)	45.00
QS	4	Methylene chloride	QS to 1 L

VI. HYDROXYMETHYL CELLULOSE/HYDROXY CELLULOSE COATING

A. Blue

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
1.00	1	Hydroxy methyl cellulose	10.00
1.00	2	Hydroxy ethyl cellulose (15 cps)	10.00
0.312	3	Titanium dioxide	3.21
1.00	4	FD&C blue dye No. 1 lake (12%)	10.00
0.375	5	Castor oil (odorless)	3.75
0.375	6	Sorbitan monooleate	3.75
50.00	7	Alcohol (200 proof), SD 3A	500.00 mL
QS	8	Methylene chloride	QS to 1 L

Manufacturing Directions

1. Premix HPMC and HPC and add to 440 mL alcohol with rapid agitation.
2. Mix for not less than 1 hour.
3. Charge FD&C blue dye and titanium dioxide into a ball mill.
4. Cover the balls and materials with 60 mL of alcohol and mill for 16 hours.
5. Add contents to mixing tank and add the castor oil and sorbitan monooleate.
6. Rinse the ball mill with methylene chloride and add the rinsings to the mixing tank.
7. Bring up to a volume of 1 L with methylene chloride and mix for at least 1 hour.

B. Clear (50:50)

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
1.00	1	Hydroxy methyl cellulose	10.00
1.00	2	Hydroxy ethyl cellulose, USP (15 cps)	10.00
0.375	3	Castor oil (odorless)	3.75
50.00	4	Alcohol (200 proof), SD 3A	500.00 mL
QS	5	Methylene chloride	QS to 1 L

VII. HYDROXYMETHYL CELLULOSE/EC COATING

A. Clear

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
1.00	1	Hydroxy methyl cellulose	10.00
1.00	2	Hydroxy ethyl cellulose, USP (15 cps)	10.00
0.375	3	Castor oil (odorless), USP	3.75
50.00	4	Alcohol (200 proof), SD 3A	500.00 mL
QS	5	Methylene chloride	QS to 1 L

Manufacturing Directions

1. Charge all the alcohol into mixing tank.
2. Turn on mixer to mixing speed. Maintain mixing speed throughout preparation of coating solution.
3. Charge HPMC and EC into the mixing tank.
4. Let mix for 1 hour.
5. Add methylene chloride (approximately 500 mL) to bring the final volume up to 1 L.
6. Mix for 1 hour.
7. Solution need not be agitated at all times.
8. Keep tank tightly closed at all times.
9. Rubber stopper on bottles must be protected from methylene chloride with a polyethylene layer.

VIII. POLYVINYLPYRROLIDONE COATINGS

A. Subcoating

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
20.00	1	Povidone USP K-29–32[a]	200.00
80.00	2	Alcohol (200 proof), SD 3A	800 mL

[a]May be substituted with Kollidon VA 64 (PVP/vinyl acetate copolymer; 10%) and item 2 can be replaced with isopropyl alcohol.

Manufacturing Directions

1. Spray the solution onto the warm tablet cores (30–40°C) for a few minutes before continuing with the main aqueous coating procedure.
2. The amount of 0.4 mg/cm^2 tablet surface is sufficient for good subcoating protection.
3. No plasticizer is needed in this formulation due to the plasticity of Kollidon VA 64.

B. Kollidon VA 64 (PVP/Vinyl Acetate Copolymer, BASF)

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
5.00	1	Kollidon VA 64	50.00
4.00	2	Lutrol E 6000	40.00
0.50	3	Glycerin, USP	5.00
1.50	4	Iron oxide or lake	15.00
3.00	5	Titanium dioxide	30.00
5.00	6	Talc	50.00
QS	7	Purified water	QS to 1 L

Manufacturing Directions

Pass the suspension through a disk mill prior to use and spray under the following conditions.

Sugar-Coating Pan

Spray gun	Walther WAXV with 1-mm nozzle
Spraying time	3 s
Pause	0.5 s
Dry air	6 s
Pause	3 s

Accela Cota (Continuous Spraying)

Spray gun	Walther WAXV with 0.8-mm nozzle
Temperature at inlet	45°C
Temperature at outlet	38°C
Spraying pressure	2 bar
Spraying time	~50 min

If the film is too sticky, a certain part of Kollidon should be substituted by HPMC or sucrose.

C. Kollidon VA 64 and Polyvinyl Alcohol

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
5.0	1	Kollidon VA 64	50.00
4.00	2	Lutrol E 6000	40.00
6.00	3	Polyvinyl alcohol	76.00
68.00	4	Purified water	680.00
0.50	5	Glycerin, USP	5.00
1.50	6	Iron oxide or lake	18.00
3.00	7	Titanium dioxide	37.00
5.00	8	Talc	50.00
QS	9	Purified water	168.00

Manufacturing Directions

1. Dissolve items 1 to 3 in item 4, add the polyvinyl alcohol, and stir 45 minutes, avoiding the formation of too many air bubbles.
2. Suspend the pigments and talc in 168 mL of water and pass this mixture through a colloid mill.
3. To obtain the final coating suspension, mix this solution with the first solution.
4. Suggested conditions for coating using Accela Cota are given below.

Tablet core loading	5.0 kg
Amount of coating suspension	1.26 kg
Inlet air temperature	59°C
Outlet air temperature	46°C
Nozzle	1.0 mm
Rotation speed of the pan	15 rpm
Spraying pressure	2.0 bar
Spraying rate	15 g/min
Spraying time (continuously)	83 min
Final drying	5 min
Quantity of film former applied	$\sim$3 mg/cm^2

D. Kollidon 30 and Shellac

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
2.00	1	Kollidon 25 or 30	20.00
17.70	2	Shellac	177.00
18.50	3	Titanium dioxide	185.00
6.50	4	Talc	65.00
1.50	5	Cetyl alcohol	15.00
3.00	6	Sorbitan trioleate	30.00
5.00	7	Color lake	50.00
QS	8	Isopropanol or alcohol	458.00

Manufacturing Directions

1. Dissolve shellac and sorbitan trioleate in the warm solvent and then the Kollidon and cetyl alcohol.
2. Add titanium dioxide, talc, and the lake and mix in the colloid mill.
3. Application of the coating suspension: approximately 50 g of suspension is applied to 1 kg of tablet cores in a conventional coating pan or in an Accela-Cota pan (1–2 mg film formers/cm^2).

E. Kollidon VA 64 and HPMC

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
4.00	1	Kollidon VA 64	53.00
1.00	2	Lutrol E 6000	12.00
6.00	3	Hydroxypropyl methyl cellulose	79.00
1.50	4	Iron oxide or lake	18.00
3.00	5	Titanium dioxide	37.00
4.00	6	Talc	50.00
QS	7	Purified water	QS to 1 kg

Manufacturing Directions

1. Dissolve Lutrol and Kollidon® in a portion of the water, add HPMC, and stir 45 minutes, avoiding the formation of too many air bubbles.
2. Suspend the pigments and talc in a portion of the water and pass this mixture through a colloid mill.
3. Mix the two portions.
4. Conditions for coating using Acela-Cota are given below.

Tablet core loading	5.0 kg
Core size	9-mm biconvex
Amount of coating suspension applied	1.2 kg
Inlet air temperature	60°C
Outlet air temperature	40°C
Nozzle	1.0 mm
Rotation speed of the pan	12 rpm
Spraying pressure	2.0 bar
Spraying rate	50 g/min
Spraying time (continuously)	34 min
Final drying	2 min
Drying after spraying	5 min at 60°C
Quantity of film former applied	3.14 mg/cm^2

F. Povidone, EC, and Talc

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
7.50	1	Povidone (PVP K-29–32), USP	75.00
4.25	2	Ethyl cellulose, NF	42.50
0.50	3	PEG-400, NF	5.00
5.00	4	Talc	50.00
45.00	5	Alcohol (200 proof), SD 3A	450.00 mL
QS	6	Methylene chloride, NF	QS to 1 L

Manufacturing Directions

1. Dissolve Povidone in alcohol and then add PEG-400.
2. Add EC to this solution.
3. Mix until evenly dispersed, then bring up to volume with methylene chloride with constant stirring.
4. Add the talc to this solution and stir to ensure distribution.
5. Solution should be freshly prepared and used within 10 days of manufacture.
6. Thoroughly disperse talc before use.
7. If batch is more than 200 L, do not add talc.
8. If coating solution is manufactured without talc, then solution should be used within 4 weeks.

IX. CELLULOSE ACETATE PHTHALATE AND CARBOWAX COATINGS

A. Brite Green

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/L (g)
6.00	1	Cellulose acetate phthalate (carbowax)	60.00
1.86	2	Propylene glycol	18.65
0.66	3	Sorbitan monooleate (Span 80)	6.00
0.12	4	Castor oil (odorless)	1.25
0.85	5	FD&C blue dye No.1	0.85
3.11	6	FD&C yellow dye No. 5 lake	31.10
5.33	7	Titanium dioxide	53.30
21.58	8	Methylene chloride	215.00
QS	9	Acetone	QS to 1 L

Manufacturing Directions

1. Place the methylene chloride in a suitably sized mixing tank.
2. While stirring, add the propylene glycol, Span 80, and castor oil.
3. To this mixture, add cellulose acetate phthalate and allow to soak overnight.
4. Load the dyes and titanium dioxide into a suitable ball jar.
5. Add sufficient acetone to cover the raw materials and balls.
6. Ball mill overnight.
7. Melt the Carbowax with a portion of the acetone using gentle heat.
8. Add the melted Carbowax to the mixture from the second step.
9. Empty contents of ball jar mill to this mixture.
10. Rinse the ball jar with acetone and add rinsings.
11. Add acetone to volume and mix well.
12. If necessary, strain solution through gauge before storage or use.

B. Cherry Red

In the formulation given above, use, FD&C red dye No. 3 (6.800 g), FD&C red dye No. 2 (Amaranth, USP; 1.00 g), and FD&C yellow dye (5.40 g).

C. Clear

Delete dyes.

D. Orange

Use FD&C yellow dye No. 6 (4.00 g) and FD&C yellow dye No. 5 (12.00 g).

X. SUGARCOATINGS

A. Basic

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
4.00	1	Kollidon VA 64	40.00
16.00	2	Sucrose	160.00
2.40	3	Titanium dioxide	24.00
1.20	4	Color lake	12.00
3.20	5	Lutrol E 4000	32.00
4.00	6	Talc	40.00
QS	7	Purified water	QS to 1 kg

Manufacturing Directions

1. Dissolve the sucrose, Kollidon, and Lutrol in the water and suspend the other components.
2. Pass through a colloid mill.
3. Use the following conditions for use in Accela-Cota.

Tablet core loading	5.00 kg
Amount of coating suspension	1.20 kg
Inlet air temperature	45°C
Outlet air temperature	35°C
Nozzle	0.80 mm
Rotation speed of the pan	15 rpm
Spraying pressure	2.0 bar
Spraying time (continuously)	50 min
Quantity of film former applied	4.00 mg/cm^2

B. Automatic

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
4.00	1	Kollidon 30	40.00
38.00	2	Sucrose	380.00
4.50	3	Titanium dioxide	45.00
QS	4	Color lake	QS
4.50	5	Calcium carbonate	45.00
14.50	6	Talc	145.00
QS	7	Purified water	QS to 1 kg

Manufacturing Directions

1. Dissolve the sucrose in the hot water, then mix with glycerol.
2. Dissolve Kollidon and suspend the other components.
3. Coating Procedure: Coat 4 kg of tablet cores with a weight of 420 mg each by spraying with 2.5 kg of the above suspension in a conventional coating pan under the following conditions:

Spray phase	5 s
Interval	10 min
Drying phase (warm air)	10 min
Total coating time	16 h

C. Manual, White

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
0.33	1	Kollidon 30	3.36
0.29	2	Carmellose sodium	2.92
0.21	3	Aerosil 200	2.14
QS	4	Color lake (white)	QS
1.62	5	Talc	16.20
0.10	6	Polysorbate or Cremophor RH40	1.00
1.40	7	Titanium dioxide	14.00
62.70	8	Sucrose	627.00
33.40	9	Purified water	334.00

Manufacturing Directions

1. Dissolve Kollidon, polysorbate or Cremophor, and sucrose in the water and suspend the other components in this solution.
2. Mix in a colloid mill.
3. Start with formulation without the color and then apply the color coat.
4. The polishing can be done by means of a solution of beeswax or PEG-6000.

XI. ENTERIC COATINGS

A. Kollicoat® and Kollidon Enteric Film Coating

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
0.50	1	Titanium dioxide	5.00
2.00	2	Talc	20.00
0.50	3	Iron oxide	5.00
0.50	4	Kollidon 25 or 30	5.00
50.00	5	Kollicoat® MAE 30 DP (methacrylic acid/ethyl acrylate copolymer, 1:1)	500.00
1.50	6	Triethyl citrate	15.00
QS	7	Purified water	QS to 1 kg

Manufacturing Directions/Conditions

Tablet core loading	5 kg
Core size	9-mm biconvex
Quantity of suspension applied	1890 g
Quantity of solids/cm^2	9 mg
Quantity of film-forming agent/cm^2	6 mg
Speed of the coating pan	12 rpm
Spray nozzle	0.8 mm
Spraying pressure	2.0 bar
Type of spraying	Continuous
Inlet air temperature	50°C
Outlet air temperature	~30°C
Spraying time	~60 min
Spraying rate	~30 g/min

XII. EUDRAGIT ENTERIC AQUEOUS

A. Brick Red

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
46.667	1	Distilled purified water	466.667
1.519	2	Talc (powder)	15.198
0.798	3	Titanium dioxide (special coating grade)	7.983
1.55	4	Iron oxide, red	15.50
0.426	5	Polysorbate 80	4.262
0.015	6	Dimethyl polysiloxane emulsion (30%)	0.155
47.60	7	Eudragit; use Eudragit L 30D-55	476.00
1.426	8	Triethyl citrate (Eudraflex®)	14.259

Manufacturing Directions

1. Weigh the quantity of water needed.
2. Put approximately 21.5% of the total quantity of water in a suitable mixing container.
3. Add the talc powder and stir vigorously until well suspended (approximately 20 minutes).
4. Add the following to this suspension and mix thoroughly: titanium dioxide, iron oxide, Tween 80, dimethyl polysiloxane emulsion (30%).
5. (*Note*: The pigments may require homogenizing with colloid, corundum disc mill, or ball mill.) Put the Eudragit in a suitable mixing vessel and add the following with continuous mixing: homogenized pigment mixture, Eudraflex (i.e., triethyl citrate), and remaining quantity of water.
6. *Note*: When PEG-8000 is used as a plasticizer, it should be incorporated as a 10% aqueous solution.

B. Yellow

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
46.66	1	Distilled purified water	466.66
1.25	2	Talc (powder)	12.57
0.77	3	Titanium dioxide (special coating grade)	7.79
1.83	4	FD&C yellow dye No. 10 aluminum lake (14–17%)	18.36
0.42	5	Polysorbate 80	4.27
0.01	6	Dimethyl polysiloxane emulsion (30%)	0.12
47.6	7	Eudragit; use methacrylic acid copolymer, NF (Eudragit L 30D-55)	476.00
1.42	8	Triethyl citrate (Eudraflex®)	14.21

C. Brown

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
46.66	1	Distilled purified water	466.66
0.47	2	Titanium dioxide (special grade coating), USP	4.76
0.85	3	Iron oxide, black	8.53
2.26	4	Iron oxide, red	22.61
0.25	5	Iron oxide, yellow	2.57
0.42	6	Polysorbate 80	4.26
0.01	7	Dimethyl polysiloxane emulsion	0.09
47.63	8	Eudragit; use Eudragit L 30D-55	476.33
1.42	9	Triethyl citrate (Eudraflex®)	14.28

D. Dark Orange

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
46.66	1	Distilled purified water	466.66
2.51	2	Talc (powder)	25.18
0.39	3	Titanium dioxide (special coating grade)	3.92
0.93	4	FD&C yellow dye No. 6 aluminum lake	9.32
0.42	5	Polysorbate 80	4.29
0.01	6	Dimethyl polysiloxane emulsion (30%)	0.13
47.63	7	Eudragit; use Eudragit L 30D-55	476.33
1.42	8	Triethyl citrate (Eudraflex®)	14.28

E. Orange

Bill of Materials			
Scale (%, w/w)	Item	Material Name	Qty/kg (g)
46.66	1	Distilled purified water	466.66
2.60	2	Talc (powder)	26.00
0.78	3	Titanium dioxide (special coating grade)	7.84
0.46	4	FD&C yellow dye No. 6 aluminum lake	4.66
0.42	5	Polysorbate 80	4.27
0.01	6	Dimethyl polysiloxane emulsion (30%)	0.11
47.61	7	Eudragit; use Eudragit L 30D-55	476.16
1.42	8	Triethyl citrate (Eudraflex®)	14.29

F. Dispersed Orange

Bill of Materials			
Scale (mg/tablet)	Item	Material Name	Qty/1000 Tablets (g)
0.92	1	Opagloss NA 7150	0.92
7.07	2	Methacrylic acid copolymer (Eudragit L 100-55)	7.07
0.09	3	Sodium hydroxide pellets (caustic soda)	0.09
0.73	4	PEG-6000	0.73
2.50	5	Talc (fine powder)	2.50
0.10	6	Simethicone emulsion 30% (simethicone antifoam M30)	0.10
0.27	7	Povidone (PVP K-25)	0.27
50.00	8	Sucrose	50.00
0.54	9	Povidone (PVP K-25)	0.54
0.36	10	Titanium dioxide	0.36
0.36	11	FD&C yellow dye No. 10 lake	0.36
0.04	12	Dispersed orange[a]	0.04
1.07	13	Sucrose	1.07
0.38	14	Polishing emulsion	0.38
–	15	Purified water	65.41

[a] Dispersed orange: This material is the aluminum lake of sunset yellow FCF (E110).

XIII. HPMCP ENTERIC COATING

A. Clear Enteric

Bill of Materials			
Scale (%)	Item	Material Name	Qty/kg
20.00 (v/v)	1	Acetone	200.00 mL
10.00 (v/v)	2	Purified water	100.00 mL
4.00 (w/v)	3	Hydroxypropyl methyl cellulose	40.00 g
0.30 (w/v)	4	Vanillin (crystals)	3.00 g
0.40 (w/v)	5	Acetylated monoglycerides	4.00 g
QS	6	Alcohol (200 proof), SD 3A	QS to 1 L

Manufacturing Directions

1. Charge acetone, purified water, and 470 mL of alcohol into a suitable mixing tank.
2. Add the HPMCP, vanillin crystals (if used), and the distilled acetylated monoglycerides.
3. Mix until a clear solution is obtained.
4. Bring up to 1 L with alcohol and record volume used.
5. Mix for 1 hour.

B. Orchid Pink Opaque

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/kg
20.00 (v/v)	1	Acetone	200.00 mL
10.00 (v/v)	2	Purified water	100.00 mL
8.00	3	Hydroxypropyl methylcellulose phthalate	80.00 g
0.80	4	Diacetylated monoglycerides	8.00 g
0.06	5	Dye red D&C No. 30 lake	0.60 g
0.006	6	FD&C blue dye No. 2 aluminum lake (14%)	0.06 g
0.70	7	Titanium dioxide	7.00 g
QS	8	Alcohol (200 proof), SD 3A	1

C. Light Apricot Orange

Bill of Materials			
Scale (%, w/v)	Item	Material Name	Qty/kg
20.00 (v/v)	1	Acetone	200.00 mL
10.00 (v/v)	2	Purified water	100.00 mL
8.00	3	Hydroxypropyl methyl cellulose phthalate	80.00 g
0.80	4	Diacetylated monoglycerides	8.00 g
0.10	5	FD&C yellow dye No. 10 aluminum lake (14–17%)	1.00 g
0.06	6	FD&C red dye No. 3 aluminum lake (14%)	0.60 g
0.70	7	Titanium dioxide	7.00 g
QS	8	Alcohol (200 proof), SD 3A	To 1 kg

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Pharmaceutical Science

about the book...

Over-the-Counter products comprise a special category of healthcare products. While these formulations have much in common with their prescription counterparts, they are presented in this series separately because of their development approach taken, labeling considerations required, and support available from suppliers of ingredients in designing these products.

Highlights from ***Over-the-Counter Products, Volume Five*** include:

- solids, liquids, and suspensions
- practical advice on how to bring manufacturing practices into compliance with regulatory requirements
- cGMP considerations in great detail
- a large number of formulations of coatings of solid dosage forms

about the author...

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VOLUME SIX

Second Edition

Handbook of Pharmaceutical Manufacturing Formulations

Sterile Products

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Pharmaceutical Scientist, Inc.
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Handbook of Pharmaceutical Manufacturing Formulations Second Edition

Volume Series

Sarfaraz K. Niazi

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To Professor Shamsuz Zoha

Preface to the Series—Second Edition

The science and the art of pharmaceutical formulation keeps evolving as new materials, methods, and machines become readily available to produce more reliable, stable, and release-controlled formulations. At the same time, globalization of sourcing of raw and finished pharmaceuticals brings challenges to regulatory authorities and results in more frequent revisions to the current good manufacturing practices, regulatory approval dossier requirements, and the growing need for cost optimization. Since the publication of the first edition of this book, a lot has changed in all of these areas of importance to pharmaceutical manufacturers. The second edition builds on the dynamic nature of the science and art of formulations and provides an evermore useful handbook that should be highly welcomed by the industry, the regulatory authorities, as well as the teaching institutions.

The first edition of this book was a great success as it brought under one umbrella the myriad of choices available to formulators. The readers were very responsive and communicated with me frequently pointing out to the weaknesses as well as the strengths of the book. The second edition totally revised attempts to achieve these by making major changes to the text, some of which include:

1. Complete, revised errors corrected and subject matter reorganized for easy reference. Whereas this series has six volumes differentiated on the basis of the type of dosage form and a separate inclusion of the U.S. OTC products, ideally the entire collection is needed to benefit from the myriad of topics relating to formulations, regulatory compliance, and dossier preparation.
2. Total number of pages is increased from 1684 to 2726.
3. Total number of formulations is expanded by about 30% with many newly approved formulations.
4. Novel formulations are now provided for a variety of drugs; these data are collected from the massive intellectual property data and suggest toward the future trend of formulations. While some of these formulations may not have been approved in the United States or Europe, these do provide additional choices, particularly for the NDA preparation. As always, it is the responsibility of the manufacturer to assure that the intellectual property rights are not violated.
5. A significant change in this edition is the inclusion of commercial products; while most of this information is culled out from the open source such as the FOIA (http://www.fda.gov/foi/default.htm), I have made attempts to reconstruct the critical portions of it based on what I call the generally acceptable standards. The drug companies are advised to assure that any intellectual property rights are not violated and this applies to all information contained in this book. The freedom of information act (FOIA) is an extremely useful conduit for reliable information and manufacturers are strongly urged to make use of this information. Whereas this information is provided free of charge, the process of obtaining the information may be cumbersome, in which case, commercial sources of these databases can prove useful, particularly for the non-U.S. companies.
6. Also included are the new Good Manufacturing Guidelines (2007) with amendments (2008) for the United States and similar updates for European Union and WHO; it is strongly urged that the companies discontinue using all old documents as there are significant changes in the revised form, many of them are likely to reduce the cost of GMP compliance.
7. Details on design of clean rooms is a new entry that will be of great use to sterile product manufacturers; whereas the design and flow of personnel and material flow is of critical nature, regulatory agencies view these differently and the manufacturer is advised always to comply with most stringent requirements.
8. Addition of a self-auditing template in each volume of the series. While the cGMP compliance is a complex issue and the requirements diversified across the globe, the basic compliance remains universal. I have chosen the European Union guidelines (as these are more in tune with the ICH) to prepare a self-audit module that I recommend that every manufacturer adopt as a routine to assure GMP compliance. In most instances reading the template by those responsible for compliance with keep them sensitive to the needs of GMP.
9. OTC products cross-referenced in other volumes where appropriate. This was necessary since the regulatory authorities worldwide define this class of drug differently. It is important to iterate that regardless of the prescription or the OTC status of a product, the requirements for compliance with the cGMP apply equally.
10. OTC monograph status is a new section added to the OTC volume and this should allow manufacturers to chose appropriate formulations that may not require a filing with the regulatory agencies; it is important to iterate that an approved OTC monograph includes details of formulation including the types and quantities of active drug and excipients, labeling, and presentation. To qualify the exemption, the manufacturer must comply with the monograph in its entirety. However, subtle modifications that are merely cosmetic in nature and where there is an evidence that the modification will not affect the safety and efficacy of the products can be made but require prior approval of the regulatory agencies and generally these approvals are granted.
11. Expanded discussion on critical factors in the manufacturing of formulations provided; from basic shortcuts to smart modifications now extend to all dosage forms. Pharmaceutical compounding is one of the oldest professions and whereas the art of formulations has been

relegated to more objective parameters, the art nevertheless remains. An experienced formulator, like an artist, would know what goes with what and why; he avoids the pitfalls and stays with conservative choices. These sections of the book present advice that is time tested, although it may appear random at times; this is intended for experienced formulators.

12. Expanded details on critical steps in the manufacturing processes provided but to keep the size of the book manageable, and these are included for prototype formulations. The reader is advised to browse through similar formulations to gain more insight. Where multiple formulations are provided for the same drug, it intended to show the variety of possibilities in formulating a drug and whereas it pertains to a single drug, the basic formulation practices can be extended to many drugs of same class or even of diversified classes. Readers have often requested that more details be provided in the Manufacturing Direction sections. Whereas sufficient details are provided, this is restricted to prototype formulations to keep the size of the book manageable and to reduce redundancy.
13. Addition of a listing of approved excipients and the level allowed by regulatory authorities. This new section allows formulators a clear choice on which excipients to choose; the excipients are reported in each volume pertaining to the formulation type covered. The listing is drawn from the FDA-approved entities. For the developers of an ANDA, it is critical that the level of excipients be kept within the range generally approved to avoid large expense in justifying any unapproved level. The only category for which the listing is not provided separately is the OTC volume since it contains many dosage forms and the reader is referred to dosage form–specific title of the series. The choice of excipients forms keeps increasing with many new choices that can provide many special release characteristics to the dosage forms. Choosing correct excipients is thus a tedious exercise and requires sophisticated multivariate statistical analysis. Whereas the formulator may choose any number of novel or classical components, it is important to know the levels of excipients that are generally allowed in various formulations to reduce the cost of redundant exercises; I have therefore included, as an appendix to each volume, a list of all excipients that are currently approved by the U.S. FDA along with their appropriate levels. I suggest that a formulator consult this table before deciding on which level of excipient to use; it does not mean that the excipient cannot be used outside this range but it obviates the need for a validation and lengthy justification studies in the submission of NDAs.
14. Expanded section on bioequivalence submission was required to highlight the recent changes in these requirements. New entries include a comprehensive listing of bioequivalence protocols in abbreviated form as approved by the U.S. FDA; these descriptions are provided in each volume where pertinent. To receive approval for an ANDA, an applicant must generally demonstrate, among other things, equivalence of the active ingredient, dosage form, strength, route of administration, and conditions of use as the listed drug, and that the proposed drug product is bioequivalent to the reference listed drug [21 USC 355(j)(2)(A); 21 CFR 314.94(a)]. Bioequivalent drug products show no significant difference in the rate and extent of absorption of the therapeutic ingredient [21 USC 355(j)(8); 21 CFR 320.1(e)]. BE studies are undertaken in support of ANDA submissions with the goal of demonstrating BE between a proposed generic drug product and its reference listed drug. The regulations governing BE are provided at 21 CFR in part 320. The U.S. FDA has recently begun to promulgate individual bioequivalence requirements. To streamline the process for making guidance available to the public on how to design product-specific BE studies, the U.S. FDA will be issuing product-specific BE recommendations (www.fda.gov/cder/ogd/index.htm). To make this vital information available, an appendix to each volume includes a summary of all currently approved products by the U.S. FDA where a recommendation on conducting bioequivalence studies is made available by the U.S. FDA. When filing an NDA or an ANDA, the filer is faced with the choice of defending the methods used to justify the bioavailability or bioequivalence data. The U.S. FDA now allows application for waiver of bioequivalence requirement; a new chapter on this topic has been added along with details of the dissolution tests, where applicable, approved for various dosage forms.
15. Dissolution testing requirements are included for all dosage forms where this testing is required by the FDA. Surrogate testing to prove efficacy and compliance is getting more acceptance at regulatory agencies; in my experience, a well-designed dissolution test is the best measure of continuous compliance. Coupled with chapters on waivers of bioequivalence testing, this information on dissolution testing should be great value to all manufacturers; it is recommended that manufacturers develop their own in-house specifications, more stringent than those allowed in these listings and the USP.
16. Best-selling products (top 200 prescription products) are identified with an asterisk and a brand name where applicable; in all instances, composition of these products is provided and formulation of generic equivalents. Despite the vast expansion of pharmaceutical sales and shifting of categories of blockbuster drugs, basic drugs affecting gastrointestinal tract, vascular system, and brain remain most widely prescribed.
17. Updated list of approved coloring agents in the United States, Canada, European Union, and Japan is included to allow manufactures to design products for worldwide distribution.
18. Tablet-coating formulations that meet worldwide requirements of color selection are included in the Volume 1 (compressed solids) and Volume 5 (OTC) because these represent the products often coated.
19. Guidelines on preparing regulatory filings are now dispersed throughout the series depending on where these guidelines are more crucial. However, the reader would, as before, need access to all volumes to benefit from the advice and guidelines provided.

As always, comments and criticism from the readers are welcomed and these can be sent to me at Niazi@pharmsci.com or Niazi@niazi.com. I would try to respond to any inquiries requiring clarification of the information enclosed in these volumes.

"I would like to express deep gratitude to Sherri R. Niziolek and Michelle Schmitt-DeBonis at Informa, the publisher of this work, for seeing an immediate value to the readers in publishing the second edition of this book and allowing me enough time to prepare this work. The diligent editing and composing staff at Informa, particularly Joseph Stubenrauch, Baljinder Kaur and others are highly appreciated. Regardless, all errors and omissions remain altogether mine."

In the first edition, I had dedicated each volume to one of my mentors; the second edition continues the dedication to these great teachers.

Sarfaraz K. Niazi, Ph.D.
Deerfield, Illinois, U.S.A.

Preface to the Series—First Edition

No industry in the world is more highly regulated than the pharmaceutical industry because of potential threat to a patient's life from the use of pharmaceutical products. The cost of taking a new chemical entity (amortized over the cost of all molecules racing) to final regulatory approval is a staggering $800 million, making the pharmaceutical industry one of the most research-intensive industries in the world. In the year 2004, it is anticipated that the industry will spend about $20 billion on research and development. The generic market of drugs as the new entities come off patent is one of the fastest growing segments of the pharmaceutical industry, with every major multinational company having a significant presence in this field.

Whereas many stages of new drug development are inherently constrained with time, the formulation of drugs into desirable dosage forms remains an area where expediency can be practiced with appropriate knowledge by those who have mastered the skills of pharmaceutical formulations. The *Handbook of Pharmaceutical Manufacturing Formulations* is the first major attempt to consolidate the available knowledge about formulations in a comprehensive, and by nature a rather voluminous, presentation.

The book is divided into six volumes, based strictly on the type of formulation science involved in the development of these dosage forms: sterile products, compressed solids, uncompressed solids, liquid products, semisolid products, and OTC products. The separation of OTC products even though they may easily fall into one of the other five categories is made to comply with the industry norms of separate research divisions for OTC products. Sterile products require skills related to sterilization of product, and of less importance is the bioavailability issue, which is an inherent problem of compressed dosage forms. These types of considerations have led to the classification of products into these six categories.

Each volume includes a description of regulatory filing techniques for the formulations described. Also included are the current regulatory guidelines on cGMP compliance specific to the dosage form. Advice is offered on how to scale up the production batches.

It is expected that formulation scientists will use this information to benchmark their internal development protocols and cut the race to file short by adopting formulae that have survived the test of time. Many of us who have worked in the pharmaceutical industry suffer from a close paradigm when it comes to selecting formulations—"not invented here" perhaps reigns in the mind of many seasoned formulations scientists subconsciously when they prefer to choose only a certain platform for development. It is expected that with the quick review of possibilities available to formulate made available in this book, scientists will benefit from the experience of others.

For the teachers of formulation sciences, this series offers a wealth of information. Whether it is a selection of a preservative system or the choice of a disintegrant, the series offers a wide choice to study and rationalize.

Many have assisted me in the development of this work that has taken years to compile, and I thank scores of my graduate students and colleagues for their help. A work of this size cannot be produced without errors, although I hope that these errors do not distract the reader from the utility of the book. I would sincerely appreciate if readers point out these mistakes for corrections in future editions.

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Preface to the Volume—First Edition

The (HPMF/SP) is written for the pharmaceutical scientist and others involved in the regulatory filing and manufacturing of new sterile products. No other area of regulatory compliance receives more attention and scrutiny by regulatory authorities than the regulation of sterile products, for obvious reasons. With the increasing number of potent products, particularly the new line of small protein products, joining the long list of proven sterile products—mainly parenteral and ophthalmic products—the technology of manufacturing sterile products has evolved into a very sophisticated industry. The entry barrier to this technology is much higher compared with those for other dosage forms. Consequently, the cost of production remains high as well. In recent years, regulatory agencies around the world have taken very serious notice of the deficiencies in the manufacturing specifications of the active raw material intended for parenteral administration. New guidelines for the API and aseptic processing of sterile products are the main issues of concern today for manufacturers. This volume of *HPMF/SP* does not delve into details related to starting material issues. Of interest in this issue are formulations of sterile dosage forms, regulatory filing requirements of sterile preparations, and cGMP compliance, all of which are tied together in the final preparation of the chemistry, manufacturing, and control (CMC) sections of regulatory applications.

Chapter 1 describes the specifications of a manufacturing facility to manufacture compliant sterile products. Chapter 2 outlines the new drug application (NDA) or abbreviated new drug application (ANDA) filing requirements of sterile products. Chapter 3 describes in detail the layout of formulations provided in the book. This chapter must be thoroughly examined to make the best use of this book. Because the intent of the information provided in this book is to help the formulator develop a product for regulatory filing, boilerplate details are left out. Chapter 3 provides these details and also makes strong recommendations on how the formulator can benefit from the information available from suppliers of components and chemicals used in the formulation.

These three chapters are followed by the body of the book, which provides an alphabetical presentation of formulations of pharmaceutical products based on their generic names. There are three types of formulation entries. In the first type, both the bill of materials and manufacturing directions are provided. This type is further composed of two types, wherein greater detail is provided for some products. This differentiation is intentional because the common details are often omitted in subsequent presentations. The second type of formulations is provided with bill of materials only. This may include products for which the manufacturing directions are obvious to a prospective manufacturer, particularly in light of the details already provided for similar products elsewhere in the book, and also those products for which such information is not readily available. The third category of formulations includes experimental formulations, which may not yet have been commercialized or received regulatory approvals. These formulations are included to show to the formulation scientist unique opportunities that exist for the chemical entity in question.

Formulations of biotechnology-derived drugs are provided with some additional details and remain restricted to declaration of composition, yet they provide a good overview of the complexities involved in such formulations.

In consolidating the details of formulations, efforts have been made to present them in as unified a form as possible; nevertheless, some nonuniformities exist because of the large variety of presentations possible for the wide diversity of formulations presented in the book. A limited number of products intended for veterinary use are also included. These products are subject to cGMP compliance similar to that for human products.

The formulations provided here meet the *4S* requirements:

1. *Safety.* This is an important issue for parenteral products; the choice of excipients is limited by this consideration. In most of the formulations, the ingredients are fully approved by the regulatory authorities; in some formulations, the active drug moiety may have been banned in some countries, for example, dipyrone.
2. *Sterility.* The compositions presented are fully sterilizable either by terminal treatment or by aseptic processing; where preservatives are added, these are in sufficient quantity to fulfill the dedicated function.
3. *Stability*. Besides the rigor of treatment in rendering a product sterile, incompatibility issues may render a sterile product prone to instability. The formulations included here have been fully validated to provide sufficient shelf life, depending on the product.
4. *Scalability.* Whereas the batch formulation is presented for a 1-l batch, these formulations are linearly scalable. Manufacturing losses have been included and these formulations can be readily scaled up to any size; of course, the requirements of size change in the validation protocol should be considered.

One of the best utilities of the database included in this book is to benchmark the products intended for development. A large number of formulation possibilities exist for any drug; though with the 4S limitations, the choice of ingredients (excipients) narrows rather rapidly. Multivitamin formulations are one such example wherein extreme instability and cost considerations have resulted in a variety of formulations. A study of many possibilities tells us about the problems we can anticipate while formulating these products. In some instances, only composition details are provided, along with raw material manufacturing details, because they are often an integral part of the formulation, such as in the case of biotechnology-derived products. Whereas this information may be at best cursory, it is useful to provide a study of these product formulations.

The information contained in this book has been obtained mainly from sources open to the public. It has taken years

to accumulate this database and no warranties are provided that these formulation compositions will not infringe on any proprietary product or intellectual property. The formulators must consider this before using the information. Also, as with all scientific experimental data, it should be understood that replication is subject to many factors, including type of equipment used, grade of material employed, and other processing techniques implemented. The road to converting these formulations to validated parts of a CMC package for submission to regulatory authorities is a long one; nevertheless, working with these formulations will reduce the risk of prolonged experimentation, and for generic formulation development, it will expedite entrance to the market. Some scientists may find this information useful in improving their products for any of the 4S considerations. More information is available on the Web site of Pharmaceutical Scientist, Inc. (http://www.pharmsci.com), wherein scientists can find updated information on regulatory compliance and additional tools for writing the CMC portions of the ANDA and NDA filings. The readers are encouraged to consult this Web site.

Although I have tried to sift through the large databases in both the formative and proofreading stages of the handbook, it is possible that errors remain. I would appreciate it if readers point these out to me by e-mailing me at niazi@pharmsci.com.

I am grateful to CRC Press for taking this lead in publishing what is possibly the largest such work in the field of pharmaceutical sciences. It has been a distinct privilege to know Mr. Stephen Zollo, senior editor at CRC Press. Stephen has done more than what any editor can do to encourage an author into conceiving, planning, drafting, and finally, despite many reasons why it could not be done, completing the work on a timely basis. I am greatly indebted to him. The editorial assistance provided by CRC Press staff was indeed exemplary, particularly the help given by Erika Dery, Gail Renard, Sara Kreisman, and others at CRC Press. Although the editors and proofreaders have pored over this book diligently, any mistakes remaining are altogether mine.

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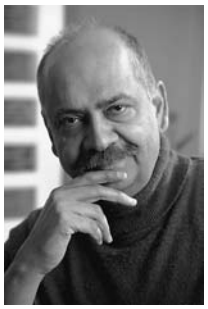
About the Author



Sarfaraz K. Niazi has been teaching and conducting research in the pharmaceutical industry for over 35 years. He has authored hundreds of scientific papers, textbooks, and presentations on the topics of pharmaceutical formulation, biopharmaceutics, and pharmacokinetics of drugs. He is also an inventor with scores of patents in the field of drug and dosage form delivery systems; he is also licensed to practice law before the U.S. Patent and Trademark Office. Having formulated hundreds of products from the most popular consumer entries to complex biotechnology-derived products, he has accumulated a wealth of knowledge in the science and art of formulating and regulatory filings of Investigational New Drugs (INDs) and New Drug Applications (NDAs). Dr. Niazi advises the pharmaceutical industry internationally on issues related to formulations, cGMP compliance, pharmacokinetics and bioequivalence evaluation, and intellectual property issues (http://www.pharmsci.com). He can be contacted at Niazi@pharmsci.com.

Contents

Part I

Regulatory and Manufacturing

1

Sterile Manufacturing Formulations Template

This chapter lists the sections and specific details of the template used for compiling the formulations:

1. Generic name (as it appears in the *Physician's Desk Reference* or United States Pharmacopoeia) is used in the following:
   - Where there is more than one active component in the formulation, the ingredients appear in alphabetical order.
   - Where there are large number of active ingredients, such as in vitamin B-complex formulations, the ingredients are listed under the generic category, for example, B-complex vitamin.
   - Individual vitamins are listed with their name first; for example, Vitamin C appears as ascorbic acid, Vitamin E as α-tocopherol, and Vitamin D as retinol.
   - Veterinary formulations are identified and listed separately from human formulations. For example, *B-Complex Vitamin, Veterinary* is a different listing from *B-Complex Vitamin*, in which no indication is made for its intended use.
   - Where a special packaging is described, such as "covial or diluent included," it is also specified in the title description because it often requires special techniques, and diluent may contain other drugs, such as lidocaine.
   - Where a specific and unique packaging is involved, such as a flexible bottle, it is listed as well.
   - Compendial references are not indicated, such as a USP or BP product; however, where there are monographs available, it is assumed that the material will comply with these monographs.
   - Where a popular alternative name is available, such as Elliott's solution, it is provided in parentheses.
   - Strength of formulation is not specified in the title.
   - The USP provides strict definitions for providing the title of a product; for example, Drug for Injection means a product that must be reconstituted or diluted before use; Suspension for Injection indicates the nature of the product. While these titles are maintained, often they are not clearly indicated.
2. Bill of Materials is a tabular presentation of the scale and quantities of materials used in the following:
   - The scale is generally presented as a per-milliliter quantity (however, watch for different scales; lyophilized products may have a per-vial specification, and in the case of premixed pharmacy packs, a 50-mL specification, for example).
   - The quantities for a 1-L batch are presented with appropriate UOM (units of measurement) and include any excesses (overages), equivalent quantities due to differences in the chemical forms, or the potency of the ingredient. In some instances, the label includes the quantity of base and the ingredient used in a salt; the quantity of salt may have to be calculated if it is an equivalent quantity so marked.
   - The term QS, or sufficient quantity, is often used for the medium such as Water for Injection, for chemicals used to adjust pH, or for those used to purge the formulations, such as nitrogen gas.
   - The raw material specifications are all of pharmacopoeia grade where available; however, a listing of a raw material without requiring compendial specification should be ignored.
   - Where an "injectable grade" material is available, it is the preferred form, although it may not be so stated, particularly in the formulation of vitamin products.
   - Purity grade of the active pharmaceutical ingredient (API) is not always defined; even the pharmacopoeia-grade starting material may be subject to different impurity profiles. The formulator should remember that the regulatory agencies place a very high degree of importance on the impurity profile of the API; the supplier must be able to provide a drug master file (DMF) description assuring that the raw material is manufactured under cGMP requirements. It is possible that a manufacturer might have a DMF on some of its products but not all; therefore, the formulator should inquire specifically about the DMF of the API (with its appropriate grade clearly spelled out).
   - Multiple bills of material (BOMs) are often listed for the same product; they may appear similar or may differ only in strength; however, often there are different excipients or methods of manufacture involved. Often there are different formulations, all very useful; a sampling of these is presented as well.
3. Manufacturing Directions include a step-by-step methodology for manufacturing the product on a commercial scale in the following:
   - To avoid redundancy and to conserve space, detailed instructions are provided for each of the types of products, such as an ampoule, vial, infusion, large volume, drops, nasal preparations, or ophthalmic drops, in some formulations only; obviously, many steps involved in the preparation of commodities, sterilization procedures such as the use of 0.22-mm membrane filter, procedures for transferring to a staging vessel, presterilization of filters, testing of filters by a bubble method, autoclaving, or heat sterilization, are common to many. The reader is advised to review the detailed formulations of the specific type to obtain additional information.
   - Where unusual precautions are necessary, such as when handling a hazardous substance, a highly sensitive substance (sensitive to light or air), or a substance requiring special handling, a warning is written as the first paragraph before the manufacturing steps.
   - It is assumed that the formulator is well versed in cGMP compliance, but the reader is referred to chapter 1 to review the most recent qualification requirements.

- Manufacturing environment, documentation, personnel, and material handling issues are addressed only when peculiarities are involved.
- It is customary and, in most cases, required that the preparation vessel be of at least 316 L resistance stainless steel or higher, and thus this step is often omitted but assumed by default.
- Where there is a need to use a glass-lined vessel, it is clearly indicated. In some instances, an option is provided wherein the preference remains toward the glass-lined vessel. In some instances, glass-lined vessels should not be used, and this too is clearly indicated.
- The order and manner of mixing, the timing of mixing, the temperature of mixing, etc., when given, form essential parts of the formulation. These should be strictly followed. With in-house validation for other methods, these can be modified. The reasons for specific directions are to assure complete mixing, avoid foam formation, and reduce physical and compatibility issues. Where no specific mention is made, these details are generally inconsequential and the formulator may use conditions convenient to the manufacturing equipment and environment.
- The formulation medium in most instances is water for injection, USP grade. While in some instances other grades of water may be used, it is advisable to keep this standard wherever possible. Experience tells us that water is often the most significant source of contamination in sterile products; this can also be a source of heavy-metal contamination coming from the pitting of the pipelines (of stainless steel that contains highly reactive metal). It should be remembered that distilled water is highly corrosive and while it does not generally promote growth of bacteria, it is capable of carrying them. A closed loop running at high temperature offers the best opportunity of assuring compliance. In some instances, a formulation may specify "freshly boiled distilled water," or a similar specification, and it is intended to assure that there were no residues or endotoxin developed during storage.
- A good practice is to qualify the quality of water at the beginning of the manufacturing operation. A typical qualification process would measure pH and conductivity of water prior to use. However, note that conductivity is *not* an indicator of sterility.
- In many instances, it is recommended to bubble nitrogen gas for a sufficient length of time; the length of time depends on the capacity of the vessel, but generally should be at least 20 min; where a cover of nitrogen gas is recommended, the preparation vessel should provide a good seal to keep the nitrogen gas contained.
- When the temperature of the preparation vessel is stated as room temperature, the definition of USP is intended here.
- Where heating or cooling is recommended, this is provided by a jacketed vessel with hot- or cold-water recirculation facility.
- The cGMP compliance considerations require a detailed record of all of these steps; in listing the formulations in this book, no effort is made to illustrate this aspect of manufacturing record keeping. A fully compliant manufacturing document will have provisions for signing off on all of these observations, including the name of the operator, the time a process was begun and finished, and the observations made; often the record will be cosigned by a supervisor.
- Sampling of products during manufacturing is required and, in some instances, recommendations are made concerning where to take the sample. Samples will be sent either to in-process quality checks or to the quality control laboratory.
- In all instances, before the product is filled, it must be cleared by the quality control laboratory.
- Where extra precautions are called for, conditions are prescribed for holding the preparation pending release from the quality control laboratory before filling ampoules, vials, or bottles. Where such conditions are not prescribed, it is assumed that the preparations will be stored at the lowest temperature compatible with the product and under cover of nitrogen gas where prescribed.
- Adjustment of pH using hydrochloric acid, sodium hydroxide, acetic acid, etc. is one of the common steps in the compliance process to assure that the product meets final specifications. Although the concentrations of these acids and bases are specified, generally a 10% concentration is acceptable (higher where volume restrictions arise). The addition of these acids and bases should be gradual and in small portions, with continuous stirring to avoid drastic changes in the localized pH at the point of addition. Experienced operators should be able to determine these conditions (such as stirring speed and time to add a portion of component) and make them a part of the manufacturing document.
- In many instances, more than one manufacturing vessel is required to make separate preparations for mixing later in the process of manufacturing. It is important to assure that these vessels are held in close proximity or have a closed system for transferring liquids between vessels. Because the starting stage of manufacturing is done in less-than-sterile conditions, the exchange between vessels can be an important source of contamination and must be carefully monitored.
- Once the preparation has been properly mixed (it is likely a clear solution), it is filtered before the filling step. In all instances, there is also a step involving transferring the product into a staging vessel that will feed the filling machine, either a mobile tank or a tank in the filling room.
- The filtration step is critical, and great care should be exercised not only in selecting a proper filter (based on the dielectric property of the preparation) but also in validating the use of a filter, especially if it is not changed in each operation cycle.
- A bubble point test before and after filling is assumed in all instances. (See chap. 1 on the requirements of aseptic processing of products.)
- The retentive power of the filter is also critical and is determined partly by the nature of product (its viscosity, polarity, etc.), but generally a 0.45-mm prefilter is recommended, followed by a 0.22-mm filter.
- Whether a product is terminally sterilized or not, the goal during processing is to reduce bioburden and thus the endotoxin levels later in the product.
- The formulator has several good options in selecting the filtration equipment. While it is not the author's intent to endorse a product or a particular brand, it is important to point to ready sources of information on critical steps. One of the best sources for information on selecting and validating the filtration system is the Pall Corporation Web site (http://www.pall.com). With its broad worldwide resources, it should help one select an

appropriate filtration system and provide methods of validating the filter. The new guidelines proposed for products that are aseptically filled require special enforcement of filter validation, and the need to develop a validation system cannot be overemphasized. The filtration assembly is sterilized in an autoclave prior to use and there must be no breach prior to the use of the filtration assembly. Compatibility between the product and the hoses used to transfer it is often critical, and in some instances a specific grade of tubing is specified, such as Tygon®. The formulation scientist is referred to http://www.tygon.com for assuring that compatibility data are available before selecting a tubing grade. These suppliers are in a better position to advise because of their experience with similar products.

- The packaging commodities, such as vials, ampoules, rubber stoppers, and aluminum seals, form an integral part of the product because their integrity is required to assure that there is no contamination from external sources and no leaching of chemicals from the packaging commodities into the product. The selection of these commodities is a critical step.
- Whereas USP requires type I glass, there may be a more detailed specification, such as using a low-alkali-type as in the case of LVPs; where flexible containers are used, the possibility of chemicals leaching into the product should be considered, and attention should also be paid to the leaching of chemical components from the rubber stoppers.
- A good source of information on selecting appropriate rubber stoppers is the West Pharmaceutical Services, Inc. (http://www.west-pharma.com). From the most common butyl rubber to highly customized compositions for stoppers, the site is a good source because West Pharmaceutical Services knows who is using what type of closures for which product. Often the formulations details provided indicate coated rubber stoppers, such as siliconized, or a Teflon® product. However, where no recommendations are made, it is not assumed that any type of product is adequate.
- The choice of vials must be made concurrently with the choice of stoppers, as vials must be compatible in size (particularly the neck) to allow proper fitting of stoppers. Most companies that manufacture glass vials offer them in dimensions that allow use of off-the-shelf rubber stoppers; nevertheless, when requirements arise, customized glass vials can be fitted to an appropriate rubber stopper and vice versa. A good source of information on selection of glass vials is Wheaton Scientific (http://www.wheaton-sci.com); ampoules are also supplied by Wheaton (http://www.alcanpackaging.com/pharma/eng/html/tubularam-poules.php).
- Treatment of stoppers, vials, and ampoules prior to their use is also an integral part of manufacturing, and details of these processes are described in the master documents. Rubber stoppers are routinely washed with surfactants, rinsed with water for injection, and then heat sterilized; open ampoules and vials are washed and sterilized. Sterilization cycles of commodities must be properly validated. Suppliers of these commodities should be able to provide optimal validated cycles.
- In-process testing of products is most rigorous for sterile products, partly because it is not possible to salvage a batch once it is packaged. All products undergo a 100% visual testing (now conducted with automated systems) and proper validation of the testing procedures is required even though it is not so stated in the formulations listed in the book.

I. AUTOCLAVES

AMSCO (American Sterilizer Co.), 2425 West 23rd Street, Erie, PA 16514, USA; Telephone: (814) 452-3100
Castle Co., 1777 E. Henrietta Road, Rochester, NY 14623, USA; Telephone: (716) 475-1400
Getinge International, Inc., 1100 Towbin Avenue, Lakewood, NJ 08701, USA; Telephone: (732) 370-8800
Gruenberg, Inc., 2121 Reach Road, Williamsport, PA 17701, USA; Telephone: (717) 326-1755
STERIS Corporation, 5960 Heisley Road, Mentor, OH 44060, Phone: 440.354.2600

II. ASEPTIC CONTRACT MANUFACTURERS

American Pharmaceutical Partners, 1101 Perimeter Drive, Schaumburg, IL 60173, USA; Telephone: (847) 330-1357

A. Manufacturing Formulations Template

Connaught Laboratories, Route 411, Swiftwater, PA 18370, USA; Telephone: (717) 839-7187
Elkins-Sinn, 2 Esterbrook Lane, Cherry Hill, NJ 08003-4099, USA; Telephone: (800) 257-8349 TWX: 710-896-0804
Pharma-Hameln, Langes Feld 30-38 D-3250 Hameln 1, Germany; Telephone: (05151) 581-255
Pharmacia, 7000 Portage Road, Kalamazoo, MI 49001, USA; Telephone: 616-833-5844, Fax: 616-833-3604
Schering-Plough, U.S. Pharmaceutical Products Division, Kenilworth, NJ 07033, USA; Telephone: (201) 558-4811/4809, Telex: 138316/138280
Smith-Kline and French Call Box SKF Cidra, PR 00639, USA; Telephone: (809) 766-4000
Steris Laboratories, Inc., 620 N. 51st Avenue, Phoenix, AZ 85043, USA; Telephone: (602) 939-7565
Summa Manufacturing Sciences, 4272 Balloon Park Road, NE, Albuquerque, NM 87109, USA; Telephone: (800) 843-4339
Survival Technology, 8101 Glenbrook Road, Bethesda, MD 20814, USA; Telephone: (301) 656-5600
Taylor Pharmacal, P. O. Box 1230 Decatur, IL 62525, USA; Telephone: (217) 428-1100
Vitamed, P. O. Box 16085 IL-61160 Tel Aviv, Israel; Telephone: (03) 551-8042

III. CLEAN-ROOM DESIGN AND CONSTRUCTION

Cambridge Filter Corp., P. O. Box 4906, Syracuse, NY 13221-4906, USA; Telephone: (315) 457-1000
Clean Room Technology, Inc., 4003 Eastbourne Drive, Syracuse, NY 13206, USA; Telephone: (315) 437-2152
Comp-Aire Systems, Inc., 4185 44th SE, Grand Rapids, MI 49508, USA; Telephone: (616) 698-9660
Flanders, P. O. Box 1708, Washington, NC 27889, USA; Telephone: (919) 946-8081
Liberty Industries, Inc., 133 Commerce Street, East Berlin, CT 06023, USA; Telephone: (203) 828-6361

IV. CLEAN-IN-PLACE/STEAM-IN-PLACE (CIPISIP)

BLH Electronics, 42 Fourth Avenue, Waltham, MA 02254, USA
Clenesco, P. O. Box 2918, Cincinnati, OH 45201, USA
Degussa Corporation, P. O. Box 2004, Teterborough, NJ 07608, USA
Diversey Wyandotte Corporation, 1532 Biddle Avenue, Wyandotte, MI 48192, USA
Electrol Specialties Company, 441 Clark Street, South Beloit, IL 61080, USA
Endress & Hauser, Inc., 2350 Endress Place, Greenwood, IN 46142, USA
Foxboro Company, 38 Neponsett Avenue, Foxboro, MA 02035, USA
Klenzade, Osborn Building, St. Paul, MN 55102, USA
Ladish-Triclover, 9201 Wilmot Road, Kenosha, WI 53141, USA
National Sonies, 250 Marcus Boulevard, Hauppauge, NY 11787, USA
Pyromation, 5211 Industrial Road Fort, Wayne, IN 46895, USA
Sarco Company, 1951 26th S. W. Allentown, PA 18105, USA
Viatran Corporation, 300 Industrial Drive Grand Island, NY 14072, USA

V. CLOSURE WASHING AND STERILIZATION

Huber Maschinenfabrik Angerstrasse 16, P O. Box 1544 D-8050 Freising, Germany; Telephone: 49-81-611-3063
Huber Seidenader Equipment, Inc., 35 Airport Park, Morristown, NJ 07960, USA; Telephone: (201) 267-8730
Paxall Schubert Division, P. O. Box 836, Pine Brook, NJ 07058, USA; Telephone: (201) 227-4677
Pharma-Technik-Smeja, Postfach 2029, D-4172 Straelen-Herongen, Germany; Telephone: 609-921-1220

VI. CONSULTANTS

Bio-Separation Consultants, 3935 Falcon Avenue, Long Beach, CA 90807, USA; Attn: Fred Rothstein, Telephone: (213) 427-2844
Filtration Specialists Ltd., Pump Green House, Evenlode (Associate offices in England, Israel, Italy, and Japan)
International Consultants Association, 199 N. El Camino Real #F-318, Encinitas, CA 92024, USA; Telephone: (619) 753-0790
Interpharm International Ltd., P. O. Box 530, Prairie View, IL 60069, USA; Telephone: (312) 459-8480, Fax: (312) 459-4536
Lachman Consultant Services, 591 Stewart Avenue, Garden City, NY 11530, USA; Telephone: (516) 222-6222
Magid-Haffher Associates, 4400 Kerrybrooke Drive, Alexandria, VA 22310, USA; Telephone: (703) 971-3988
Niazi Consultants, Inc., 20 Riverside Drive, Deerfield, IL 60015, USA; Telephone: 847-267-8038
Planning Masters, 3343 William Drive, Newbury Park, CA 91320, USA; Telephone: (805) 499-7526
RI&D Engineering Associates, 22 Foxwood Drive, Somerset, NJ 08873, USA; Telephone: (201) 545-2002
Skyland Scientific Services, Gallatin Field, P. O. Box 34, Belgrade, MT 59714, USA; Telephone: (406) 388-4051
Swift Technical Services Ltd., 7 Manor Close, Oadby Leicester LE 2 4FE, England; Telephone: (0533) 712500

VII. DISINFECTANTS AND PRESERVATIVES

Alcide, Inc., One Willard Road, Norwalk, CT 06851, USA; Telephone: (203) 847-2555, Telex: 510-1003-219
Lonza, Inc., 22-10 Route 208, Fairlawn, NJ 07410, USA; Telephone: (201) 794-2400
Mallinckrodt, Inc., P. O. Box 5439, St. Louis, MO 63147, USA; Telephone: (314) 895-2000
Spectrum Chemical Co., 14422 South San Pedro Street, Gardena, CA 90248, USA; Telephone: (800) 543-0652
Sporicidin International, 4000 Massachusetts Avenue NW, Washington, D.C. 20016, USA; Telephone: (800) 424-3733
Vestal Laboratories, Inc., 5035 Manchester Avenue, St. Louis, MO 63110, USA; Telephone: (800) 325-8690

VIII. DISTILLATION EQUIPMENT

Aqua-Chem, Inc., P. O. Box 421, Milwaukee, WI 53201, USA; Telephone: (414) 961-2829
Consolidated Stills/Sterilizers, 76 Ashford Street, P. O. Box 297, Boston, MA 02134, USA; Telephone: 617-782-6072
Finn-Aqua America, Inc., 11105 Main Street, Bellevue, WA 98004, USA; Telephone: (206) 451-1900
MECO, 861 Carondelet Street, New Orleans, LA 70130, USA; Telephone: (504) 523-7271
Pennwalt Corp., Stokes Vacuum Components Dept., 5500 Tabor Road, Philadelphia, PA 19120, USA
Santasalo-Sohlberg Oy, Hankasuontie, 4-6 SF-00390 Helsinki 39, Finland
Stilmas S.p.a., Viale delle Industrie I-20090 Settala, Milano, Italy
Vaponies, Inc., Cordage Park, Plymouth, MA 02360, USA; Telephone: (617) 746-7555

IX. ENGINEERING AND CONSTRUCTION

CRS Sirrine, Inc., P. O. Box 5456, Greenville, SC 29606, USA; Telephone: (803) 281-8518
Daniel Engineering Services, Daniel Building, Greenville, SC 29602, USA; Telephone: (803) 298-3262
Davy McKee Engineers, 300 S. Riverside Plaza, Chicago, IL 60606, USA; Telephone: (312) 902-1218
Kling Lindquist, Inc., 2301 Chestnut Street, Philadelphia, PA 19103, USA; Telephone: (215) 665-9930 Telex: 244423 KLIN UR

X. FILLING MACHINES

Adtech, Inc., 1170 Church Road, Lansdale, PA 19446, USA; Telephone: (215) 368-7040
Bausch und Strobel, P. O. Box 20, D-7174 llshoven, Germany; Telephone: (07904) 701-256
Cozzoli Machine Co., 401 East 3rd Street, Plainfield, NJ 07060, USA; Telephone: (201) 757-2040
Perry Industries, 1163 Glory Road, P. O. Box 19043, Green Bay, WI 54307-9043, USA; Telephone: (414) 336-4343
TL Systems, 5617 Corvallis Avenue, North Minneapolis, MN 35429, USA; Telephone: (612) 535-51232
Vetter Pharma Fertigung, P. O. Box 2380, D-7980 Ravensburg, Germany; Telephone: (0751) 3700-0

XI. FILTER AIDS

Cuno, Inc., 400 Research Parkway, Meriden, CT 06450, USA Telephone: (800) 243-6894
Eagle-Picher Industries, 580 A Walnut Street, Cincinnati, OH 45202, USA; Telephone: (1513) 721-7010
Filter Media Co., 3603 Westcenter Drive, Houston, TX 77042, USA; Telephone: (713) 780-9000
Manville Corp., Ken-Caryl Ranch, Denver, CO 80217, USA; Telephone: (303) 979-1000, Telex: 454404

XII. FLOWMETERS (SANITARY)

Foxboro Co., 120 Norfolk Street, Foxboro, MA 02035, USA; Telephone: (617) 543-8750
Leeds & Northrup, Sumneytown Park, North Wales, PA 19454, USA; Telephone: (215) 643-2000
Micro Motion, Inc. 7070 Winchester Circle, Boulder, CO 80301, USA; Telephone: (800) 522-6277

XIII. FREEZE-DRYERS (STERILIZABLE)

Edwards High Vacuum Manor Royal, Crawley West Sussex BH10 2LW, England; Telephone: (0293) 28844
Hull Corp., Davisville Road, Hatboro, PA 19040, USA; Telephone: (215) 672-7800
Leybold-Heraeus GmbH, Postfach 1555, D-6450 Hanau 1, Germany; Telephone: (06181) 34-0
Pennwalt (Stokes Division), 5500 Tabor Road, Philadelphia, PA 19120, USA; Telephone: (215) 831-5400
Usifroid Rue Claude Bernard Z. A. de Coignieres-Maurepas, 78310 Maurepas, France; Telephone: (33-3) 051-21-27
VirTis Route, 208 Gardiner, NY 12525, USA; Telephone: (800) 431-8232

XIV. MICROFILTRATION EQUIPMENT AND FILTERS

Alsop Engineering Co., Route 10, Milldale, CT 06467, USA; Telephone: (203) 628-9661
Ametek, Plymouth Products Div., 502 Indiana Avenue, Sheboygan, WI 53081, USA; Telephone: (414) 457-9435
Ballston, Inc., P. O. Box C, Lexington, MA 02173, USA; Telephone: (617) 861-7240
Brunswick GmbH, Mergenthalerallee 45-47, D-6236 Eschborn, Germany; Telephone: (06196) 427-0
Cumo, Inc., 400 Research Parkway Meriden, CT 06450, USA; Telephone: (800) 243-6894
Domnick Hunter Filters, 1Ad Durham Road D-3400 Birtley, County Durham DH3 2SF, UK; Telephone: (091) 4105121
Ertel Engineering, 20 Front Street Kingston, NY 12401, USA; Telephone: (914) 331-4552

A. Manufacturing Formulations Template

Filterite Corp., 4116 Sorrento Valley Building, San Diego, CA 92121, USA; Telephone: (800) 854-1571
Filtrox Werk AG, CH-9001 Street, Gallen, Switzerland
FPI (Filter Products, Inc.), 8314 Tiogawoods Drive, Sacramento, CA 95828, USA; Telephone: (916) 689-2328
Fuji Filter Mfg. Co. Ltd., Shiu-Muromachi Building, 4 Nihombahi-Huroshi 2-Chome Cuo-Ku, Tokyo 103, Japan; Telephone: (03) 241-4201
Gelman Sciences, 600 S. Wagner Road, Ann Arbor, MI 48106, USA; Telephone: (800) 521-1520
Gusmer-Cellulo Co., 27 North Avenue, East, Cranford, NJ 07016, USA; Telex: 96113
Kurita Machinery, Mfg. Co., 1-44 2-Chome, Sakaigawa, Nishiku, Osaka 550, Japan; Telephone: (06) 582-3001
Membrana (USA) See Gelman Sciences
Millipore Corp., Ashby Road, Bedford, MA 01730, USA; Telephone: (800) 225-1380
Nuclepore Corp., 2036 Commerce Circle, Pleasanton, CA 94566, USA; Telephone: (415) 462-2230
Pall Corp., 30 Sea Cliff Avenue, Glen Cove, NY 11542, USA; Telephone: (800) 645-6262
PTI (Purolator Technologies), 2323 Teller Road, Newbury Park, CA 91320, USA; Telephone: (800) 235-3518
Sartorius GmbH, Postfach 19, Gottingen, Germany; Telephone: (0551) 308219
Sartorius Filters, Inc., 30940 San Clemente Street, Hayward, CA 94544, USA; Telephone: (800) 227-2842
Schenk Filterbau GmbH, Postfach 95, D-7070 Schwabisch, Gmund, Germany; Telephone: (07171) 82091
Schleicher u. Schull GmbH, Postfach D-3354 Dassel, Germany; Telephone: (05564) 8995
Seitz-Filter-Werke GmbH, Planiger Street, 137 D-6550, Bad Kreuznach, Germany; Telephone: (0671) 66026
Sperry Filter Presses, 112 North Grant Street, North Aurora, IL 60542, USA; Telephone: (312) 892-4361
Star Systems, P. O. Box 518, Timmonsville, SC 29161, USA; Telephone: (803) 346-3101
Toyo Roshi Kaisha, 7, Nihonbacki Honcho 3-Chome, Chuo-Ku, Tokyo, Japan; Telephone: (03) 270-7441
Whatman Filter, Springfield Mill, Maidstone Kent ME14 2LE, UK; Telephone: (0622) 62692

XV. PUMPS (SANITARY)

Abex Corp., Waukesha Foundry 5510 Lincoln Avenue, Waukesha, WI 53186, USA; Telephone: (414) 542-0741
Alfa-Laval, P. O. Box 1008 S-221 03, Lund, Sweden; Telephone: (046) 105000
American Lewa, 132 Hopping Brook Road, Holliston, MA 01746, USA; Telephone: (617) 429-7403
Randolph Corp., 1112 Rosine Street, Houston, TX 77019, USA; Telephone: (713) 461-3400
Warren Rupp-Houdaille Co., P. O. Box 1568 TR, Mansfield, OH 44901, USA; Telephone: (419) 524-8388
Wilden Pump & Engineering, 22069 Van Buren Street, Colton, CA 92324, USA; Telephone: (714) 783-0621
The Ladish Co., 9201 Wilmot Road, Kenosha, WI 53141, USA; Telephone: (414) 694-5511, Fax: (414) 694-7104

XVI. STERILE TANKS AND RELATED STAINLESS EQUIPMENT

Bioengineering AG, Tannerstrasse 1 CH-8630, Rueti, Switzerland; Telephone: (055) 95 35 81
Cherryl Burrell, P. O. Box 1028, Little Falls, NY 13365, USA; Telephone: (315) 823-2000, Fax: (315) 823-2666
Paul Mueller Co., P. O. Box 828, Springfield, MO 65801, USA; Telephone: (800) 641-2830
Pfaudler Co., P. O. Box 1600, Rochester, NY 14692, USA; Telephone: (716) 235-1000

Stainless Metals, Inc., 43-49 10th Street, Long Island City, NY 11101, USA; Telephone: (718) 784-1454
Valex, 6080 Leland Street, Ventura, CA 93003, USA; Telephone: (805) 658-0944, Fax: (805) 658-1376
Walker Stainless Equipment, New Lisbon, WI 53950, USA; Telephone: (608) 562-3151

XVII. STERILITY TEST EQUIPMENT

Gelman Sciences, 600 Wagner Road, Ann Arbor, MI 48106, USA; Telephone: (800) 521-1520
MFS Division-Toyo Roshi, 6800 Sierra Court, Dublin, CA 94566, USA; Telephone: (415) 828-6010
Millipore Corp., Ashby Road, Bedford, MA 01730, USA; Telephone: (800) 225-1380
Sartorius GmbH, Postfach 19, D-3400 Göttingen, Germany; Telephone: (0551) 308219
Toyo Roshi Kaisha, 7, Nihonbacki Honcho 3-Chome, Chuo-Ku, Tokyo, Japan; Telephone: (03) 270-7441

XVIII. STERILIZING AND DRYING TUNNELS (HOT AIR)

Calumatic BV, 3 Steenstraat NE-5107, Dongen, The Netherlands; Telephone: (031) 1623-13454
Hans Gilowy Maschinefabrik "Meteorwerk" GmbH & Co., Schmalenbachstrasse 12-16 D-1000, Berlin 44, Germany; Telephone: (030) 684-6071
H. Strunck Maschinenfabrik, 7 Postfach 301269 D-5000 Köln 30, Germany

XIX. STOPPERING MACHINES

Adtech Inc., 1170 Church Road, Lansdale, PA 19446, USA; Telephone: (215) 368-7040
Calumatic BV, 3 Steenstraat 7, NE-5107 Dongen, The Netherlands; Telephone: (031) 1623-13454
Perry Industries, 1163 Glory Road, P. O. Box 19043, Green Bay, WI 54307-9043, USA; Telephone: (414) 336-4343
TL Systems, 5617 Corvallis Avenue, North Minneapolis, MN 55429-3594, USA; Telephone: (612) 535-5123

XX. VIAL AND BOTTLE WASHERS

Bausch und Strobel, P. O. Box 20, D-7174 llshofen, Germany; Telephone: (07904) 701-256
Calumatic BV, 3 Steenstraat 7, NE-5107 Dongen, The Netherlands; Telephone: (031) 1623-13454
Cozzoli Machine Co., 401 East 3rd Street, Plainfield, NJ 07060, USA; Telephone: (201) 757-2040
Dawson Bros. Ltd., 406 Roding Lane, South Woodford Green, Essex, UK
Hans Gilowy Maschinenfabrik "Meteorwerk" GmbH & Co., Schmalenbachstrasse 12-1, 6 D-1000 Berlin 44, Germany; Telephone: (030) 684-6071
Schubert & Co., Vallenbaksvej 24, DK-2600 Glostrup, Denmark
H. Strunck Maschinenfabrik, Postfach 301269, D-5000 Köln 30, Germany

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GMP Audit Template, EU Guidelines (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm)

		Compliance 1 2 3[a]	Remarks	EU-Guide
1	**PERSONNEL**			
1.1	Qualified personnel available?	☐ ☐ ☐		2.1
1.2	Organization charts available?	☐ ☐ ☐		2.2
1.3	Job descriptions available?	☐ ☐ ☐		2.2
1.4	Responsibilities clearly defined?	☐ ☐ ☐		2.2
	Key personnel			
	Responsible persons designated for			
1.5	• production?	☐ ☐ ☐		2.5
1.6	• quality control?	☐ ☐ ☐		2.6
1.7	Are they independent from each other?	☐ ☐ ☐		2.3
1.8	Are joint functions clearly defined?	☐ ☐ ☐		2.7
1.9	Are the responsible persons working full time?	☐ ☐ ☐		2.3
1.10	Do the responsible persons have the appropriate formation, knowledge, and experience?	☐ ☐ ☐		2.1/2.2
1.11	Do the relevant departments have enough personnel?	☐ ☐ ☐		2.1
	Training			
1.12	Continuous training programs for the production and QC staff?	☐ ☐ ☐		2.8
1.13	Initial job training for all employees?	☐ ☐ ☐		2.9
1.14	Teaching aids (videos, slides, brochures) available?	☐ ☐ ☐		2.9
1.15	External training courses for the staff?	☐ ☐ ☐		2.9
1.16	Training records?	☐ ☐ ☐		2.9
1.17	Special training in sensitive areas? (sterile prod. and toxic subs.)	☐ ☐ ☐		2.10
1.18	Information for visitors to the manufacturing area?	☐ ☐ ☐		2.11
2	**HYGIENE**			
	Personnel hygiene			
	Detailed written hygiene programs for			
2.1	• clothing?	☐ ☐ ☐		2.13
2.2	• use of washrooms?	☐ ☐ ☐		2.13
2.3	• behaviour in production areas?	☐ ☐ ☐		2.13
2.4	Precautions against sick or personnel with open wounds in production?	☐ ☐ ☐		2.14
	Medical examination			
2.5	• on recruitment?	☐ ☐ ☐		2.15
2.6	• regular reexaminations?	☐ ☐ ☐		2.15

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Duty of notification after			
2.7	• trips to tropical countries?	☐ ☐ ☐		2.15
2.8	• cases of contagious illness in the family?	☐ ☐ ☐		2.15
2.9	Instructions for appropriate working clothes?	☐ ☐ ☐		2.16
2.10	Absence of food and drinks (chewing gum) in the working area?	☐ ☐ ☐		2.17
2.11	Measures against contact with open product (gloves etc.)?	☐ ☐ ☐		2.18
2.12	Instructions for hand washing in production?	☐ ☐ ☐		2.19
2.13	Change of clothes when entering and leaving the production area?	☐ ☐ ☐		5.19
2.14	Change rooms and toilets easily within reach?	☐ ☐ ☐		3.31
2.15	Toilets and restrooms sufficiently separated from production areas?	☐ ☐ ☐		3.30/3.31
2.16	Workshops separate from production areas?	☐ ☐ ☐		3.32
2.17	Laboratory animal rooms totally segregated from production rooms?	☐ ☐ ☐		3.33
3	**WAREHOUSE**			
	Rooms, general			
3.1	Suitable for the intended use?	☐ ☐ ☐		3
3.2	• Adequate size?	☐ ☐ ☐		3
3.3	• Clean?	☐ ☐ ☐		3
3.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
3.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
3.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
3.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
3.8	Recording of temperature and humidity?	☐ ☐ ☐		
3.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
3.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
	Type of warehousing:			
3.11	Separation of goods sufficient?	☐ ☐ ☐		3.18
3.12	Provision for different storage temperatures?	☐ ☐ ☐		3.19
3.13	Goods receiving zone weather protected?	☐ ☐ ☐		3.20
3.14	Cleaning zone for incoming goods?	☐ ☐ ☐		3.20
3.15	Separate quarantine area with controlled access?	☐ ☐ ☐		3.21
3.16	Separate, protected sampling area?	☐ ☐ ☐		3.22
	Separate and safe storage of			
3.17	• returned goods?	☐ ☐ ☐		3.23
3.18	• rejected goods?	☐ ☐ ☐		3.23
3.19	Separate and safe storage of highly active, toxic, or dangerous substances?	☐ ☐ ☐		3.24
3.20	Safe storage of narcotics?	☐ ☐ ☐		3.24
3.21	Safe storage of printed packaging materials?	☐ ☐ ☐		3.25
3.22	Security measurements against theft?	☐ ☐ ☐		3.25

		Compliance 1 2 3[a]	Remarks	EU-Guide
3.23	Smoke detectors?	☐ ☐ ☐		3.25
3.24	Fire extinguishing system?	☐ ☐ ☐		3.25
	Operations			
3.25	Reception, sampling, and labeling according to written procedures?	☐ ☐ ☐		5.2
3.26	Is a sampling plan available?	☐ ☐ ☐		suppl. 4
3.27	Cleaning of incoming containers?	☐ ☐ ☐		5.3
3.28	Investigation and recording of damaged deliveries?	☐ ☐ ☐		5.4
3.29	FIFO principle?	☐ ☐ ☐		5.7
3.30	Inventory system?	☐ ☐ ☐		5.8
3.31	The location of materials can be detected at all times?	☐ ☐ ☐		
3.32	Incoming goods: containers and seals intact?	☐ ☐ ☐		5.27
3.33	Incoming goods: conformity with bill of delivery?	☐ ☐ ☐		5.27
	Labeling of incoming containers with			
3.34	• internal name and code?	☐ ☐ ☐		5.29
3.35	• allocated batch number?	☐ ☐ ☐		5.29
3.36	• quarantine status?	☐ ☐ ☐		5.29
3.37	• expiry date or reanalysis date?	☐ ☐ ☐		5.29
3.38	Identity test for each incoming container?	☐ ☐ ☐		5.29
3.39	Are the sampled containers marked?	☐ ☐ ☐		5.30
3.40	Are reference samples taken?	☐ ☐ ☐		5.30
3.41	Safe storage of printed packaging materials?	☐ ☐ ☐		5.41
3.42	Lot tracing of all packaging materials possible?	☐ ☐ ☐		5.42
3.43	Are excessive packaging materials destroyed?	☐ ☐ ☐		5.43
	Release of starting materials by physical/inventory checks on raw materials, packaging materials, and finished goods:			
	Item: / Stocks: Physical:	Stocks: Inventory:	Storage conditions:	
4	**DISPENSING/ASSEMBLING**			
	Rooms, general			
4.1	Suitable for the intended use?	☐ ☐ ☐		3
4.2	• Adequate size?	☐ ☐ ☐		3
4.3	• Clean?	☐ ☐ ☐		3
4.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
4.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2

		Compliance 1 2 3[a]	Remarks	EU-Guide
4.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
4.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
4.8	Recording of temperature and humidity?	☐ ☐ ☐		
4.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
4.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
4.11	Segregated from production and warehouse?	☐ ☐ ☐		3.13
4.12	Separate weighing cabins?	☐ ☐ ☐		3.13
4.13	Separate AHU for each cabin?	☐ ☐ ☐		3.12
	Air pressure gradient from weighing cabin → corridor:			3.3
4.14	Dust extraction systems available?	☐ ☐ ☐		5.11
	Operations			
4.15	Balances regularly calibrated?	☐ ☐ ☐		3.41
4.16	Only pharmaceutical raw materials in this area?	☐ ☐ ☐		5.17
4.17	Check on remains from previous materials before entering of new materials into a weighing cabin?	☐ ☐ ☐		5.9/5.35
4.18	Only one material in one cabin?	☐ ☐ ☐		5.9
4.19	Are dispensed materials correct labeled?	☐ ☐ ☐		5.29
4.20	Only released products in the dispensing?	☐ ☐ ☐		5.31
4.21	Cleaning SOPs for the dispensing?	☐ ☐ ☐		4.28
4.22	Previously dispensed material recorded on weighing protocol?	☐ ☐ ☐		4.8
4.23	Safety measures against mix-up's during assembling (e.g., cage pallets)?	☐ ☐ ☐		5.32/5.34
5	**SOLIDS MANUFACTURING**			
	Field of activity:			
	• Granulation	☐		
	• Compression	☐		
	• Encapsulation	☐		
	• Film and sugar coating	☐		
	• Visual inspection (capsules, tablets, etc.)	☐		
	• Premix (human)	☐		
	Rooms, general			
5.1	Suitable for the intended use?	☐ ☐ ☐		3
5.2	• adequate size?	☐ ☐ ☐		3
5.3	• clean?	☐ ☐ ☐		3
5.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
5.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
5.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
5.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
5.8	Recording of temperature and humidity?	☐ ☐ ☐		
5.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
5.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Rooms, special requirements			
5.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6
5.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
5.13	Logical flow of materials?	☐ ☐ ☐		3.7
5.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
5.15	Easy cleaning possible?	☐ ☐ ☐		3.10
5.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
5.17	Appropriate air-handling system?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
5.18	Appropriate dust extraction system?	☐ ☐ ☐		3.14
5.19	Appropriate lighting?	☐ ☐ ☐		3.16
5.20	Separate rest rooms?	☐ ☐ ☐		3.30
5.21	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
5.22	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
5.23	Suitable for the intended use?	☐ ☐ ☐		3.34
5.24	Well maintained?	☐ ☐ ☐		3.34
5.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
5.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
5.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
5.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
5.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
5.30	Calibration records available?	☐ ☐ ☐		3.41
5.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
5.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
5.33	Not functioning equipment in the production area (if yes: clearly marked)?	**Y N** ☐ ☐ ☐		3.44
5.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
5.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
5.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
5.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
5.38	Check of each single container of the starting materials (contents, weight, and identity)?	☐ ☐ ☐		5.3
5.39	Limits for yields?	☐ ☐ ☐		5.8
5.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
5.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
5.42	Appropriate measures against generation of dust (e.g., closed systems)?	☐ ☐ ☐		5.11

		Compliance 1 2 3[a]	Remarks		EU-Guide
	Correct labeling of containers, materials, equipment, and rooms with				5.12
5.43	• product name and batch no.	☐ ☐ ☐			5.12
5.44	• quarantine status?	☐ ☐ ☐			5.12
5.45	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐			5.14
5.46	Special procedures for the production of antibiotics, hormones etc.?	☐ ☐ ☐			5.19
5.47	• Campaign production?	☐ ☐ ☐			5.19
5.48	• Special monitoring?	☐ ☐ ☐			5.19
5.49	• Validated decontamination procedure?	☐ ☐ ☐			5.19
5.50	Double check on weight?	☐ ☐ ☐			5.34
5.51	Line clearance before start of production?	☐ ☐ ☐			5.35
5.52	Investigation of deviations in yields?	☐ ☐ ☐			5.39
5.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐			5.62
5.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐			5.63
5.55	Special release procedure (QA) for those batches?	☐ ☐ ☐			5.64
5.56	Use of protective clothing (hair cover, shoes, masks, gloves)?	☐ ☐ ☐			2.16
5.57	Clothing regulation for visitors?	☐ ☐ ☐			2.11
	IPC				5.38
	Who performs IPC?				
5.58	Are IPC methods approved by QC?	☐ ☐ ☐			6.18
	Performance of IPCs:	*During Start-up?* **Yes/No**	*Frequency*	*Automatic* data *recording?* **Yes/No**	
	Tablets/Kernels				
5.59	Individual weights	☐ ☐		☐ ☐	
5.60	Disintegration	☐ ☐		☐ ☐	
5.61	Thickness	☐ ☐		☐ ☐	
5.62	Hardness	☐ ☐		☐ ☐	
5.63	Friability/Abrasion	☐ ☐		☐ ☐	
	Sugar-/Film-coated tablets				
5.64	Weights	☐ ☐		☐ ☐	
5.65	Disintegration	☐ ☐		☐ ☐	
5.66	Residual absolute humidity (IR or)	☐ ☐		☐ ☐	
	Capsules				
5.67	Individual weights	☐ ☐		☐ ☐	
5.68	Disintegration	☐ ☐		☐ ☐	
	Validation				
5.69	Validation according to fixed procedures?	☐ ☐ ☐			5.21
5.70	New procedures released only after validation?	☐ ☐ ☐			5.22
	Validation of changes of				
5.71	• processes?	☐ ☐ ☐			5.23
5.72	• starting materials?	☐ ☐ ☐			5.23
5.73	• equipment?	☐ ☐ ☐			5.23

		Compliance 1 2 3[a]	Remarks	EU-Guide
5.74	Revalidation in fixed intervals?	☐ ☐ ☐		5.24
5.75	Procedures for the retrospective validation of old procedures?	☐ ☐ ☐		
6	**LIQUIDS MANUFACTURING**			
	Operations carried out:			
	• Dispensing (if different from solid)	☐ ☐ ☐		
	• Syrups and suspensions	☐ ☐ ☐		
	• Drops	☐ ☐ ☐		
	• Ointment manufacture	☐ ☐ ☐		
	• Ointment filling	☐ ☐ ☐		
	• Ampoule solution manufacture	☐ ☐ ☐		
	• Sterile or aseptic ampoule filling	☐ ☐ ☐		
	• Sterile freeze drying	☐ ☐ ☐		
	• Sterile powder filling	☐ ☐ ☐		
	Rooms, general			
6.1	Suitable for the intended use?	☐ ☐ ☐		3
6.2	• adequate size?	☐ ☐ ☐		3
6.3	• clean?	☐ ☐ ☐		3
6.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
6.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
6.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
6.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
6.8	Recording of temperature and humidity?	☐ ☐ ☐		
6.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
6.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
	Rooms, special requirements			
6.11	Separate manufacturing area for penicillins/cephalosporins or highly sensitizing substances?	☐ ☐ ☐		3.6
6.12	Only for processing of pharmaceuticals?	☐ ☐ ☐		3.6
6.13	Logical flow of materials?	☐ ☐ ☐		3.7
6.14	Walls, floors, and ceilings: smooth surface and free of cracks?	☐ ☐ ☐		3.8
6.15	Easy cleaning possible?	☐ ☐ ☐		3.10
6.16	Adequate drains with traps and grilles?	☐ ☐ ☐		3.11
6.17	Appropriate air-handling system with filtered air where open products are exposed to the environment?	☐ ☐ ☐		3.12
	Air pressure gradient from working bay → corridor:			
	Classification according to EC guide?			
6.18	Appropriate lighting?	☐ ☐ ☐		3.16
6.19	Separate rest rooms?	☐ ☐ ☐		3.30
6.20	Changing rooms designed to avoid contamination?	☐ ☐ ☐		3.31
6.21	Toilets segregated from manufacturing areas?	☐ ☐ ☐		3.31
	Equipment			
6.22	Suitable for the intended use?	☐ ☐ ☐		3.34
6.23	Well maintained?	☐ ☐ ☐		3.34

		Compliance 1 2 3[a]	Remarks	EU-Guide
6.24	Tanks, containers, pipework, and pumps designed for easy cleaning and sanitation (dead legs!)?	☐ ☐ ☐		Suppl. 2
6.25	Written & validated cleaning procedures?	☐ ☐ ☐		3.36
6.26	Maintenance without contamination risk (sep. area)?	☐ ☐ ☐		3.35
6.27	Equipment in contact with product: suitable materials quality?	☐ ☐ ☐		3.39
6.28	Machinery equipped with measuring and control devices?	☐ ☐ ☐		3.40
6.29	Calibration in fixed intervals acc. to written procedures?	☐ ☐ ☐		3.41
6.30	Calibration records available?	☐ ☐ ☐		3.41
6.31	Contents and flow direction marked on pipes?	☐ ☐ ☐		3.42
6.32	Pipes for distilled and demineralized water regularly monitored and sanitized?	☐ ☐ ☐		3.43
6.33	Not functioning equipment in the production area (if yes: clearly marked)?	Y/N ☐ ☐ ☐		3.44
6.34	Status of cleanliness indicated?	☐ ☐ ☐		5.13
6.35	Previous product indicated?	☐ ☐ ☐		5.13
	Operations			
6.36	Are written and validated procedures for all manufacturing steps available?	☐ ☐ ☐		5.2
6.37	Are all manufacturing steps recorded with actual parameters?	☐ ☐ ☐		5.2
6.38	Check of each single container of the starting materials (contents, weight, identity)?	☐ ☐ ☐		5.3
6.39	Limits for yields?	☐ ☐ ☐		5.8
6.40	Only one batch of one product processed?	☐ ☐ ☐		5.9
6.41	Protection against microbial contamination?	☐ ☐ ☐		5.10
	Correct labeling of containers, materials, equipment, and rooms with			5.12
6.42	• product name and batch no.	☐ ☐ ☐		5.12
6.43	• quarantine status?	☐ ☐ ☐		5.12
6.44	Deviations from standard procedures recorded and signed by the supervisor?	☐ ☐ ☐		5.14
6.45	Special procedures for the production of antibiotics, hormones, etc.?	☐ ☐ ☐		5.19
6.46	• Campaign production?	☐ ☐ ☐		5.19
6.47	• Special monitoring?	☐ ☐ ☐		5.19
6.48	• Validated decontamination procedure?	☐ ☐ ☐		5.19
6.49	Double check on weight?	☐ ☐ ☐		5.34
6.50	Line clearance before start of production?	☐ ☐ ☐		5.35
6.51	Investigation of deviations in yields?	☐ ☐ ☐		5.39
6.52	Specification of max. storage time and storage conditions if products are not immediately filled or packaged?	☐ ☐ ☐		Suppl. 9
6.53	Validated procedures for reworking of rejected batches?	☐ ☐ ☐		5.62
6.54	Detailed procedures for the addition of previous batches?	☐ ☐ ☐		5.63
6.55	Special release procedure (QA) for those batches?	☐ ☐ ☐		5.64
6.56	Use of protective clothing (hair cover, shoes, masks, gloves)?	☐ ☐ ☐		2.16
6.57	Clothing regulation for visitors?	☐ ☐ ☐		2.11

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Water			
6.58	Loop system for purified water?	☐ ☐ ☐		Suppl. 4
6.59	Antimicrobial treatment of purified water?	☐ ☐ ☐		Suppl. 4
6.60	Loop system for water for injection?	☐ ☐ ☐		Suppl. 4
	Storage temperature of water for injection:			Suppl. 4
6.61	Loop system constructed to avoid dead legs?	☐ ☐ ☐		Suppl. 4
6.62	Regular microbiological monitoring?	☐ ☐ ☐		Suppl. 4
6.63	Regular endotoxin control?	☐ ☐ ☐		Suppl. 4
	Special requirements for sterile and aseptic products			Suppl.
	Rooms and equipment			
6.64	Access of staff and materials to clean areas *only* through air locks?	☐ ☐ ☐		1
6.66	Rooms classified according to the EC Guide?	☐ ☐ ☐		3
	Classification for products to be sterilized:			
6.67	• Solution preparation (EC: class C, with special precautions class D):	Class:		5
6.68	• Filling (EC: under LF in class C):	Class:		5
	Classification for aseptic products:			
6.69	• Handling of starting materials that can be sterile filtered (EC: class C):	Class:		6
6.70	• Handling of starting materials that cannot be sterile filtered (EC: class A in class B):	Class:		6
6.71	• Handling and filling of bulk (EC: class A in Class B):	Class:		6
6.72	All rooms easy to clean disinfect?	☐ ☐ ☐		17
6.73	Doors, windows, frames, lighting, etc. without edges?	☐ ☐ ☐		18
6.74	Suspended ceilings (if yes: sealed?)?	☐ ☐ ☐		19
6.75	Traps constructed to avoid microb. contamination?	☐ ☐ ☐		21
6.76	Appropriate constructed changing rooms?	☐ ☐ ☐		22
6.77	Measures against opening of both doors of air locks?	☐ ☐ ☐		23
6.78	Overpressure gradient from cleanest areas to others?	☐ ☐ ☐		24
6.79	AHU validated and regularly revalidated?	☐ ☐ ☐		25
6.80	Control instruments for pressure gradient?	☐ ☐ ☐		26
6.81	Warning system for errors in air supply?	☐ ☐ ☐		26
6.82	Recording of pressure gradients?	☐ ☐ ☐		26
6.83	Do conveyor belts leave sterile areas?	☐ ☐ ☐		28
6.84	Maintenance works outside from clean areas possible?	☐ ☐ ☐		28
6.85	Cleaning and disinfection procedure after maintenance works?	☐ ☐ ☐		29
6.86	Regular revalidation of all equipment and systems?	☐ ☐ ☐		30
6.87	Water prepared, circulated, and stored to exclude microb. contamination?	☐ ☐ ☐		31
6.88	Cleaning and disinfection of rooms according to validated SOPs rooms?	☐ ☐ ☐		32
	• Disinfection methods?			
6.89	Microb. monitoring of cleaning and disinfection agents?	☐ ☐ ☐		33

		Compliance 1 2 3[a]	Remarks	EU-Guide
6.90	Microb. monitoring program of production areas?	☐ ☐ ☐		35
6.91	Results recorded and considered for the release?	☐ ☐ ☐		35
	Personnel and hygiene			
6.92	Minimal no. of personnel in clean areas?	☐ ☐ ☐		7
6.93	Special and regular training?	☐ ☐ ☐		8
6.94	Regular medical examinations?	☐ ☐ ☐		10
6.95	Appropriate clean room clothes (material, and design)?	☐ ☐ ☐		12
6.96	Protective clothes worn correctly?	☐ ☐ ☐		12
6.97	Prohibition of cosmetics, jewelry, and watches?	☐ ☐ ☐		13
6.98	New clean room clothes for each working cycle?	☐ ☐ ☐		15
6.99	Appropriate washing and sterilization of clothes?	☐ ☐ ☐		16
	Operations			
6.100	Validation (media filling) in regular intervals?	☐ ☐ ☐		38
	Monitoring of water preparation system, frequency:			
6.101	• microbiological			40
6.102	• chemical			40
6.103	• particles			40
6.104	• endotoxins			40
6.105	Microbiological monitoring of starting materials?	☐ ☐ ☐		42
6.106	Max. storage times defined for sterilized equipment?	☐ ☐ ☐		45
6.107	Max. storage time defined between solution preparation and filtration?	☐ ☐ ☐		46
6.108	Material transfer to clean areas through double door autoclaves?	☐ ☐ ☐		48
	Sterilization processes			
6.109	All processes validated?	☐ ☐ ☐		50
6.110	Sterilized and not sterilized materials clearly separated?	☐ ☐ ☐		54
	Trays and boxes clearly labeled with			
6.111	• product name and code	☐ ☐ ☐		54
6.112	• batch no.	☐ ☐ ☐		54
6.113	• status: sterilized or nonsterilized	☐ ☐ ☐		54
	Sterilizers			
6.114	• Recording of temp., pressure, and time?	☐ ☐ ☐		55
6.115	• Coldest point determined?	☐ ☐ ☐		55
6.116	• Independent counter check probe?	☐ ☐ ☐		55
6.117	• Heat-up time for each product determined?	☐ ☐ ☐		56
6.118	• Sterile cooling media?	☐ ☐ ☐		57
6.119	• Tightness tests for vacuum autoclaves?	☐ ☐ ☐		58
6.120	• Clean steam for steam autoclaves?	☐ ☐ ☐		58
6.121	• Circulated air with overpressure?	☐ ☐ ☐		61
6.122	• Recirculated air: sterile filtered?	☐ ☐ ☐		61
6.123	• Ethylene oxide autoclaves: humidity, temp., and time recorded?	☐ ☐ ☐		69
6.124	• Ethylene oxide autoclaves: use of bioindicators?	☐ ☐ ☐		70

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Filtration			
6.125	Double filtration?	☐ ☐ ☐		75
6.126	Integrity testing of filters immediately after use?	☐ ☐ ☐		77
6.127	Are results part of the batch protocol?	☐ ☐ ☐		77
6.128	Optical control of each single container of ampoules, vials, and infusions?	☐ ☐ ☐		82
	IPC			
6.129	Written IPC procedures and SOPs?	☐ ☐ ☐		
	Particle testing of			
6.130	• rooms	☐ ☐ ☐		
6.131	• primary packaging materials	☐ ☐ ☐		
6.132	• system of warning and action limits?	☐ ☐ ☐		
	Microbiological monitoring of			
6.133	• rooms			
6.134	• personnel			
6.135	• euipment			
6.136	Residual O_2 of ampoules, infusions, and syrups?	☐ ☐ ☐		
6.137	Endotoxin testing of water and packaging materials?	☐ ☐ ☐		
6.138	Calibration of equipment?	☐ ☐ ☐		
6.139	Regular revalidation of equipment?	☐ ☐ ☐		
7	**PACKAGING**			
	Operations carried out: • Blistering • Foil–packaging • Filling into tablet glasses • Effervescent packaging • Powder filling • Syrup/drops filling • Ointment filling	 ☐ ☐ ☐ ☐ ☐ ☐ ☐		
	Rooms			
7.1	Suitable for the intended use?	☐ ☐ ☐		3
7.2	• adequate size?	☐ ☐ ☐		3
7.3	• clean?	☐ ☐ ☐		3
7.4	Located and designed to exclude external contamination?	☐ ☐ ☐		3.1
7.5	Appropriate level of maintenance?	☐ ☐ ☐		3.2
7.6	Maintenance works possible without contamination risk?	☐ ☐ ☐		3.2
7.7	Appropriate lighting and air-conditioning?	☐ ☐ ☐		3.3
7.8	Recording of temperature and humidity?	☐ ☐ ☐		
7.9	Protection against the entry of insects or other animals?	☐ ☐ ☐		3.4
7.10	Controlled access for authorized personnel only?	☐ ☐ ☐		3.5
7.11	Adequate separation of the packaging lines?	☐ ☐ ☐		3.15
	Operations			
7.12	Only *one* product per line?	☐ ☐ ☐		5.44

		Compliance 1 2 3[a]	Remarks	EU-Guide
7.13	Check list for clearance before processing a new product/new batch?	☐ ☐ ☐		5.45
7.14	Adequate labeling of the lines (product name and code)?	☐ ☐ ☐		5.46
7.15	Check of all materials delivered to the line (quantity, identity, conformity with order)?	☐ ☐ ☐		5.47
7.16	Cleaning of primary packaging materials?	☐ ☐ ☐		5.48
7.17	Immediate labeling after filling?	☐ ☐ ☐		5.49
7.18	Careful check of all printing processes (code, and expiry date)?	☐ ☐ ☐		5.50
7.19	Special safety measures for off-line printing?	☐ ☐ ☐		5.51
7.20	Regular checks of all control devices (code reader, counter, etc.)?	☐ ☐ ☐		5.52
7.21	Printings clear and durable?	☐ ☐ ☐		5.53
7.22	Balancing of printed packaging materials and bulk?	☐ ☐ ☐		5.56
7.23	Destruction of excessive coded packaging material after completion of an order?	☐ ☐ ☐		5.57
7.24	Are the finished products kept in quarantine until final release?	☐ ☐ ☐		5.58
7.25	Appropriate storage after release?	☐ ☐ ☐		5.60
	IPC			
7.26	Checks on identity of bulk and packaging materials?	☐ ☐ ☐		5.47
	Regular line checks on			
7.27	• aspect of the packages	☐ ☐ ☐		5.54a
7.28	• completeness	☐ ☐ ☐		5.54b
7.29	• conformity of quantity and quality of materials with packaging order	☐ ☐ ☐		5.54c
7.30	• correct imprint	☐ ☐ ☐		5.54d
7.31	• correct function of control devices	☐ ☐ ☐		5.54d
	Are the following IPC checks performed?			
7.32	• Leaking	☐ ☐ ☐		
7.33	• Release torque of screw caps	☐ ☐ ☐		
7.34	• pH, density, drop weight, viscosity, sedimentation	☐ ☐ ☐		
8	**DOCUMENTATION**			
	Specifications			
8.1	Specifications for raw/packaging materials available?	☐ ☐ ☐		4.10
	Do they include			
8.2	• internal name and code	☐ ☐ ☐		4.11
8.3	• name of supplier and/or manufacturer?	☐ ☐ ☐		4.11
8.4	• reference sample (printed pack. mat.)?	☐ ☐ ☐		4.11
8.5	• sampling procedure?	☐ ☐ ☐		4.11
8.6	• qualitative/quantitative specifications with limits?	☐ ☐ ☐		4.11
8.7	• storage conditions?	☐ ☐ ☐		4.11
8.8	• maximum storage period?	☐ ☐ ☐		4.11
	Goods receiving			
8.9	Written procedures for the reception of deliveries?	☐ ☐ ☐		4.19

		Compliance 1 2 3[a]	Remarks	EU-Guide
	Do records receipt include			
8.10	• product name on labels and delivery note?	☐ ☐ ☐		4.20
8.11	• internal name and code?	☐ ☐ ☐		4.20
8.12	• receiving date?	☐ ☐ ☐		4.20
8.13	• name of supplier and/or manufacturer?	☐ ☐ ☐		4.20
8.14	• batch number of supplier?	☐ ☐ ☐		4.20
8.15	• total quantity and number of containers?	☐ ☐ ☐		4.20
8.16	• allocated internal batch number?	☐ ☐ ☐		4.20
8.17	SOPs for labeling, quarantine, and storage conditions of all incoming goods available?	☐ ☐ ☐		4.21
	SOPs include			
8.18	• authorized sampling personnel?	☐ ☐ ☐		4.22
8.19	• methods, equipment, and quantities?	☐ ☐ ☐		4.22
8.20	• safety measures?	☐ ☐ ☐		4.22
	Master formulae			
8.21	Are master formulae for each product and batch size available?	☐ ☐ ☐		4.3
8.22	Is the master formula approved and signed by the authorized persons?	☐ ☐ ☐		4.3
	The master formula includes			
8.23	• product name and code?	☐ ☐ ☐		4.14a
8.24	• description of galenical form, dosage, and batch size?	☐ ☐ ☐		4.14b
8.25	• all active ingredients with name, code, and weight?	☐ ☐ ☐		4.14c
8.26	• all excipients used during manufacture with name, code, and weight?	☐ ☐ ☐		4.14c
8.27	• yields with limits?	☐ ☐ ☐		4.14d
	Does the working procedure include			
8.28	• the production line?	☐ ☐ ☐		4.15a
8.29	• equipment to be used?	☐ ☐ ☐		4.15a
8.30	• reference to methods for cleaning, assembling, and calibration of machines?	☐ ☐ ☐		4.15b
8.31	• detailed stepwise manufacturing prescription?	☐ ☐ ☐		4.15c
8.32	• IPCs to be performed with limits?	☐ ☐ ☐		4.15d
8.33	• precautions to be followed?	☐ ☐ ☐		4.15e
8.34	Are batch records kept for each batch processed?	☐ ☐ ☐		4.17
	Do batch records include			
8.35	• protocol of line clearance?	☐ ☐ ☐		4.17
8.36	• name of the product and batch no.?	☐ ☐ ☐		4.17a
8.37	• date and time of start and end of production?	☐ ☐ ☐		4.17b
8.38	• name and initials of responsible workers for each step?	☐ ☐ ☐		4.17c, d
8.39	• batch and analytical no. and actual weight of all starting materials?	☐ ☐ ☐		4.17e
8.40	• equipment used?	☐ ☐ ☐		4.17f
8.41	• results of IPCs with initials of person who carries them out?	☐ ☐ ☐		4.17g
8.42	• yields of the relevant manufacturing steps?	☐ ☐ ☐		4.17h
8.43	• detailed notes on problems and process deviations?	☐ ☐ ☐		4.17i

		Compliance 1 2 3[a]	Remarks	EU-Guide
8.44	Records on reprocessing of batches?	☐ ☐ ☐		
	Packaging instructions			
8.45	Packaging instructions for each product, package size, and presentation?	☐ ☐ ☐		4.16
	Do they include			
8.46	• product name?	☐ ☐ ☐		4.16a
8.47	• description of galenical form and strength?	☐ ☐ ☐		4.16b
8.48	• package size?	☐ ☐ ☐		4.17c
8.49	• list of all packaging materials with code for a standard batch size?	☐ ☐ ☐		4.17d
8.50	• samples of printed packaging materials?	☐ ☐ ☐		4.17e
8.51	• special precautions?	☐ ☐ ☐		4.17f
8.52	• description of the process and equipment?	☐ ☐ ☐		4.17g
8.53	• IPCs to be performed with sampling instruction?	☐ ☐ ☐		4.17h
8.54	Are packaging batch records kept for each batch or part batch?	☐ ☐ ☐		4.18
	Do the packaging batch records include			
8.55	• protocol of line clearance?	☐ ☐ ☐		4.18
8.56	• name of the product?	☐ ☐ ☐		4.18a
8.57	• date and time when operations have been performed?	☐ ☐ ☐		4.18b
8.58	• name of the responsible person?	☐ ☐ ☐		4.18c
8.59	• initials of workers carrying out operations?	☐ ☐ ☐		4.18d
8.60	• notes on identity checks and conformity with packaging instructions?	☐ ☐ ☐		4.18e
8.61	• results of IPCs	☐ ☐ ☐		4.18e
8.62	• details of operations and equipment used?	☐ ☐ ☐		4.18f
8.63	• samples of printed packaging materials with codes (MFD, EXP, batch no. etc.)?	☐ ☐ ☐		4.18g
8.64	• record of problems and process deviations?	☐ ☐ ☐		4.18h
8.65	• quantities of packaging materials delivered, used, destroyed, or returned?	☐ ☐ ☐		4.18i
8.66	• no. of packs consumed?	☐ ☐ ☐		4.18j
	Testing			
	Do the written testing procedures include			
8.67	• test methods?	☐ ☐ ☐		4.23
8.68	• equipment for testing?	☐ ☐ ☐		4.23
8.69	Tests documented?	☐ ☐ ☐		4.23
	Others			
8.70	Procedures for release and rejection of materials and finished products?	☐ ☐ ☐		4.24
8.71	Final release by authorized person?	☐ ☐ ☐		4.24
8.72	Records about distribution of each batch?	☐ ☐ ☐		4.25
	Procedures and protocols about			
8.73	• validation?	☐ ☐ ☐		4.26
8.74	• set up and calibration of equipment?	☐ ☐ ☐		4.26
8.75	• maintenance, cleaning, and disinfection?	☐ ☐ ☐		4.26

		Compliance 1 2 3[a]	Remarks	EU-Guide
8.76	• training records?	☐ ☐ ☐		4.26
8.77	• environmental monitoring of production areas?	☐ ☐ ☐		4.26
8.78	• pest control?	☐ ☐ ☐		4.26
8.79	• complaints?	☐ ☐ ☐		4.26
8.80	• recalls?	☐ ☐ ☐		4.26
8.81	• returned goods?	☐ ☐ ☐		4.26
8.82	Instructions for use of manufacturing and testing equipment?	☐ ☐ ☐		4.27
	Log books for major equipment incl. date and name of persons who performed			
8.83	• validation?	☐ ☐ ☐		4.28
8.84	• calibration?	☐ ☐ ☐		4.28
8.85	• maintenance, cleaning, and repair works?	☐ ☐ ☐		4.28
8.86	Chronological records of use of major equipment and manufacturing areas?	☐ ☐ ☐		4.29
9	**QUALITY CONTROL**			**6**
	General requirements			
9.1	Independent QC department available?	☐ ☐ ☐		6.1
9.2	Head of QC well qualified and sufficiently experienced?	☐ ☐ ☐		6.1
9.3	Qualified personnel available?	☐ ☐ ☐		2.1
9.4	Organization charts available?	☐ ☐ ☐		2.2
9.5	Job descriptions available?	☐ ☐ ☐		2.2
9.6	Responsibilities clearly defined?	☐ ☐ ☐		2.2
9.7	Continuous training programs for QC staff?	☐ ☐ ☐		2.2
9.8	Initial job training for all employees?	☐ ☐ ☐		2.9
9.9	Training records?	☐ ☐ ☐		
9.10	QC personnel admitted to the production rooms for sampling?	☐ ☐ ☐		
	QC laboratories			
9.11	Suitable for the intended use?	☐ ☐ ☐		3.26
9.12	Laboratories of adequate size?	☐ ☐ ☐		3.26
9.13	Appropriate level of maintenance?	☐ ☐ ☐		3.1
9.14	Adequate separation from the production area?	☐ ☐ ☐		3.26
9.15	Controlled access of authorized personnel only?	☐ ☐ ☐		3.5
9.16	Special laboratory to handle biological samples available?	☐ ☐ ☐		3.29
9.17	Special laboratory to handle radioactive material available?	☐ ☐ ☐		3.29
9.18	Separate recreation rooms for the personnel available?	☐ ☐ ☐		3.30
9.19	Animal laboratories present?	☐ ☐ ☐		3.33
9.20	Animal laboratories separated from other areas?	☐ ☐ ☐		3.33
9.21	Animal laboratories equipped with a separate air-handling system?	☐ ☐ ☐		3.33
	QC Documentation			
9.22	Do procedures exist for			
	• self-inspection?	☐ ☐ ☐		
	• release or rejection of products or raw material?	☐ ☐ ☐		
	• product complaints?	☐ ☐ ☐		
	• product recalls?	☐ ☐ ☐		

		Compliance 1 2 3[a]	Remarks	EU-Guide
	• local stability testing? • storage of reference samples? • validation of analytical procedures?	☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		
9.23	Specifications available for • raw materials? • bulk products? • packaging materials?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.7
9.24	Analytical procedures for every product?	☐ ☐ ☐		
9.25	Are Basel methods followed?	☐ ☐ ☐		
9.26	Validation of locally developed test methods?	☐ ☐ ☐		
9.27	Sampling procedures available for • raw materials? • bulk products? • packaging materials?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.7
9.28	Suppliers certificates available?	☐ ☐ ☐		6.7
9.29	Calibration program for analytical instruments installed?	☐ ☐ ☐		6.7
9.30	Maintenance program for analytical instruments?	☐ ☐ ☐		6.7
9.31	Retention system for QC records?	☐ ☐ ☐		6.8
9.32	Batch documents stored for expiry + 1 year or 5 years (EEC 75/319, article 22) minimum?	☐ ☐ ☐		6.8
9.33	Are original data like notebooks stored in addition to the batch documents?	☐ ☐ ☐		6.10
9.34	Can the original data be traced back easily and quickly from the analytical report number or batch number?	☐ ☐ ☐		6.10
9.35	Are trend analyses being performed for • analytical results? • yields? • environmental monitoring data?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.9
	Sampling			
9.36	Written procedures for taking samples?	☐ ☐ ☐		6.11
9.37	Do procedures define • method of sampling? • necessary equipment? • quantity of the sample? • subdivision of the sample? • sample container? • labeling of samples? • storage conditions? • cleaning and storage of sampling equipment? • identification of containers sampled	 ☐		
9.38	Are samples representative for the batch they are taken from (sampling plan)?	☐ ☐ ☐		6.12
9.39	Are critical steps being surveilled and validated by additional sampling (e.g., beginning or end of a process).	☐ ☐ ☐		6.12
9.40	Sample containers labeled with • name of the content • batch number • date of sampling • batch containers sampled	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		6.13
9.41	Are samples taken by QC/QA?	☐ ☐ ☐		

		Compliance 1 2 3[a]	Remarks	EU-Guide
9.42	Reference samples retained for validity +1 year?	☐ ☐ ☐		6.14
9.43	Storage of reference samples under the recommended storage conditions?	☐ ☐ ☐		6.14
9.44	Finished products stored in the final packaging?	☐ ☐ ☐		6.14
9.45	Quantity of the reference sample makes 1 (better 2) complete reanalysis possible?	☐ ☐ ☐		6.14
9.46	Sample room secure?	☐ ☐ ☐		
9.47	Sample room neatly organized and not overcrowded?	☐ ☐ ☐		
	Testing			
9.48	Are the applied analytical methods validated?	☐ ☐ ☐		6.15
9.49	Analytical methods in compliance with the registration?	☐ ☐ ☐		6.16
9.50	Are all results recorded and checked for correctness?	☐ ☐ ☐		6.16
9.51	Are all calculations checked?	☐ ☐ ☐		6.16
9.52	Do the testing protocols contain			6.17
	• name and galenical form of material?	☐ ☐ ☐		
	• batch number?	☐ ☐ ☐		
	• supplier if applicable?	☐ ☐ ☐		
	• specification reference?	☐ ☐ ☐		
	• method reference?	☐ ☐ ☐		
	• analytical results?	☐ ☐ ☐		
	• reference to analytical certificates?	☐ ☐ ☐		
	• date of the analysis?	☐ ☐ ☐		
	• name of the analyst?	☐ ☐ ☐		
	• name of the person verifying the data?	☐ ☐ ☐		
	• statement of release or rejection?	☐ ☐ ☐		
	• date and signature of the release person?	☐ ☐ ☐		
9.53	Are all IPC methods in production approved by QC?	☐ ☐ ☐		6.18
9.54	Are written methods available for the preparation of reagents and volumetric solutions?	☐ ☐ ☐		6.19
9.55	Is a record maintained of standardization of volumetric solutions?	☐ ☐ ☐		6.2
9.56	Are reagents for prolonged use labeled with			6.20
	• date of the preparation?	☐ ☐ ☐		
	• sign of the preparator?	☐ ☐ ☐		
9.57	Are unstable reagents labeled with			6.20
	• expiry date?	☐ ☐ ☐		
	• storage conditions?	☐ ☐ ☐		
9.58	Are volumetric solutions labeled with			6.20
	• the last date of standardization?	☐ ☐ ☐		
	• last current factor?	☐ ☐ ☐		
9.59	Are reference standards labeled with			6.21
	• name and potency	☐ ☐ ☐		
	• suppliers' reference	☐ ☐ ☐		
	• date of receipt	☐ ☐ ☐		
	• date of expiry	☐ ☐ ☐		
9.60	Are reference standards stored properly and under the control of a designated person?	☐ ☐ ☐		
9.61	• Are animals used for testing of components, materials, or products?	☐ ☐ ☐		
	• Quarantined before use?	☐ ☐ ☐		
	• Checked for suitability?	☐ ☐ ☐		
	• Are records maintained showing the history of their use?			

		Compliance 1 2 3[a]	Remarks	EU-Guide
10	**COMPLAINTS AND PRODUCT RECALLS**			**8**
	Complaints			8.1
10.1	Does a written complaint procedure exist?	☐ ☐ ☐		8.2
10.2	Are product complaints carefully reviewed?	☐ ☐ ☐		8.1
10.3	Is a person designated to handle complaints and to decide on measures to be taken?	☐ ☐ ☐		8.1
10.4	Is each complaint concerning a product recorded with all original details?	☐ ☐ ☐		8.3
10.5	Are product complaints thoroughly investigated?	☐ ☐ ☐		8.3
10.6	Is a responsible person of QC involved in the study?	☐ ☐ ☐		8.3
10.7	Is it considered that other batches might be concerned as well?	☐ ☐ ☐		8.4
10.8	Are decisions and measures as a result recorded?	☐ ☐ ☐		8.5
10.9	Is this record added to the corresponding batch documents?	☐ ☐ ☐		8.5
10.10	Are the complaint records regularly revised with respect to specific or recurring problems?	☐ ☐ ☐		8.6
10.11	Are the authorities informed of serious quality problems with a product?	☐ ☐ ☐		8.7
	Recalls			8.8
10.12	Does a written recall procedure exist?	☐ ☐ ☐		8.9
10.13	Is a person nominated responsible for the execution and coordination of a recall?	☐ ☐ ☐		8.8
10.14	Responsible person independent of the marketing and sales organization?	☐ ☐ ☐		8.8
10.15	Are the competent authorities informed of an imminent recall?	☐ ☐ ☐		8.11
10.16	Does the person responsible for a recall have access to the distribution records?	☐ ☐ ☐		8.12
10.17	Do the distribution records contain sufficient information on customers with • addresses? • phone numbers inside or outside working hours? • batches and amounts delivered? • medical samples?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		8.12
10.18	Are recalled products stored separately in a secure area?	☐ ☐ ☐		8.13
10.19	Is a final record made including a reconciliation between the delivered and recovered quantities?	☐ ☐ ☐		8.14
10.20	Is the effectiveness of the arrangements for recalls checked critically from time to time?	☐ ☐ ☐		8.15
11	**SELF-INSPECTION**			**9**
11.1	Does a self-inspection procedure exist which defines frequency and program?	☐ ☐ ☐		9.1
11.2	Are self-inspections carried out to check compliance with GMP rules?	☐ ☐ ☐		9.1
11.3	Are self-inspections conducted in an independent and detailed way? by designated competent persons from the company or external experts?	 ☐ ☐ ☐ ☐ ☐ ☐		9.2
11.4	Are self-inspections recorded?	☐ ☐ ☐		9.3

		Compliance 1 2 3[a]	Remarks	EU-Guide
11.5	Do reports contain • the observations made during a self-inspection? • proposals for corrective measures?	 ☐ ☐ ☐ ☐ ☐ ☐		9.3
11.6	Are actions subsequently taken recorded?	☐ ☐ ☐		9.3
12	**CONTRACT MANUFACTURE AND ANALYSIS**			**7**
12.1	Written contract between contract giver and contract acceptor available?	☐ ☐ ☐		7.1
12.2	Are responsibilities and duties clearly defined?	☐ ☐ ☐		7
12.3	All arrangements in accordance with the marketing authorization of the product concerned?	☐ ☐ ☐		7.2
	The contract giver			
12.4	Competence of the acceptor to carry out the work successful and according to GMP assessed?	☐ ☐ ☐		7.3
12.5	Acceptor provided with all the informations necessary to carry out the contract work?	☐ ☐ ☐		7.4
12.6	Acceptor informed of safety aspects?	☐ ☐ ☐		7.4
12.7	Conformance of products supplied by the acceptor ensured?	☐ ☐ ☐		7.5
12.8	Product released by a qualified person on the acceptor's side?	☐ ☐ ☐		7.5
	The contract acceptor			
12.9	Does the acceptor have • adequate premises and equipment? • knowledge and experience? • competent personnel? • a manufacturing authorization?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.6
12.10	Does the acceptor ensure that all products or materials delivered to him are suitable?	☐ ☐ ☐		7.7
12.11	There must be no work passed to a third party without the permission of the giver.	☐ ☐ ☐		7.8
12.12	If a third party is involved it must have the necessary manufacturing and analytical information.	☐ ☐ ☐		7.8
	The contract			
12.13	Does the written contract specify the responsibilities?	☐ ☐ ☐		7.10
12.14	Have technical aspects been drawn-up by competent persons?	☐ ☐ ☐		7.10
12.15	Release of material and check for compliance with the marketing authorization defined?	☐ ☐ ☐		7.11
12.16	Is defined who is responsible for • purchasing of materials? • IPC controls • testing and release of materials? • manufacturing and quality control? • sampling? • storage of batch documentation?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		7.12
12.17	Are manufacturing, analytical, and distribution records available to the contract giver?	☐ ☐ ☐		7.13
12.18	Contract permits the giver to visit the facilities of the acceptor?	☐ ☐ ☐		7.14
12.19	In the case of contract analysis: Does the contract acceptor understand that he is subject to inspection by the competent authorities?	☐ ☐ ☐		7.15

		Compliance 1 2 3[a]	Remarks	EU-Guide
13	**AUDIT OF SUPPLIERS**			**2.7**
13.1	Supplier audits performed for • excipients? • active substances? • packaging material?	 ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐		

[a] 1. Fulfilled or available; 2. partially fulfilled; 3. not fulfilled or not available.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of test results.

Active Pharmaceutical Ingredient (API) (or Drug Substance)—Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

Air Lock—An enclosed space with two or more doors, which is interposed between two or more rooms, for example, of differing classes of cleanliness, for the purpose of controlling the airflow between those rooms when they need to be entered. An air lock is designed for use either by people or for goods and/or equipment.

API Starting Material—A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API Starting Material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in house. API Starting Materials are normally of defined chemical properties and structure.

Authorized Person—The person recognized by the national regulatory authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested, and approved for release in compliance with the laws and regulations in force in that country.

Batch (or Lot)—A specific quantity of material produced in a process or series of processes so that it is expected to be homogeneous within specified limits. In the case of continuous production, a batch may correspond to a defined fraction of the production. The batch size can be defined either by a fixed quantity or by the amount produced in a fixed time interval. A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it is expected to be homogeneous. It may sometimes be necessary to divide a batch into a number of subbatches, which are later brought together to form a final homogeneous batch. In the case of terminal sterilization, the batch size is determined by the capacity of the autoclave. In continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. The batch size can be defined either as a fixed quantity or as the amount produced in a fixed time interval.

Batch Number (or Lot Number)—A unique combination of numbers, letters, and/or symbols that identifies a batch (or lot) and from which the production and distribution history can be determined. A distinctive combination of numbers and/or letters which uniquely identifies a batch on the labels, its batch records, and corresponding certificates of analysis, and so on.

Batch Records—All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

Bioburden—The level and type (e.g., objectionable or not) of microorganisms that can be present in raw materials, API starting materials, intermediates, or APIs. Bioburden should not be considered contamination unless the levels have been exceeded or defined objectionable organisms have been detected.

Bulk Product—Any product that has completed all processing stages up to, but not including, final packaging.

Calibration—The demonstration that a particular instrument or device produces results within specified limits by comparison with those produced by a reference or traceable standard over an appropriate range of measurements. The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (especially weighing), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

Clean Area—An area with defined environmental control of particulate and microbial contamination, constructed, and used in such a way as to reduce the introduction, generation, and retention of contaminants within the area.

Computer System—A group of hardware components and associated software, designed and assembled to perform a specific function or group of functions. A process or operation integrated with a computer system.

Consignment (or Delivery)—The quantity of a pharmaceutical(s), made by one manufacturer and supplied at one time in response to a particular request or order. A consignment may comprise one or more packages or containers and may include material belonging to more than one batch.

Contamination—The undesired introduction of impurities of a chemical or microbiological nature, or of foreign matter, into or on to a starting material or intermediate during production, sampling, packaging or repackaging, and storage or transport.

Contract Manufacturer—A manufacturer performing some aspect of manufacturing on behalf of the original manufacturer.

Critical—Describes a process step, process condition, test requirement, or other relevant parameter or item that must be controlled within predetermined criteria to ensure that the API meets its specification.

Critical Operation—An operation in the manufacturing process that may cause variation in the quality of the pharmaceutical product.

Cross-Contamination—Contamination of a material or product with another material or product. Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Deviation—Departure from an approved instruction or established standard.

Drug (Medicinal) Product—The dosage form in the final immediate packaging intended for marketing. (Reference Q1A)

Drug Substance—See Active Pharmaceutical Ingredient.

Expiry Date (or Expiration Date)—The date placed on the container/labels of an API designating the time during which the API is expected to remain within established shelf life specifications if stored under defined conditions, and after which it should not be used.

Finished Product—A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labeling.

Impurity—Any component present in the intermediate or API that is not the desired entity.

Impurity Profile—A description of the identified and unidentified impurities present in an API.

In-Process Control (or Process Control)—Checks performed during production in order to monitor and, if appropriate, to adjust the process, and/or to ensure that the intermediate or API conforms to its specifications.

In-process Control—Checks performed during production in order to monitor and, if necessary, to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

Intermediate—A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated. Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Large-Volume Parenterals—Sterile solutions intended for parenteral application with a volume of 100 mL or more in one container of the finished dosage form.

Lot—See Batch.

Lot Number—See Batch Number.

Manufacture—All operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage, and distribution of APIs and related controls.

Manufacturer—A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of pharmaceuticals.

Marketing Authorization (Product License, Registration Certificate)—A legal document issued by the competent drug regulatory authority that establishes the detailed composition and formulation of the product and the pharmacopoeial or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labeling, and shelf life.

Master Formula—A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

Master Record—A document or set of documents that serve as a basis for the batch documentation (blank batch record).

Material—A general term used to denote raw materials (starting materials, reagents, solvents), process aids, intermediates, APIs, and packaging and labeling materials.

Mother Liquor—The residual liquid which remains after the crystallization or isolation processes. A mother liquor may contain unreacted materials, intermediates, levels of the API, and/or impurities. It may be used for further processing.

Packaging—All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Filling of a sterile product under aseptic conditions or a product intended to be terminally sterilized, would not normally be regarded as part of packaging.

Packaging Material—Any material intended to protect an intermediate or API during storage and transport. Any material, including printed material, employed in the packaging of a pharmaceutical, but excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Pharmaceutical Product—Any material or product intended for human or veterinary use presented in its finished dosage form or as a starting material for use in such a dosage form, that is subject to control by pharmaceutical legislation in the exporting state and/or the importing state.

Procedure—A documented description of the operations to be performed, the precautions to be taken and measures to be applied directly or indirectly related to the manufacture of an intermediate or API.

Process Aids—Materials, excluding solvents, used as an aid in the manufacture of an intermediate or API that do not themselves participate in a chemical or biological reaction (e.g., filter aid, activated carbon, and so on).

Process Control—See In-Process Control.

Production—All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing, packaging and repackaging, labeling and relabeling, to completion of the finished product.

Qualification—Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.

Quality Assurance (QA)—The sum total of the organised arrangements made with the object of ensuring that all APIs are of the quality required for their intended use and that quality systems are maintained.

Quality Control (QC)—Checking or testing that specifications are met.

Quality Unit(s)—An organizational unit independent of production which fulfills both Quality Assurance and Quality Control responsibilities. This can be in the form of separate QA and QC units or a single individual or group, depending upon the size and structure of the organization.

Quarantine—The status of starting or packaging materials, intermediates, or bulk or finished products isolated physically or by other effective means while a decision is awaited on their release, rejection, or reprocessing.

Raw Material—A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Reconciliation—A comparison between the theoretical quantity and the actual quantity.

Recovery—The introduction of all or part of previous batches (or of redistilled solvents and similar products) of the required quality into another batch at a defined stage of manufacture. It includes the removal of impurities from waste to obtain a pure substance or the recovery of used materials for a separate use.

Reference Standard, Primary—A substance that has been shown by an extensive set of analytical tests to be authentic material that should be of high purity.

Reference Standard, Secondary—A substance of established quality and purity, as shown by comparison to a primary reference standard, used as a reference standard for routine laboratory analysis.

Reprocessing—Subjecting all or part of a batch or lot of an in-process drug, bulk process intermediate (final biological bulk intermediate) or bulk product of a single batch/lot to a previous step in the validated manufacturing process due to failure to meet predetermined specifications. Reprocessing procedures are foreseen as occasionally necessary for biological drugs and, in such cases, are validated and preapproved as part of the marketing authorization.

Retest Date—The date when a material should be reexamined to ensure that it is still suitable for use.

Reworking—Subjecting an in-process or bulk process intermediate (final biological bulk intermediate) or final product of a single batch to an alternate manufacturing process due to a failure to meet predetermined specifications. Reworking is an unexpected occurrence and is not preapproved as part of the marketing authorization.

Self-Contained Area—Premises which provide complete and total separation of all aspects of an operation, including personnel and equipment movement, with well established procedures, controls, and monitoring. This includes physical barriers as well as separate air-handling systems, but does not necessarily imply two distinct and separate buildings.

Signature (Signed)—See definition for signed.

Signed (Signature)—The record of the individual who performed a particular action or review. This record can be initials, full handwritten signature, personal seal, or authenticated and secure electronic signature.

Solvent—An inorganic or organic liquid used as a vehicle for the preparation of solutions or suspensions in the manufacture of an intermediate or API.

Specification—A list of detailed requirements with which the products or materials used or obtained during manufacture have to conform. They serve as a basis for quality evaluation.

Standard Operating Procedure (SOP)—An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (e.g., equipment operation, maintenance, and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Starting Material—Any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

Validation—A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria. Action of proving, in accordance with the principles of GMP, that any procedure, process, equipment, material, activity, or system actually leads to the expected results (see also qualification).

Validation Protocol—A written plan stating how validation will be conducted and defining acceptance criteria. For example, the protocol for a manufacturing process identifies processing equipment, critical process parameters/operating ranges, product characteristics, sampling, test data to be collected, number of validation runs, and acceptable test results.

Yield, Expected—The quantity of material or the percentage of theoretical yield anticipated at any appropriate phase of production based on previous laboratory, pilot scale, or manufacturing data.

Yield, Theoretical—The quantity that would be produced at any appropriate phase of production, based upon the quantity of material to be used, in the absence of any loss or error in actual production.

3

Inspection of Sterile Product Manufacturing Facilities

I. INTRODUCTION

Typically, a sterile drug contains no viable microorganisms and is nonpyrogenic. Drugs for intravenous injection, for irrigation, and those used as ophthalmic preparations meet these criteria. In addition, other dosage forms might be labeled as sterile, for instance, an ointment applied to a puncture wound or skin abrasion.

Parenteral drugs must be nonpyrogenic, because the presence of pyrogens can cause a febrile reaction in humans. Pyrogens are the products of the growth of microorganisms. Therefore, any condition that permits bacterial growth should be avoided in the manufacturing process. Pyrogens may develop in water located in stills, storage tanks, dead-legs, and piping, or from surface contamination of containers, closures, or other equipment. Parenterals may also contain chemical contaminants that produce a pyretic response in humans or animals although no pyrogens are present.

The sterile product manufacturing system includes measures that minimize the hazard of contamination with microorganisms and particulates of sterile drugs. This chapter describes what manufacturers should evaluate about their facilities regarding compliance with the existing (and, in some instances, upcoming) standards of inspection. Highlighted in this chapter are the areas of concern to regulatory inspectors, the problem areas, the often-overlooked systems, and, above all, the attributes where most inspections fail. It is assumed that the manufacturer is fully cognizant of the existing current good manufacturing practice (cGMP) compliance conditions as described in the Code of Federal Regulations (CFR).

This chapter includes an outline of the general cGMP compliance requirements [particularly those laid out by the U.S. Food and Drug Aministration (FDA)] for sterile manufacturing areas, detailed description of compliance problem areas regarding aseptic processing, terminal sterilization, blow-fill sealing, lyophilization, and the quality of water systems. Portions of the watch list provided here are still in the draft phase at the regulatory agencies, but might be fully adopted by the time this book is published. The guidelines given therefore present state-of-the-art sterile product manufacturing inspection audit requirements.

II. cGMP COMPLIANCE BASICS

A. Personnel

Greater emphasis is placed by regulatory agencies on the training of personnel involved in the manufacturing of sterile products than any other type. The company must always assure that the training program ensures that personnel performing production and control procedures have experience and training commensurate with their intended duties. It is important that personnel be trained in aseptic procedures. The employees must be properly gowned and use good aseptic techniques.

B. Buildings

The nonsterile preparation areas for sterile drugs should also be controlled. Refer to subpart C of the proposed Current Good Manufacturing Practice Requirements for large volume parenterals (LVPs) for further details. Evaluate the air cleanliness classification of the area. For guidance in this area, review Federal Standard #209E entitled "Airborne Particulate Cleanliness Classes in Clean-Rooms and Clean Zones." The formulation practices or procedures used in the preparation areas are important in minimizing routes of contamination. It is best to minimize traffic and unnecessary activity in the preparation area. The filling rooms and other aseptic areas should be so constructed as to eliminate possible areas for microbiological or particulate contamination, for instance, in the dust-collecting ledges or porous surfaces. Detailed plans of the cleaning and maintenance of aseptic areas should be developed and appropriate records kept assuring compliance.

C. Air

Air supplied to the nonsterile preparation or formulation area for manufacturing solutions prior to sterilization should be filtered as necessary to control particulates. Air supplied to product exposure areas where sterile drugs are processed and handled should be high-efficiency particulate air (HEPA) filtered under positive pressure. The system description for HEPA filters should include certification or dioctyl phthalate (DOP) testing, indicating the frequency of testing, or both.

The compressed air system requires that the air be filtered at the point of use to control particulates. Diagrams of the HEPA-filtered and compressed air systems should be made and be readily available for inspection.

D. Environmental Controls

Specifications for viable and nonviable particulates must be established. Specifications for viable particulates must include provisions for both air and surface sampling of aseptic processing areas and equipment. A comprehensive environmental control program, specifications, and test data should be available, particularly the procedures for reviewing out-of-limit test results. Review of environmental test data should be included as a part of the release procedures. (*Note*: In the preparation of media for environmental air and surface sampling, suitable inactivating agents should be added; e.g., the addition of penicillinase to media used for monitoring sterile penicillin operations and cephalosporin products.)

E. Equipment

Instructions should be available on how the equipment operates, including cleaning and maintenance practices. How the equipment used in the filling room is sterilized, and if the sterilization cycle has been validated, should be properly documented. The practice of resterilizing equipment if sterility has been compromised should be clearly described.

A listing of the type of filters used; the purpose of the filters; and how they are assembled, cleaned, and inspected

for damage should be maintained. Microbial retentive filters require an integrity testing (i.e., bubble point testing before and after the filtration operation).

F. Water for Injection

Water used in the production of sterile drugs must be controlled to assure that it meets USP (United States Pharmacopoeia) specifications. A detailed description of water quality systems is presented later in the chapter. The description of the system used for producing water for injection (WFI) storage and of the delivery system should be present in a written form and in sufficient detail for the operators to understand it fully. The stills, filters, storage tanks, and pipes should be installed and operated in a manner that will not contaminate the water. The procedures and specifications that assure the quality of the WFI should be periodically audited for compliance and records of audit available for inspection.

G. Containers and Closures

The system for handling and storing containers and closures should be established to show that cleaning, sterilization, and depyrogenization are adequate and have been validated.

H. Sterilization

1. Methods

Depending on the method of sterilization used, appropriate guidelines should be followed. A good source of reference material on validation of various sterilization processes is the *Parenteral Drug Association Technical Reports*. For instance, Technical Report No. 1 covers validation of steam sterilization cycles. Establish that the validation data are in order.

If steam under pressure is used, an essential control is a mercury thermometer and a recording thermometer installed in the exhaust line. The time required to heat the center of the largest container to the desired temperature must be known. Steam must expel all air from the sterilizer chamber to eliminate cold spots. The drain lines should be connected to the sewer by means of an air break to prevent back siphoning. The use of paper layers or liners and other practices that might block the flow of steam should be avoided. Charts of time, temperature, and pressure should be filed for each sterilizer load.

If sterile filtration is used, establish criteria for selecting the filter and the frequency of changing. Review the filter validation data. Know what the bioburden of the drug is and develop the procedures for filter integrity testing. If filters are not changed after each batch is sterilized, establish data to justify the integrity of the filters for the time used and that "grow through" has not occurred.

If ethylene oxide sterilization is used, establish tests for residues and degradation. A record of the ethylene oxide (EtO) sterilization cycle, including preconditioning of the product, EtO concentration, gas exposure time, chamber and product temperature, and chamber humidity should be available.

2. Indicators

Establish which type of indicator will be used to assure sterility, such as lag thermometers, peak controls, Steam Klox, test cultures, or biological indicators (BIs). (*Caution:* When spore test strips are used to test the effectiveness of ethylene oxide sterilization, be aware that refrigeration may cause condensation on removal to room temperature. Moisture on the strips converts the spore to the more susceptible vegetative forms of the organism, which may affect the reliability of the sterilization test. Do not store the spore strips where they could be exposed to low levels of ethylene oxide.)

If BIs are used, assure that the current USP guidelines on sterilization and BIs are followed. In some cases, testing BIs may become all or part of the sterility testing.

BIs are of two forms, each incorporating a viable culture of a single species of microorganism. In one form, the culture is added to representative units of the lot to be sterilized or to a simulated product that offers no less resistance to sterilization than the product to be sterilized. The second form is used when the first form is not practical, as in the case of solids. In the second form, the culture is added to disks or strips of filter paper, or metal, glass, or plastic beads. Data on the use of BIs include the following:

- Surveys of the types and numbers of organisms in the product before sterilization.
- Data on the resistance of the organism to the specific sterilization process.
- Data used to select the most resistant organism and its form (spore or vegetative cell).
- Studies of the stability and resistance of the selected organism to the specific sterilization process.
- Studies on the recovery of the organism used to inoculate the product.
- If a simulated product or surface similar to the solid product is used, validation of the simulation or similarity is required. The simulated product or similar surface must not affect the recovery of the numbers of indicator organisms applied.
- Validation of the number of organisms used to inoculate the product, simulated product, or similar surface, to include stability of the inoculum during the sterilization process.

Because qualified personnel are crucial to the selection and application of these indicators, their qualifications, including experience dealing with the process, expected contaminants, testing of resistance of organisms, and technique, should be frequently reviewed and records kept current. Policies regarding use, control, and testing of the BI by product, including a description of the method used to demonstrate presence or absence of viable indicator in or on the product, should be established.

Check data used to support the use of the indicator each time it is used. Include the counts of the inoculum used; recovery data to control the method used to demonstrate the sterilization of the indicator organism; counts on unprocessed, inoculated material to indicate the stability of the inoculum for the process time; and results of sterility testing specifically designed to demonstrate the presence or absence of the indicator organism for each batch or filling operation. In using indicators, assure that the organisms are handled so they do not contaminate the drug manufacturing area and product.

3. Filled Containers

Challenge the procedure of how the filled vials or ampoules leave the filling room. Is the capping or sealing done in the sterile fill area? If not, how is sterility maintained until capped? Review the tests done on finished vials, ampoules, or other containers to assure proper fill and seal, for instance, leak and torque tests.

Keep a good record of examinations made for particulate contamination. Know that inspectors can quickly check for suspected particulate matter by using a polariscope. Practice this in-house on a representative sample of production frequently. Employees doing visual examinations online

must be properly trained. If particle counts are done by machine, this operation must be validated. Know that even when 100% inspection is performed, defective vials and ampoules are picked up afterward.

I. Personnel Practices

Establish how employees sterilize and operate the equipment used in the filling area. Be critical of filling room personnel practices. Are the employees properly dressed in sterile gowns, masks, caps, and shoe coverings? Establish the gowning procedures, and determine whether good aseptic technique is maintained in the dressing and filling rooms. Check on the practices after lunch and other absences. Is fresh sterile garb supplied, or are soiled garments reused? If the dressing room is next to the filling area, how employees and supplies enter the sterile area is important.

J. Laboratory Controls

Pharmaceutical quality control laboratories are subject to strict guidelines established by the FDA. Review the "FDA Guide to Inspections of Pharmaceutical Quality Control Laboratories" and the "FDA Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories." Clear standard operating procedures (SOPs) should be established.

1. Retesting for Sterility

See the USP for guidance on sterility testing. Sterility retesting is acceptable provided the cause of the initial nonsterility is known, thereby invalidating the original results. It cannot be assumed that the initial sterility test failure is a false positive. This conclusion must be justified by sufficient documented investigation. Additionally, spotty or low-level contamination may not be identified by repeated sampling and testing. Review sterility test failures and determine the incidence, procedures for handling, and final disposition of the batches involved.

2. Retesting for Pyrogens

As with sterility, pyrogen retesting can be performed provided it is known that the test system was compromised. It cannot be assumed that the failure is a false positive without documented justification. Review any initial pyrogen test failures and establish a justification for retesting.

3. Particulate Matter Testing

Particulate matter consists of extraneous, mobile, and undissolved substances other than gas bubbles unintentionally present in parenteral solutions. Cleanliness specifications or levels of nonviable particulate contamination must be established. Limits are usually based on the history of the process. The particulate matter test procedure and limits for LVPs in the USP can be used as a general guideline. However, the levels of particulate contamination in sterile powders are generally greater than in LVPs. LVP solutions are filtered during the filling operation. However, sterile powders, except powders lyophilized in vials, cannot include filtration as a part of the filling operation. Considerable particulate contamination is also present in sterile powders that are spray dried due to charring during the process.

Establish the particulate matter test procedure and release criteria. Have available production and control records of any batches for which complaints of particulate matter have been received.

4. Production Records

Production records should be similar to those for other dosage forms. Critical steps, such as integrity testing of filter, should be signed and dated by a second responsible person. The production records must ensure that directions for significant manufacturing steps are included and reflect a complete history of production.

III. ASEPTIC PROCESSING

A. Introduction

There are basic differences between the production of sterile drug products by aseptic processing and by terminal sterilization. Terminal sterilization usually involves filling and sealing product containers under conditions of a high-quality environment; the product, container, and closure in most cases have low bioburden but are not sterile. The environment in which filling and sealing is performed is of high quality in order to minimize the microbial content of the in-process product and to help ensure that the subsequent sterilization process is successful. The product in its final container is then subjected to a sterilization process such as heat or radiation. Because of their nature, certain products are aseptically processed from either an earlier stage in the process or in their entirety. Cell-based therapy products are an example. All components and excipients for these products are rendered sterile, and release of the final product is contingent on determination of sterility.

In aseptic processing, the drug product, container, and closure are subjected to sterilization processes separately, as appropriate, and then brought together. Because there is no further processing to sterilize the product after it is in its final container, it is critical that containers be filled and sealed in an environment of extremely high quality. Manufacturers should be aware that there are more variables associated with aseptic processing than with terminal sterilization. Before aseptic assembly, different parts of the final product are generally subjected to different sterilization processes, such as dry heat for glass containers, moist-heat sterilization for rubber closures, and sterile filtration for a liquid dosage form. Each of the processes of the aseptic manufacturing operation requires thorough validation and control. Each also introduces the possibility of error that might ultimately lead to the distribution of contaminated product. Any manual or mechanical manipulation of the sterilized drug, components, containers, or closures prior to or during aseptic assembly poses a risk of contamination and thus necessitates careful control. The terminally sterilized drug product, on the other hand, undergoes a single sterilization process in a sealed container, thus limiting the possibilities for error. Nearly all drugs recalled due to nonsterility or lack of sterility assurance from 1980 to 2000 were produced via aseptic processing. Manufacturers should have a keen awareness of the public health implication of distributing a nonsterile drug purporting to be sterile. Poor cGMP conditions at a manufacturing facility can ultimately pose a life-threatening health risk to a patient.

B. Buildings and Facilities

Section 211.42, "Design and Construction Features," of CFR requires, in part, that aseptic processing operations be "performed within specifically defined areas of adequate size. There shall be separate or defined areas for the operations to prevent contamination or mix-ups." Aseptic processing operations must also "include, as appropriate, an air supply

Table 1 Room Area Classification

Clean-Area Classification	>0.5-mm Particles/ft^3	>0.5-mm Particles/m^3	Microbiological Limits[b] CFU/10 ft^3	CFU/m^3
100	100	3500	<1[c]	<3[c]
1000	1000	35,000	<2	<7
10,000	10,000	350,000	<5	<18
100,000	100,000	3,500,000	<25	<88

[a] All classifications based on data measured in the vicinity of exposed articles during periods of activity.
[b] Alternative microbiological standards may be established where justified by the nature of the operation.
[c] Samples from Class 100 environments should normally yield no microbiological contaminants
Source: From Ref. Cleanrooms and Associated Controlled Environments (1972). These classifications are now replaced by ISO 14644–1 (see chapter 13).

filtered through HEPA filters under positive pressure," as well as systems for "monitoring environmental conditions" and "maintaining any equipment used to control aseptic conditions." Section 211.46, "Ventilation, Air Filtration, Air Heating and Cooling," states, in part, that "equipment for adequate control over air pressure, microorganisms, dust, humidity, and temperature shall be provided when appropriate for the manufacture, processing, packing, or holding of a drug product." This regulation also states that "air filtration systems, including prefilters and particulate matter air filters, shall be used when appropriate on air supplies to production areas."

In aseptic processing, various areas of operation require separation and control, with each area having different degrees of air quality depending on the nature of the operation. Area design is based on satisfying microbiological and particulate standards defined by the equipment, components, and products exposed as well as the particular operation conducted in the given area. Critical and support areas of the aseptic processing operation should be classified and supported by microbiological and particulate data obtained during qualification studies. Initial clean-room qualification includes some assessment of air quality under as-built and static conditions, whereas the final room or area classification should be derived from data generated under dynamic conditions, that is, with personnel present, equipment in place, and operations ongoing. The aseptic processing facility-monitoring program should assess on a routine basis conformance with specified clean-area classifications under dynamic conditions. Table 1 summarizes clean-area air classifications (Cleanrooms and Associated Controlled Environments, 1972). Two clean areas are of particular importance to sterile drug product quality: the critical area and the supporting clean areas associated with it.

1. Critical Area (Class 100)

A critical area is one in which the sterilized drug product, containers, and closures are exposed to environmental conditions designed to preserve sterility. Activities conducted in this area include manipulations (e.g., aseptic connections, sterile ingredient additions) of sterile materials prior to and during filling and closing operations. This area is critical because the product is not processed further in its immediate container and is vulnerable to contamination. To maintain product sterility, the environment in which aseptic operations are conducted should be of appropriate quality throughout operations. One aspect of environmental quality is the particulate content of the air. Particulates are significant because they can enter a product and contaminate it physically or, by acting as a vehicle for microorganisms, biologically. Particle content in critical areas should be minimized by effective air systems.

Air in the immediate proximity of exposed sterilized containers or closures and filling or closing operations is of acceptable particulate quality when it has a per-cubic-foot particle count of no more than 100 in a size range of 0.5 mm and larger (Class 100) when counted at representative locations normally not more than 1 ft away from the work site, within the airflow, and during filling or closing operations. Deviations from this critical area monitoring parameter should be documented as to origin and significance.

Measurements to confirm air cleanliness in aseptic processing zones should be taken with the particle counting probe oriented in the direction of oncoming airflow and at specified sites where sterilized product and container/closure are exposed. Regular monitoring should be performed during each shift. Nonviable particulate monitoring with a remote counting system is generally less invasive than the use of portable particle counting units and provides the most comprehensive data.

Some powder-filling operations can generate high levels of powder particulates that, by their nature, do not pose a risk of product contamination. It may not, in these cases, be feasible to measure air quality within the 1-ft distance and still differentiate "background noise" levels of powder particles from air contaminants. In these instances, air should be sampled in a manner that, to the extent possible, characterizes the true level of extrinsic particulate contamination to which the product is exposed. Initial certification of the area under dynamic conditions without the actual powder-filling function should provide some baseline information on the nonproduct particle generation of the operation.

Air in critical areas should be supplied at the point of use as HEPA-filtered laminar flow air at a velocity sufficient to sweep particulate matter away from the filling or closing area and maintain laminarity during operations. The velocity parameters established for each processing line should be justified, and appropriate to maintain laminarity and air quality under dynamic conditions within a defined space (Cleanrooms and Associated Controlled Environments, 1972). (A velocity of 90–100 ft/min is generally established, with a range of ±20% around the set point. Higher velocities may be appropriate in operations generating high levels of particulates.)

Proper design and control should prevent turbulence or stagnant air in the aseptic processing line or clean zone. Once relevant parameters are established, airflow patterns should be evaluated for turbulence. Air pattern or "smoke" studies demonstrating laminarity and sweeping action over and away from the product under dynamic conditions should be conducted. The studies should be well documented with written conclusions. Videotape or other recording mechanisms have been found to be useful in assessing airflow initially as well as facilitating evaluation of subsequent equipment configuration changes. However, even successfully qualified systems can be compromised by poor personnel or operational or maintenance practices. Active air monitoring of critical areas should normally yield no microbiological contaminants. Contamination in this environment should receive investigative attention.

2. Supporting Clean Areas

Supporting clean areas include various classifications and functions. Many support areas function as zones in which nonsterile components, formulated product, in-process materials, equipment, and containers or closures are prepared, held, or transferred. These environments should be designed to minimize the level of particulate contaminants in the final product and control the microbiological content (bioburden) of articles and components that are subsequently sterilized.

The nature of the activities conducted in a supporting clean area should determine its classification. An area classified as Class 100,000 is used for less critical activities (such as initial equipment preparation). The area immediately adjacent to the aseptic processing line should, at a minimum, meet Class 10,000 standards (see Table 1) under dynamic conditions. Depending on the operation, manufacturers can also classify this area as Class 1000 or maintain the entire aseptic filling room at Class 100.

3. Clean Area Separation

Adequate separation is necessary between areas of operation to prevent contamination. To maintain air quality in areas of higher cleanliness, it is important to achieve a proper airflow and a positive pressure differential relative to adjacent less clean areas. Rooms of higher classification should have a positive pressure differential relative to adjacent lower classified areas of generally at least 0.05 in H_2O (with doors closed). When doors are open, outward airflow should be sufficient to minimize ingress of contamination (Ljungqvist and Reinmuller, 1997). Pressure differentials between clean rooms should be monitored continuously throughout each shift and frequently recorded, and deviations from established limits investigated.

An adequate air change rate should be established for a clean room. For Class 100,000 supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable.

Facility monitoring systems should be established to rapidly detect atypical changes that can compromise the facility's environment. Operating conditions should be restored to established, qualified levels before reaching action levels. For example, pressure differential specifications should enable prompt detection (i.e., alarms) of any emerging low-pressure problem in order to preclude ingress of unclassified air into a classified room.

4. Air Filtration

a. Membrane (Compressed Gases)

A compressed gas should be of appropriate purity (e.g., free from oil and water vapor) and its microbiological and particulate quality should be equal to or better than air in the environment into which the gas is introduced. Compressed gases such as air, nitrogen, and carbon dioxide are often used in clean rooms and are frequently employed in operations involving purging or overlaying.

Membrane filters allow for the filtration of compressed gases to meet an appropriate high-quality standard, and can be used to produce a sterile compressed gas. A sterile-filtered gas is used when the gas contacts a sterilized material. Certain equipment should also be supplied with a sterile-filtered gas. For example, sterile bacterial retentive membrane filters should be used for autoclave air lines, lyophilizer vacuum breaks, vessels containing sterilized materials, and hot-air sterilizer vents. Sterilized tanks or liquids should be held under continuous overpressure to prevent microbial contamination. Safeguards should be in place to prevent a pressure change that can result in contamination due to backflow of nonsterile air or liquid.

Gas filters (including vent filters) should be dry. Condensate in a gas filter can cause blockage or microbial contamination. Frequent replacement, heating, and use of hydrophobic filters prevent moisture residues in a gas supply system. These filters also should be integrity tested on installation and periodically thereafter (e.g., including at end of use). Integrity test failures should be investigated.

b. High-Efficiency Particulate Air

The same broad principles can be applied to ultra-low particulate air (ULPA) filters as described here for HEPA filters. An essential element in ensuring aseptic conditions is the maintenance of HEPA filter integrity. Integrity testing should be performed at installation to detect leaks around the sealing gaskets, through the frames or through various points on the filter media. Thereafter, integrity tests should be performed at suitable time intervals for HEPA filters in the aseptic processing facility. For example, such testing should be performed twice a year for the aseptic processing room. Additional testing may be needed when air quality is found to be unacceptable, or as part of an investigation into a media fill or drug product sterility failure. Among the filters that should be integrity tested are those installed in dry-heat depyrogenation tunnels commonly used to depyrogenate glass vials.

One recognized method of testing the integrity of HEPA filters is use of a DOP aerosol challenge. However, alternative aerosols may be acceptable. Poly-alpha-olefin can also be used, provided it meets specifications for critical physicochemical attributes such as viscosity. Some alternative aerosols are problematic because they pose a risk of microbial contamination of the environment being tested. It should be ensured that any alternative does not promote microbial growth.

An intact HEPA filter is capable of retaining at least 99.97% of particulates greater than 0.3 mm in diameter. It is important to ensure that the aerosol used for the challenge has a sufficient number of particles of this size range. Performing an integrity test without introducing particles of known size upstream of the filter is ineffective to detect leaks. The DOP challenge should introduce the aerosol upstream of the filter in a concentration of 80 to l00 mg/L of air at the filter's designed airflow rating. The downstream side of the filter is then scanned with an appropriate photometer probe at a sampling rate of at least 1 ft^3/min. Scanning should be conducted on the entire filter face and frame at a position about 1 to 2 in from the face of the filter. This comprehensive scanning of HEPA filters should be fully documented. Although vendors often provide these services, the drug manufacturer is responsible to ensure that these essential certification activities are conducted satisfactorily.

A single probe reading equivalent to 0.01% of the upstream challenge should be considered as indicative of a significant leak and should result in replacement of the HEPA filter or perhaps repair in a limited area. A subsequent confirmatory retest should be performed in the area of any repair. Whereas there is a major difference between filter integrity testing and efficiency testing, the purpose of regularly scheduled integrity testing is to detect leaks from the filter media, filter frame, and seal.

The challenge is a polydispersed aerosol usually composed of particles ranging in size from 1 to 3 mm. The test is done in place and the filter face is scanned with a probe; the measured downstream leakage is taken as a percent of the

upstream challenge. The efficiency test, on the other hand, is a test used only to determine the rating of the filter. (The efficiency test uses a monodispersed aerosol of particles of size 0.3 μm, relates to filter media, and usually requires specialized testing equipment. Downstream readings represent an average over the entire filter surface. Therefore, the efficiency test is not intended to test for leakage in a filter.)

HEPA filter integrity testing alone is not sufficient to monitor filter performance. This testing is usually done only on a semiannual basis. It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters). Variations in velocity generally increase the possibility of contamination, as these changes (e.g., velocity reduction) can have an effect on the laminarity of the airflow. Airflow velocities are measured 6 in from the filter face or at a defined distance proximal to the work surface for each HEPA filter. For example, velocity monitoring as frequently as weekly may be appropriate for the clean zone in which aseptic processing is performed. HEPA filters should be replaced when inadequate airflow (e.g., due to blockage) or nonuniformity of air velocity across an area of the filter is detected.

5. Design

Section 211.42 requires that aseptic processing operations be "performed within specifically defined areas of adequate size. There shall be separate or defined areas for the firm's operations to prevent contamination or mix-ups." Section 211.42 further states that "flow of components, drug products containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination." HEPA-filtered air as appropriate, as well as "floors, walls and ceilings of smooth, hard surfaces that are easily cleanable" are some additional requirements of this section. Section 211.63 states that equipment "shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance." Section 211.65 states that "equipment shall be constructed so that surfaces that contact the components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

Section 211.68 includes requirements for "automatic, mechanical and electronic equipment." Section 211.113 states that "appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed."

An aseptic process is designed to minimize exposure of sterile articles to dynamic conditions and potential contamination hazards presented by the operation. Limiting the duration of open container exposure, providing the highest possible environmental control, and designing equipment to prevent entrainment of lower quality air into the Class 100 zone are essential to this goal (Ljungqvist and Reinmuller, 1997).

Any intervention or stoppage during an aseptic process can increase the risk of contamination. Personnel and material flow should be optimized to prevent unnecessary activities that increase the potential for introducing contaminants to exposed product, container/closures, or the surrounding environment. The layout of equipment should provide for ergonomics that optimize comfort and movement of operators. The flow of personnel should be designed to limit the frequency with which entries and exits are made to and from the aseptic processing room and, more significantly, its critical area. To prevent changes in air currents that introduce lower quality air, movement adjacent to the critical area should be limited. For example, personnel intervention can be reduced by integrating an on-line weight check device, thus eliminating a repeated manual activity within the critical zone. It is also important to minimize the number of personnel in the aseptic processing room.

Transfer of products should be performed under appropriate clean-room conditions. For example, lyophilization processes include transfer of aseptically filled product in partially sealed containers. To prevent contamination, partially closed sterile product should be staged and transferred only in critical areas. Facility design should assure that the area between a filling line and the lyophilizer, and the transport and loading procedures, provide Class 100 protection. The sterile product and container closures should also be protected from activities occurring adjacent to the line. Carefully designed curtains, rigid plastic shields, or other barriers should be used in appropriate locations to partially segregate the aseptic processing line. Airlocks and interlocking doors facilitate better control of air balance throughout the aseptic processing area. Airlocks should be installed between the aseptic processing area entrance and the adjoining uncontrolled area. Other interfaces such as personnel entries, or the juncture of the aseptic processing room and its adjacent room, are also appropriate locations for airlocks. Clean rooms are normally designed as functional units with specific purposes. A well-designed clean room is constructed with material that allows for ease of cleaning and sanitizing. Examples of adequate design features include seamless and rounded floor-to-wall junctions as well as readily accessible corners. Floors, walls, and ceilings are constructed of smooth, hard surfaces that can be easily cleaned (section 211.42). Ceilings and associated HEPA filter banks should be designed to protect sterile materials from contamination. Clean rooms also should not contain unnecessary equipment, fixtures, or materials.

Processing equipment and systems should be equipped with sanitary fittings and valves. Drains are not considered appropriate for rooms in classified areas of the aseptic processing facility. When applicable, equipment must be suitably designed for ease of sterilization (section 211.63). The effect of equipment layout and design on the clean-room environment should be addressed. Flat surfaces or ledges that accumulate dust and debris should be avoided. Equipment should not obstruct airflow and, in critical zones, its design should not perturb airflow.

C. Personnel Training, Qualification, and Monitoring

Section 211.22 states that "the quality control unit shall have the responsibility for approving or rejecting all procedures or specifications impacting on the identity, strength, quality, and purity of the drug product." Section 211.113(b) addresses the procedures designed to prevent microbiological contamination, stating that "appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed." Section 211.25, "Personnel Qualifications," requires that:

> Each person engaged in manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. . . . Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the

> drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.

This section also requires "an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product." Section 211.25 also requires that continuing training in cGMP "shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with cGMP requirements applicable to them." The training "shall be in the particular operations that the employee performs and in cGMP (including the current good manufacturing practice regulations in this chapter and written procedures required by these regulations), as they relate to the employee's functions."

Section 211.28, "Personnel Responsibilities," states that "personnel engaged in the manufacture, processing, packing, or holding of a drug product shall wear clean clothing appropriate for the duties they perform." It also states that "personnel shall practice good sanitization and health habits" and specifies that "protective apparel, such as head, face, hand, and arm coverings, shall be worn as necessary to protect drug products from contamination." It also states:

> Any person shown at any time (either by medical examination or supervisory examination) to have an apparent illness or open lesions that may adversely affect the safety or quality of drug products shall be excluded from direct contact with components, drug product containers, closures, in-process materials, and drug products until the condition is corrected or determined by competent medical personnel not to jeopardize the safety or quality of drug products. All personnel shall be instructed to report to supervisory personnel any health conditions that may have an adverse effect on drug products.

This section also addresses restrictions on entry into limited-access areas: "Only personnel authorized by supervisory personnel shall enter those areas of the buildings and facilities designated as limited-access areas." Section 211.42 requires the establishment of a "system for monitoring environmental conditions."

1. Manufacturing Personnel

A well-designed aseptic process minimizes personnel intervention. As operator activities increase in an aseptic processing operation, the risk to finished product sterility also increases. It is essential that operators involved in aseptic manipulations adhere to the basic principles of aseptic technique at all times to assure maintenance of product sterility. Appropriate training should be conducted before an individual is permitted to enter the aseptic processing area and perform operations. For example, such training should include aseptic technique, clean-room behavior, microbiology, hygiene, gowning, and patient safety hazard posed by a nonsterile drug product, and the specific written procedures covering aseptic processing area operations. After initial training, personnel should be updated regularly by an ongoing training program. Supervisory personnel should routinely evaluate each operator's conformance to written procedures during actual operations. Similarly, the quality control unit should provide regular oversight of adherence to established, written procedures, and basic aseptic techniques during manufacturing operations.

Adherence to basic aseptic technique is a continuous requirement for operators in an aseptic processing operation. The following are some techniques aimed at maintaining sterility of sterile items and surfaces:

1. Contact sterile materials with sterile instruments only. Always use sterile instruments (e.g., forceps) while handling sterilized materials. Between uses, place instruments in sterilized containers only. Replace these instruments as necessary throughout the operation. Regularly sanitize initial gowning and sterile gloves to minimize the risk of contamination. Personnel should not directly contact sterile products, containers, closures, or critical surfaces.
2. Move slowly and deliberately. Rapid movements can create unacceptable turbulence in the critical zone. Such movements disrupt the sterile field, presenting a challenge beyond intended clean-room design and control parameters. Follow the principle of slow, careful movement throughout the clean room.
3. Keep the entire body out of the path of laminar air. Laminar airflow design is used to protect sterile equipment surfaces, container/closures, and product. Personnel should not disrupt the path of laminar flow air in the aseptic processing zone.
4. Approach a necessary manipulation in a manner that does not compromise sterility of the product. To maintain sterility of nearby sterile materials, approach a proper aseptic manipulation from the side and not above the product (in vertical laminar flow operations). Also, speaking when in direct proximity to an aseptic processing line is not an acceptable practice.
5. Personnel who have been qualified and permitted access to the aseptic processing area should be appropriately gowned. An aseptic processing-area gown should provide a barrier between the body and exposed sterilized materials, and prevent contamination from particles generated by, and microorganisms shed from, the body. Gowns need to be sterile and nonshedding, and should cover the skin and hair. Face masks, hoods, beard or moustache covers, protective goggles, elastic gloves, clean-room boots, and shoe overcovers are examples of common elements of gowns. An adequate barrier should be created by the overlapping of gown components (e.g., gloves overlapping sleeves). If an element of the gown is found to be torn or defective, change it immediately. There should be an established program to regularly assess or audit conformance of personnel to relevant aseptic manufacturing requirements. An aseptic gowning qualification program should assess the ability of a clean-room operator to maintain the sterile quality of the gown after performance of gowning procedures. Gowning qualification should include microbiological surface sampling of several locations on a gown (e.g., glove fingers, facemask, forearm, chest, and other sites). Following an initial assessment of gowning, periodic requalification should monitor various gowning locations over a suitable period to ensure the consistent acceptability of aseptic gowning techniques. Semiannual or yearly requalification is acceptable for automated operations where personnel involvement is minimized. To protect exposed sterilized product, personnel are expected to maintain sterile gown quality and aseptic method standards in a consistent manner. Written procedures should adequately address circumstances under which personnel should be retrained, requalified, or reassigned to other areas.

2. Laboratory Personnel

The basic principles of training, aseptic technique, and personnel qualification in aseptic manufacturing are equally applicable to those performing aseptic sampling and microbiological laboratory analyses. Processes and systems cannot be

considered to be under control and reproducible if there is any question regarding the validity of data produced by the laboratory.

3. Monitoring Program

Personnel can have substantial impact on the quality of the environment in which the sterile product is processed. A vigilant and responsive personnel-monitoring program should be established. Monitoring should be accomplished by obtaining surface samples of each aseptic processing operator's gloves on at least a daily basis or in association with each batch. This sampling should be accompanied by an appropriate frequency of sampling for other strategically selected locations of the gown (Current Practices in the Validation of Aseptic Processing, 2002). The quality control unit should establish a more comprehensive monitoring program for operators involved in operations that are especially labor intensive, that is, those requiring repeated or complex aseptic manipulations. Asepsis is fundamental to an aseptic processing operation. An ongoing goal for manufacturing personnel in the aseptic processing room is to maintain contamination-free gloves throughout operations. Sanitizing gloves just prior to sampling is inappropriate because it can prevent recovery of microorganisms that were present during an aseptic manipulation. When operators exceed established levels or show an adverse trend, an investigation should be conducted promptly. Follow-up actions may include increased sampling, increased observation, retraining, gowning requalification, and, in certain instances, reassigning the individual to operations outside of the aseptic processing area. Microbiological trending systems and assessment of the impact of atypical trends are discussed in more detail under the section on laboratory controls.

D. Components and Containers/Closures

1. Components

Section 210.3(b)(3) defines a component as "any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product." Section 211.80, "General Requirements," requires, in part, "the establishment of written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures. . . . Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination."

Section 211.84, "Testing and Approval or Rejection of Components, Drug Product Containers, and Closures," requires that "each lot of a component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use."

A drug product produced by aseptic processing can become contaminated by use of one or more components (e.g., active ingredients, excipients, WFI) contaminated with microorganisms or endotoxins. It is important to characterize the microbial content of each component liable to contamination and establish appropriate acceptance or rejection limits based on information on bioburden. Knowledge of bioburden is critical in assessing whether the sterilization process is adequate.

In aseptic processing, each component is individually sterilized or several components are combined, with the resulting mixture sterilized. There are several methods to sterilize components. A widely used method is filtration of a solution formed by dissolving the component(s) in a solvent such as USP WFI. The solution is passed through a sterilizing membrane or cartridge filter. Filter sterilization is used when the component is soluble and is likely to be adversely affected by heat. A variation of this method involves subjecting the filtered solution to aseptic crystallization and precipitation of the component as a sterile powder. However, this method involves more handling and manipulation and therefore has a higher potential for contamination during processing. If a component is not adversely affected by heat and is soluble, it may be made into a solution and subjected to steam sterilization, typically in an autoclave or a pressurized vessel. Dry-heat sterilization is a suitable method for components that are heat stable and insoluble. However, carefully designed heat penetration and distribution studies should be performed for powder sterilization because of the insulating effects of the powder.

Ethylene oxide exposure is often used for surface sterilization. Such methods should be carefully controlled and validated if used for powders to evaluate whether consistent penetration of the sterilant is achieved and to minimize residual ethylene oxide and by-products.

Parenteral products are intended to be nonpyrogenic. There should be written procedures and appropriate specifications for acceptance or rejection of each lot of components that might contain endotoxins. Any components failing to meet endotoxin specifications should be rejected.

2. Containers/Closures

Section 211.94, "Drug Product Containers and Closures," states that "drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use." It also states that "standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures." Section 211.113(b) requires "validation of any sterilization process" as part of designing procedures "to prevent microbiological contamination of drug products purporting to be sterile."

a. Preparation

Containers and closures should be rendered sterile and, for parenteral drug products, pyrogen-free. The type of processes used will depend primarily on the nature of the material comprising the container or closure, or both. The validation study for any such process should be adequate to demonstrate its ability to render materials sterile and pyrogen-free. Written procedures should specify the frequency of revalidation of these processes as well as time limits for holding sterile, depyrogenated containers and closures.

Presterilization preparation of glass containers usually involves a series of wash-and-rinse cycles. These cycles serve an important role in removing foreign matter. Rinse water should be of high purity so as not to contaminate containers. For parenteral products, final rinse water should meet the specifications of WFI, USP.

The adequacy of the depyrogenation process can be assessed by spiking containers or closures with known quantities of endotoxin, followed by measuring endotoxin content after depyrogenation. The challenge studies should be performed with a reconstituted endotoxin solution applied directly onto the surface being tested and air-dried. Positive controls should be used to measure the percentage of endotoxin recovery by the test method. Validation study data

should demonstrate that the process reduces the endotoxin content by at least 99.9% (3 logs).

Glass containers are generally subjected to dry heat for sterilization and depyrogenation. Validation of dry-heat sterilization or depyrogenation should include appropriate heat distribution and penetration studies as well as the use of worst-case process cycles, container characteristics (e.g., mass), and specific loading configurations to represent actual production runs.

Pyrogen on plastic containers can be generally removed by multiple WFI rinses. Plastic containers can be sterilized with an appropriate gas, irradiation, or other suitable means. For gases such as EtO, the parameters and limits of the EtO sterilization cycle (e.g., temperature, pressure, humidity, gas concentration, exposure time, degassing, aeration, and determination of residuals) should be specified and monitored closely. BIs are of special importance in demonstrating the effectiveness of EtO and other gas sterilization processes.

Rubber closures (e.g., stoppers and syringe plungers) are cleaned by multiple cycles of washing and rinsing prior to final steam or irradiation sterilization. At minimum, the initial rinses for the washing process should employ purified water USP of minimal endotoxin content, followed by final rinse(s) with WFI for parenteral products. Normally, depyrogenation is achieved by multiple rinses of hot WFI. The time between washing and sterilizing should be minimized because moisture on the stoppers can support microbial growth and the generation of endotoxins. Because rubber is a poor conductor of heat, extra attention should be given to the validation of processes that use heat to sterilize rubber stoppers. Validation data should also demonstrate successful endotoxin removal from rubber materials.

A potential source of contamination is the siliconization of rubber stoppers. Silicone used in the preparation of rubber stoppers should be rendered sterile and not have an adverse effect on the safety, quality, or purity of the drug product. It is important to establish production time limits for the holding of sterilized containers and closures.

Contract facilities that perform sterilization and depyrogenation of containers and closures are subject to the same cGMP requirements as those established for in-house processing. The finished dosage from the manufacturer is subject to the review and approval of the contractor's validation protocol and final validation report.

b. Inspection of Container/Closure System

A container–closure system that permits penetration of air, or microorganisms, is unsuitable for a sterile product. Any damaged or defective units should be detected and removed during inspection of the final sealed product. Safeguards should be implemented to strictly preclude shipment of product that may lack container–closure integrity and lead to nonsterility. Equipment suitability problems or incoming container or closure deficiencies have caused loss of container–closure system integrity. As examples, failure to detect vials fractured by faulty machinery or by mishandling of bulk finished stock has led to drug recalls. If damage that is not readily detected leads to loss of container–closure integrity, improved procedures should be rapidly implemented to prevent and detect such defects.

Functional defects in delivery devices (e.g., syringe device defects, delivery volume) can also result in product quality problems, and should be monitored by appropriate in-process testing.

Any defects or results outside the specifications established for in-process and final inspection should be investigated in accord with section 211.192.

E. Endotoxin Control

Section 211.63, "Equipment Design, Size, and Location," states that equipment "shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance." Section 211.65, "Equipment Construction," requires, in part, that equipment shall be constructed so that surfaces that contact the components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements."

Section 211.67, "Equipment Cleaning and Maintenance," states that "equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements." Section 211.94 states that "drug product containers and closures shall be clean, and where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use." Section 211.167 states: "For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed."

Endotoxin contamination of an injectable product can be a result of poor cGMP controls. Certain patient populations (e.g., neonates), those receiving other injections concomitantly, or those administered a parenteral in atypically large volumes or doses, can be at greater risk for pyrogenic reaction than that anticipated by the established limits based on body weight of a normal healthy adult (Grandics, 2000; Lord and Levchuk, 1989; Current Practices in the Validation of Aseptic Processing, 2002). Such clinical concerns reinforce the need for appropriate cGMP controls to prevent generation of endotoxin. Drug product components, container/closures, equipment, and storage time limitations are among the concerns to address in establishing endotoxin control.

Adequate cleaning, drying, and storage of equipment provide for control of bioburden and prevent contribution of endotoxin load. Equipment should be designed such that it is easily assembled and disassembled, cleaned, sanitized, and sterilized. Endotoxin control should be exercised for all product contact surfaces both prior to and after sterile filtration. Endotoxin on equipment surfaces is inactivated by high-temperature dry heat, or removed from equipment surfaces by validated cleaning procedures. Some clean-in-place procedures employ initial rinses with appropriate high-purity water or a cleaning agent (e.g., acid, base, surfactant), or both, followed by final rinses with heated WFI. Equipment should be dried following cleaning. Sterilizing filters and moist-heat sterilization have not been shown to be effective in removing endotoxins. Processes that are designed to achieve depyrogenation should demonstrate a 3-log reduction of endotoxin.

F. Time Limitations

Section 211.111, "Time Limitations on Production," states: "When appropriate, time limits for the completion of each phase of production shall be established to assure the quality of the drug product."

Time limits should be established for each phase of aseptic processing. Time limits should include, for example,

the period between the start of bulk product compounding and its filtration; filtration processes; product exposure while on the processing line; and storage of sterilized equipment, containers, and closures. Maintenance of in-process quality at different production phases should be supported by data. Bioburden and endotoxin load should be assessed when establishing time limits for stages such as the formulation processing stage. The total time for product filtration should be limited to an established maximum in order to prevent microorganisms from penetrating the filter. Such a time limit should also prevent a significant increase in upstream bioburden and endotoxin load. Sterilizing filters should generally be replaced following each manufactured lot. Because they can provide a substrate for microbial attachment, maximum use times for those filters used upstream for solution clarification or particle removal should also be established and justified.

G. Process Validation and Equipment Qualification

Section 211.113(b), "Control of Microbiological Contamination," states: "Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process." Section 211.63 is "Equipment, Design, Size, and Location"; section 211.65 is "Equipment Construction"; and section 211.67 is "Equipment Cleaning and Maintenance." Section 211.84(c)(3) states that "sterile equipment and aseptic sampling techniques shall be used when necessary."

The following sections primarily discuss routine qualification and validation study expectations. Change control procedures are only briefly addressed, but they are an important part of the quality systems. A change in equipment, process, test method, or systems requires evaluation through the written change control program and should trigger an evaluation of the need for revalidation or requalification.

1. Process Simulations

To ensure the sterility of products purporting to be sterile, both sterilization and aseptic filling or closing operations must be adequately validated (section 211.113). The goal of even the most effective sterilization processes can be defeated if the sterilized elements of a product (the drug, the container, and the closure) are brought together under conditions that contaminate those elements. Similarly, product sterility is compromised when the product elements are nonsterile at the time they are assembled.

Validation of an aseptic processing operation should include the use of a microbiological growth nutrient medium in place of product. This has been termed a *media fill* or *process simulation.* The nutrient medium is exposed to product contact surfaces of equipment, container systems, critical environments, and process manipulations to closely simulate the same exposure that the product itself will undergo. The sealed containers filled with the media are then incubated to detect microbial contamination. The results are interpreted to determine the potential for any given unit of drug product to become contaminated during actual operations (e.g., start-up, sterile ingredient additions, aseptic connections, filling, and closing). Environmental monitoring data is integral to the validation of an aseptic processing operation.

a. Study Design

A validation protocol should detail the overall strategy, testing requirements, and acceptance criteria for the media fill. Media-fill studies should simulate aseptic manufacturing operations as closely as possible, incorporating a worst-case approach. A media-fill study should address applicable issues such as

- factors associated with the longest permitted run on the processing line;
- ability to produce sterile units when environmental conditions impart a greater risk to the product;
- number and type of normal interventions, atypical interventions, unexpected events (e.g., maintenance), stoppages, equipment adjustments, or transfers;
- lyophilization, when applicable;
- aseptic assembly of equipment (e.g., at start-up, during processing);
- number of personnel and their activities;
- number of aseptic additions (e.g., charging containers and closures as well as sterile ingredients);
- shift changes, breaks, and gown changes (when applicable);
- number and type of aseptic equipment disconnections or connections;
- aseptic sample collections;
- line speed and configurations;
- manual weight checks;
- operator fatigue;
- container/closure systems (e.g., sizes, type, compatibility with equipment);
- temperature and humidity set point extremes; and
- specific provisions of aseptic processing–related SOPs (conditions permitted before line clearance is mandated, etc.).

A written batch record documenting conditions and activity simulated should be prepared for each media fill run. The same vigilance should be observed in both media fill and routine production runs. Media fills cannot be used to validate an unacceptable practice.

b. Frequency and Number of Runs

When a processing line is initially validated, separate media fills should be repeated enough times to ensure that results are consistent and meaningful. This approach is important because a single run can be inconclusive, whereas multiple runs with divergent results signal a process that is not in control. A minimum of three consecutive separate successful runs should be performed during initial line qualification. Subsequently, routine semiannual revalidation runs should be conducted for each shift and processing line to evaluate the state of control of the aseptic process. All personnel who enter the aseptic processing area, including technicians and maintenance personnel, should participate in a media fill at least once a year.

Each change to a product or line change should be evaluated by a written change control system. Any changes or events that appear to affect the ability of the aseptic process to exclude contamination from the sterilized product should be assessed through additional media fills. For example, facility and equipment modification, line configuration change, significant changes in personnel, anomalies in environmental testing results, container/closure system changes, or end-product sterility testing showing contaminated products may be cause for revalidation of the system.

When a media fill's data indicate that the process may not be in control, a comprehensive documented investigation should be conducted to determine the origin of the contamination and the scope of the problem. Once corrections are instituted, multiple repeat process simulation runs should be performed to confirm that deficiencies in practices and

procedures have been corrected and the process has returned to a state of control. However, when an investigation fails to reach well-supported, substantive conclusions as to the cause of the media fill failure, three consecutive successful runs and increased scrutiny (i.e., extra supervision, monitoring) of the production process should be implemented.

c. Size and Duration of Runs

The duration of aseptic processing operations is a major consideration in determining the size of the media fill run. Although the most accurate simulation model would be the full batch size and duration because it most closely simulates the actual production run, other appropriate models can be justified. In any study protocol, the duration of the run and the overall study design should adequately mimic worst-case operating conditions and cover all manipulations that are performed in the actual processing operation. Adequate batch sizes are needed to simulate commercial production conditions and accurately assess the potential for commercial batch contamination. The number of units filled should be sufficient to reflect the effects of potential operator fatigue, as well as the maximum number of interventions and stoppages. The run should be large enough to accurately simulate production conditions and sensitive enough to detect a low incidence of contaminated units. For batches produced over multiple shifts or yielding an unusually large number of units, the media fill protocol should adequately encompass conditions and any potential risks associated with the larger operation. Although conventional manufacturing lines are highly automated, often operate at relatively high speeds, and are designed to limit operator intervention, some processes include considerable operator involvement. When aseptic processing employs manual filling or closing, or extensive manual manipulations, the duration of the process simulation should generally be no less than the length of the actual manufacturing process in order to best simulate operator fatigue.

For simulation of lyophilization operations, unsealed containers should be exposed to pressurization and partial evacuation of the chamber in a manner that is representative of process stresses. Vials should not be frozen, as this may inhibit the growth of microorganisms.

d. Line Speed

The media fill program should adequately address the range of line speeds (e.g., by bracketing all vial sizes and fill volumes) employed during production. In some cases, more than one line speed should be evaluated in the course of a study.

Each individual media fill run should evaluate a single worst-case line speed, and the speed chosen for each batch during a study should be justified. For example, use of high line speed is justified for manufacturing processes characterized by frequent interventions or a significant degree of manual manipulation. Use of slow line speed is justified for manufacturing processes characterized by prolonged exposure of sterile components in the aseptic area.

e. Environmental Conditions

Media fills should be conducted under environmental conditions that simulate normal as well as worst-case conditions of production. An inaccurate assessment (making the process appear cleaner than it actually is) can result from conducting a media fill under extraordinary air particulate and microbial quality, or under production controls and precautions taken in preparation for the media fill. To the extent SOPs permit stressful conditions, it is crucial that media fills should include rigorous challenges in order to support the validity of these studies.

f. Media

In general, a microbiological growth medium such as soybean casein digest medium should be used. Use of anaerobic growth media (e.g., fluid thioglycollate medium) is appropriate in special circumstances. Media selected should be demonstrated to promote growth of USP Media units should be incubated for a sufficient time (a period of not less than 14 days) at a temperature adequate to enhance detection of organisms that can otherwise be difficult to culture. Each media-filled unit should be examined for contamination by personnel with appropriate education, training, and experience in microbiological techniques. There should be direct quality control unit oversight throughout any such examination. Clear containers with otherwise identical physical properties should be used as a substitute for amber or other opaque containers to allow visual detection of microbial growth.

When a final product inspection is performed of units immediately following the media fill run, all integral units should proceed to incubation. Units found to have defects not related to integrity (e.g., cosmetic defect) should be incubated; units that lack integrity should be rejected. (Separate incubation of certain categories of rejected units may nonetheless provide valuable information with respect to contamination that may arise from container/closure integrity deficiencies.) Erroneously rejected units should be returned promptly for incubation with the media fill lot.

After incubation is underway, any unit found to be damaged should be included in the data for the media fill batch, because the incubation of the units simulates release to the market. Any decision to exclude such incubated units (i.e., nonintegral) from the final batch tally should be fully justified, and the deviation explained in the media fill report. If a correlation emerges between difficult-to-detect damage and microbial contamination, a thorough investigation should be conducted to determine its cause.

Written procedures regarding aseptic interventions should be clear and specific (e.g., intervention type, quantity of units removed), providing for consistent production practices and assessment of these practices during media fills. If written procedures and batch documentation are adequate, these intervention units do not need to be incubated during media fills. Where procedures lack specificity, there would be insufficient justification for exclusion of units removed during an intervention from incubation. As an example, if a production procedure requires removal of 10 units after an intervention at the stoppering station infeed, batch records (i.e., for production and media fills) should clearly document conformance with this procedure. In no case should more units be removed during a media fill intervention than would be cleared during a production run. The ability of a media fill run to detect potential contamination from a given simulated activity should not be compromised by a large-scale line clearance, which can result in removal of a positive unit caused by an unrelated event or intervention. If unavoidable, appropriate study provisions should be made to compensate in such instances.

Appropriate criteria should be established for yield and accountability. Batch record reconciliation documentation should include an accurate accounting and description of units rejected from a batch.

g. Interpretation of Test Results

The process simulation run should be observed, and contaminated units should be reconcilable with the approximate time and the activity being simulated during the media fill. Videotaping of a media fill has been found to be useful in identifying personnel practices that could negatively impact on the aseptic process.

Any contaminated unit should be considered as objectionable and fully investigated. The microorganisms should be identified to species level. In the case of a media fill failure, a comprehensive investigation should be conducted, surveying all possible causes of the contamination. The impact on commercial drugs produced on the line since the last successful media fill should also be assessed.

Whenever contamination exists in a media fill batch, it should be considered as indicative of a potential production problem. The use of statistics has limitations for media fill evaluation in that the number of contaminated units should not be expected to increase in a directly proportional manner with the number of vials in the media fill run. Test results should show, with a high degree of confidence, that the units produced by an aseptic processing operation are sterile. Modern aseptic processing operations in suitably designed facilities have demonstrated a capability of meeting contamination levels approaching zero (Leahy and Sullivan, 1978) and should normally yield no media fill contamination. For example, a single contaminated unit in a 10,000-unit media fill batch should be fully investigated, but is normally not considered on its own to be sufficient cause for line revalidation. However, intermittent incidents at this media fill contamination level can be indicative of a persistent low-level contamination problem. Accordingly, any pattern of media fill batches with such low-level contamination should be comprehensively investigated and would be cause for line revalidation.

The use of media fill acceptance criteria allowing infrequent contamination does not mean that a distributed lot of drug product purporting to be sterile may contain a nonsterile unit. The purpose of an aseptic process is to prevent any contamination. A manufacturer is fully liable for the shipment of any nonsterile unit, an act that is prohibited under the FD&C Act. FDA also recognizes that there might be some scientific and technical limitations on how precisely and accurately validation can characterize a system of controls intended to exclude contamination.

As with any validation batch, it is important to note that "invalidation" of a media fill run should be a rare occurrence. A media fill lot should be aborted only under circumstances in which written procedures require commercial lots to be equally handled. Supporting documentation and justification should be provided in such cases.

2. Filtration Efficacy

Filtration is a common method of sterilizing drug product solutions. An appropriate sterilizing grade filter is one that reproducibly removes all microorganisms from the process stream, producing a sterile effluent. Such filters usually have a rated porosity of 0.2 mm or smaller. Whatever filter or combination of filters is used, validation should include microbiological challenges to simulate worst-case production conditions regarding the size of microorganisms in the material to be filtered and integrity test results of the filters used for the study. The microorganisms should be small enough to both challenge the nominal porosity of the filter and simulate the smallest microorganism that may occur in production. The microorganism *Brevundimonas diminuta* (ATCC 19146) when properly grown, harvested, and used can be satisfactory in this regard because it is one of the smallest bacteria (0.3-mm mean diameter). Bioburden of unsterilized bulk solutions should be determined in order to trend the characteristics of potentially contaminating organisms. In certain cases, when justified as equivalent or better than use of *B. diminuta*, it may be appropriate to conduct bacterial retention studies with a bioburden isolate. The number of microorganisms in the challenge is important because a filter can contain a number of pores larger than the nominal rating that have potential to allow passage of microorganisms (Pall et al, 1980). The probability of such passage is considered to increase as the number of organisms (bioburden) in the material to be filtered increases (Sterilizing Filtration of Liquids, 1998). A challenge concentration of at least 107 organisms/cm^2 effective filtration area of *B. diminuta* is generally used. Actual influent bioburden of a commercial lot should not include microorganisms of a size or concentration that would present a challenge beyond that considered by the validation study.

Direct inoculation into the drug formulation provides an assessment of the effect of drug product on the filter matrix and on the challenge organism. However, directly inoculating *B. diminuta* into products with inherent bactericidal activity or into oil-based formulations can lead to erroneous conclusions. When sufficiently justified, the effects of the product formulation on the membrane's integrity can be assessed by an appropriate alternative method. For example, the drug product could be filtered in a manner in which the worst-case combination of process specifications and conditions is simulated. This step could be followed by filtration of the challenge organism for a significant period of time, under the same conditions, using an appropriately modified product (e.g., lacking an antimicrobial preservative or other antimicrobial component) as the vehicle. Any divergence from a simulation using the actual product and conditions of processing should be justified. Factors that can affect filter performance normally include viscosity of the material to be filtered, pH, compatibility of the material or formulation components with the filter itself, pressures, flow rates, maximum use time, temperature, osmolality, and the effects of hydraulic shock.

When designing the validation protocol, it is important to address the effect of the extremes of processing factors on the filter capability to produce sterile effluent. Filter validation should be conducted by using the worst-case conditions, such as maximum filter use time and pressure (Pall et al, 1980; Parenteral Drug Association, 1998; Commentary on the Sterility Tests and Sterilization Chapters of the U.S. Pharmacopoeia, 1980). Filter validation experiments, including microbial challenges, need not be conducted in the actual manufacturing areas. However, it is essential that laboratory experiments simulate actual production conditions. The specific type of filter used in commercial production should be evaluated in filter validation studies. When the more complex filter validation tests go beyond the capabilities of the filter user, tests are often conducted by outside laboratories or by filter manufacturers. However, it is the responsibility of the filter user to review the validation data on the efficacy of the filter in producing a sterile effluent. The data should be applicable to the user's products and conditions of use because filter performance may differ significantly for various conditions and products.

After a filtration process is properly validated for a given product, process, and filter, it is important to ensure that identical filter replacements (membrane or cartridge) used in production runs perform in the same manner. Sterilizing

filters should be routinely discarded after processing a single batch. Normally, integrity testing of the filter is performed after the filter unit is assembled and sterilized prior to use. It is important that the integrity testing be conducted after filtration in order to detect any filter leaks or perforations that might have occurred during the filtration. Forward flow and bubble point tests, when appropriately employed, are two acceptable integrity tests. A production filter's integrity test specification should be consistent with data generated during filtration efficacy studies.

3. Sterilization of Equipment and Containers/Closures

To maintain sterility, equipment surfaces that contact sterilized drug product or sterilized container/closure surfaces must be sterile so as not to alter purity of the drug (sections 211.63 and 211.113). Surfaces in the vicinity of the sterile product or not directly in contact with the product should also be rendered sterile where reasonable contamination potential exists. It is as important in aseptic processing to properly validate the processes used to sterilize such critical equipment as it is to validate processes used to sterilize the drug product and its container/closure. Moist-heat and dry-heat sterilization are most widely used as the primary processes discussed in this document. It should be noted that many of the heat-sterilization principles discussed in this document are also applicable to other sterilization methods.

Sterility of aseptic processing equipment (e.g., stopper hoppers) should be maintained by batch-by-batch sterilization. Following sterilization of equipment, containers, or closures, any transportation or assembly needs to be performed in a manner in which its sterile state is protected and sustained, with adherence to strict aseptic methods.

a. Sterilizer Qualification and Validation

Validation studies should be conducted demonstrating the efficacy of the sterilization cycle. Requalification studies should also be performed on a periodic basis. For both the validation studies and routine production, use of a specified load configuration should be documented in the batch records.

Unevacuated air's insulating properties prevent moist heat from penetrating or heating up materials, and achieving the lethality associated with saturated steam. Consequently, there is a far slower thermal energy transfer and rate of kill from the dry heat in insulated locations in the load. It is important to remove all of the air from the autoclave chamber during the sterilization cycle. Special attention should be given to the nature or type of the materials to be sterilized and the placement of BI within the sterilization load. *D*-value of the BI can vary widely depending on the material (e.g., glass vs. Teflon) to be sterilized. Difficult-to-reach locations within the sterilizer load and specific materials should be an important part of the evaluation of sterilization cycle efficacy. Thereafter, requalification or revalidation should continue to focus on load areas identified as the most difficult to penetrate or heat [e.g., worst-case locations of tightly wrapped or densely packed supplies (Clinical sepsis and death in a newborn nursery associated with contaminated medications, 1998), securely fastened load articles, lengthy tubing, the sterile filter apparatus, hydrophobic filters, stopper load]. The formal program providing for regular (i.e., semiannual, annual) revalidation should consider the age of the sterilizer and its past performance. Change control procedures should adequately address issues such as a load configuration change or a modification of the sterilizer.

i. *Qualification: Empty Chamber*
   Temperature distribution studies evaluate numerous locations throughout an empty sterilizing unit (e.g., steam autoclave, dry-heat oven) or equipment train (e.g., large tanks, immobile piping). It is important that these studies assess temperature uniformity at various locations throughout the sterilizer to identify potential "cold spots" where there can be insufficient heat to attain sterility. These heat uniformity or "temperature mapping" studies should be conducted by placing calibrated temperature measurement devices in numerous locations throughout the chamber.
ii. *Validation: Loaded Chamber*
   Heat penetration studies should be performed using the established sterilizer load(s). Validation of the sterilization process with a loaded chamber demonstrates the effects of loading on thermal input to the items being sterilized, and may identify cold spots where there is insufficient heat to attain sterility. The placement of BIs at numerous positions in the load, including the most difficult-to-sterilize places, is a direct means of demonstrating the efficacy of any sterilization procedure.

In general, the thermocouple is placed adjacent to the BI so as to assess the correlation between microbial lethality and thermal input. Sterilization can be validated by a partial or half-cycle approach. In some cases, the bioburden-based cycle is used for sterilization validation. For further information on validation by moist-heat sterilization, refer to FDA guidance "Guideline for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" (November 1994).

Sterilization cycle specifications are based on the delivery of adequate thermal input to the slowest-to-heat locations. When determining which articles are most difficult to sterilize, special attention should be given to the sterilization of filters. For example, some filter installations in piping cause a significant pressure differential across the filter, resulting in a significant temperature drop on the downstream side. BIs should be placed at appropriate downstream locations of this equipment to determine whether the drop in temperature affects the thermal input at these sites. Established load configuration should be part of batch record documentation. A sterility assurance level of 10^6 or better should be demonstrated for the sterilization process.

b. Equipment Controls and Instrument

Calibration For both validation and routine process control, the reliability of the data generated by sterilization cycle monitoring devices should be considered to be of utmost importance. Devices that measure cycle parameters should be routinely calibrated. Written procedures should be established to ensure that these devices are maintained in a calibrated state. Temperature monitoring devices for heat sterilization should be calibrated at suitable intervals, as well as before and after validation runs. Devices used to monitor dwell time in the sterilizer should be periodically calibrated. The microbial count and *D*-value of a BI should be confirmed before a validation study. Instruments used to determine the purity of steam should be calibrated. For dry-heat depyrogenation tunnels, devices (e.g., sensors and transmitters) used to measure belt speed should be routinely calibrated.

Sterilizing equipment should be properly maintained to allow for consistently satisfactory function. Evaluation of sterilizer performance attributes such as equilibrium

("come up") time studies should be helpful to assess whether the unit continues to operate properly.

H. Laboratory Controls

Section 211.160, "General Requirements," states: "Laboratory controls shall include the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of identity, strength, quality, and purity." Sections 211.165 and 211.194 require that validation of test methods be established and documented. Section 211.22(c) states that "the quality control unit shall have the responsibility for approving or rejecting all procedures and specifications impacting on the identity, strength, quality, and purity of the drug product." Section 211.42 requires, for aseptic processes, the establishment of a "system for monitoring environmental conditions." Section 211.56 requires "written procedures assigning responsibility for sanitation and describing in sufficient detail the cleaning schedules, methods, equipment, and materials to be used in cleaning the buildings and facilities." The "written procedures shall be designed to prevent the contamination of equipment, components, drug product containers, closures, packaging, labeling materials, or drug products and shall be followed." Section 211.113(b) requires that "appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed." Section 211.192 states that "all drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved, written procedures before a batch is released or distributed."

1. Environmental Monitoring

a. General Written Program

In aseptic processing, one of the most important laboratory controls is the establishment of an environmental monitoring program. This monitoring provides meaningful information on the quality of the aseptic processing environment when a given batch is being manufactured as well as environmental trends of the manufacturing area. An adequate program identifies potential routes of contamination, allowing for implementation of corrections before product contamination occurs (sections 211.42 and 211.113).

Evaluating the quality of air and surfaces in the clean-room environment should start with a well-defined written program and validated methods. The monitoring program should cover all production shifts and include air, floors, walls, and equipment surfaces, including the critical surfaces in contact with product and container/closures. Written procedures should include a list of locations to be sampled. Sample timing, frequency, and location should be carefully selected based on their relationship to the operation performed. Samples should be taken throughout the aseptic processing facility (e.g., aseptic corridors, gowning rooms) by appropriate, scientifically sound sampling procedures, standards, and test limits.

Locations posing the most microbiological risk to the product are a critical part of the program. It is especially important to monitor the microbiological quality of the aseptic processing clean zone to determine whether aseptic conditions are maintained during filling/closing activities. Critical surfaces which contact sterile product should be sterile. Critical surface sampling should be performed at the conclusion of the aseptic processing operation to avoid direct contact with sterile surfaces during processing. Air and surface samples should be taken at the actual working site and at locations where significant activity or product exposure occurs during production.

Environmental monitoring methods do not always recover microorganisms present in the sampled area. In particular, low-level contamination can be particularly difficult to detect. Because of the likelihood of false negatives, consecutive growth results are only one type of adverse trend. Increased incidence of contamination over a given period in comparison to that normally detected is an equally significant trend to be tracked.

All environmental monitoring locations should be described in SOPs with sufficient detail to allow for reproducible sampling of a given location surveyed. Written SOPs should also address areas such as frequency of sampling, when the samples are taken (i.e., during or at the conclusion of operations), duration of sampling, sample size (e.g., surface area, air volume), specific sampling equipment and techniques, alert and action limits, and appropriate response to deviations from alert or action limits.

b. Establishing Limits and a Trending Program

Microbiological monitoring limits should be established based on the relationship of the sampled location to the operation. The limits should be based on the need to maintain adequate microbiological control throughout the entire sterile manufacturing facility. One should also consider environmental monitoring data from historical databases, media fills, clean-room qualification, and sanitization procedure studies in developing monitoring limits. Microbiological environmental monitoring should include both alert and action limits. Each individual sample result should be evaluated for its significance by comparing to the alert or action limits. Averaging of results can mask unacceptable localized conditions. A result at the alert limit urges attention to the approaching action conditions. A result at the action level should prompt a more thorough investigation. Written procedures should be established, detailing data review frequency, identification of contaminants, and actions to be taken. The quality control unit should provide routine oversight of near-term (e.g., daily, weekly, monthly, or quarterly) and long-term trends in environmental and personnel monitoring data. Trend reports should include data generated by location, shift, lot, room, operator, or other search parameters. The quality control unit is responsible for producing specialized data reports (e.g., a search on a particular atypical isolate over a year period) in order to investigate results beyond established limits and identify any appropriate follow-up actions. In addition to microbial counts beyond alert and action limits, the presence of any atypical microorganisms in the clean-room environment should be investigated, with any appropriate corrective action promptly implemented. Written procedures should define the system whereby the most responsible managers are regularly informed and updated on trends and investigations.

c. Sanitization Efficacy

The suitability, efficacy, and limitations of sanitization agents should be assessed with their implementation for use in clean areas. The effectiveness of these sanitization procedures should be measured by their ability to ensure that potential contaminants are adequately removed from surfaces (i.e., via obtaining samples before and after sanitization). On preparation, disinfectants should be rendered sterile and used for a

limited time, as specified by written procedures. Disinfectants should retain efficacy against the normal microbial flora and be effective against spore-forming microorganisms. Many common sanitizers are ineffective against spores; for example, 70% isopropyl alcohol is not effective against spores of *Bacillus* species. A sporicidal agent should be used regularly to prevent contamination of the manufacturing environment with otherwise difficult to eradicate spore-forming bacteria or fungi. After the initial assessment of sanitization procedures, ongoing sanitization efficacy should be frequently monitored through specific provisions in the environmental monitoring program, with a defined course of action in the event samples are found to exceed limits.

d. Monitoring Methods

The following are some acceptable methods of monitoring the microbiological quality of the environment.

i. *Surface Monitoring*
Environmental monitoring should include testing of various surfaces for microbiological quality. For example, product contact surfaces, floors, walls, ceilings, and equipment should be tested on a regular basis. Routinely used for such tests are touch plates, swabs, and contact plates. Other surfaces in controlled areas should be tested to show the adequacy of cleaning and sanitizing procedures.

ii. *Active Air Monitoring*
The method of assessing the microbial quality of air should involve the use of active devices such as slit to agar samplers, those using liquid impingement and membrane filtration, or centrifugal samplers. Each device has certain advantages and disadvantages, although all allow a quantitative testing of the number of organisms per volume of air sampled. The use of such devices in aseptic areas is considered an essential part of evaluating the environment during each production shift at carefully chosen critical locations. Manufacturers should be aware of a device's air-monitoring capabilities and should determine suitability of any new or current devices with respect to sensitivity and limit of quantification.

iii. *Passive Air Monitoring (Settling Plates)*
Another method is the use of passive air samplers such as settling plates (petri dishes containing nutrient growth medium exposed to the environment). These settling plates lack value as quantitative air monitors because only microorganisms that settle onto the agar surface will be detected. Their value as qualitative indicators in critical areas is enhanced by positioning plates in locations that pose the greatest risk of product contamination. As part of methods validation, the quality control laboratory should evaluate what media exposure conditions optimize recovery of low levels of environmental isolates. Exposure conditions should preclude desiccation (e.g., caused by lengthy sampling periods or high airflows), which inhibits recovery of microorganisms. The data generated by passive air sampling can be useful when considered in combination with results from other types of air samples.

2. Microbiological Media and Identification

The environmental monitoring program should include routine characterization of recovered microorganisms. Monitoring of critical and immediately surrounding areas as well as personnel should include routine identification of microorganisms to the species (or, where appropriate, genus) level. In some cases, environmental trending data have revealed migration of microorganisms into the aseptic processing room from either uncontrolled or lesser-controlled areas. To detect such trends, an adequate program of differentiating microorganisms in lesser-controlled environments (e.g., Class 100,000) should be in place. At minimum, the program should require species (or, where appropriate, genus) identification of microorganisms in ancillary environments at frequent intervals to establish a valid, current database of contaminants present in the facility during processing (and to demonstrate that cleaning and sanitization procedures continue to be effective). Environmental isolates often correlate with the contaminants found in a media fill or product sterility testing failure, and the overall environmental picture provides valuable information for the associated investigation.

The goal of microbiological monitoring is to reproducibly detect microorganisms for purposes of monitoring the state of environmental control. Consistent methods will yield a database that allows for sound data comparisons and interpretations. The microbiological culture media used in environmental monitoring should be validated as capable of detecting fungi (i.e., yeasts and molds) as well as bacteria, and incubated at appropriate conditions of time and temperature. Total aerobic bacterial count can be obtained by incubating at 30°C to 35°C for 48 to 72 hours. Total combined yeast and mold count is generally obtained by incubating at 20°C to 25°C for 5 to 7 days.

Incoming lots of environmental monitoring media should include positive and negative controls. Growth promotion testing should be performed on all lots of prepared media. Where appropriate, inactivating agents should be used to prevent inhibition of growth by clean-room disinfectants.

a. Prefiltration Bioburden

For any parenteral manufacturing process, prefiltration bioburden should be minimal. In addition to increasing the challenge to the sterilizing filter, high bioburden can contribute endotoxin or other impurities to the drug formulation. An in-process limit for bioburden level for each formulated product (generally sampled immediately preceding sterile filtration) should be established.

b. Particulate Monitoring

Routine particle monitoring is useful in detecting significant deviations in air cleanliness from qualified processing norms (e.g., clean-area classification). A result outside the established specifications at a given location should be investigated consistent with the severity of the "excursion." Appropriate corrective action should be implemented to prevent future deviations.

I. Sterility Testing

Section 211.167, "Special Testing Requirements," states: "For each batch of drug product purporting to be sterile and/or pyrogen-free, there shall be appropriate laboratory testing to determine conformance to such requirements. The test procedures shall be in writing and shall be followed." Section 211.165 states that "for each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product . . . prior to release." Section 211.165(e) requires methods for testing to be validated as reliable and reproducible (e.g., bacteriostasis/fungistasis, method robustness, etc.), stating: "The accuracy, sensitivity, specificity, and reproducibility

of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with section 211.194(a)(2)." Section 211.110 requires, in part, that sampling procedures be established in order to ensure batch uniformity. The "control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product." Section 211.160 requires the establishment of sound and appropriate sampling plans representative of the batch.

Section 210 defines "representative sample" as one based on rational criteria that provide an "accurate portrayal" of the material or batch being sampled. Section 211.180 requires a review of "at least annually, the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures." Investigations conducted under section 211.192 for each drug product are required to be addressed within this annual review.

Certain aspects of sterility testing are of particular importance, including controlling the testing environment, understanding the test limitations, and the investigating manufacturing systems following a positive test. The testing laboratory environment should employ facilities and controls comparable to those used for filling or closing operations. Poor or deficient sterility test facilities or controls can result in a high rate of test failures. If production facilities and controls are significantly better than those for sterility testing, there is the danger of attributing the cause of a positive sterility test result to the faulty laboratory even when the product tested could have, in fact, been nonsterile. Therefore, some manufacturing deficiency may go undetected. The use of isolators to perform sterility testing is a well-established means to minimize false positives.

1. Choice of Methods

Sterility testing methodologies are required to be accurate and reproducible, in accord with sections 211.194 and 211.165. The methodology selected should present the lowest potential for yielding a false positive. The USP specifies membrane filtration as the method of choice, when feasible. As a part of methods validation, appropriate bacteriostasis or fungistasis testing should be conducted. Such testing should demonstrate reproducibility of the method in recovering each of a panel of representative microorganisms. Study documentation should include evaluation of whether microbial recovery from inoculated controls and product samples is comparable throughout the incubation period. If growth is inhibited, modifications (e.g., increased dilution, additional membrane filter washes, addition of inactivating agents) in the methodology should be implemented to optimize recovery. Ultimately, methods validation studies should demonstrate that the methodology does not provide an opportunity for false negatives.

2. Media

It is essential that the media used to perform sterility testing be rendered sterile and demonstrated as growth promoting.

3. Personnel

Personnel performing sterility testing should be qualified and trained for the task. A written program should be in place to regularly update training of personnel and confirm acceptable sterility testing practices.

4. Sampling and Incubation

Sterility tests are limited in their ability to detect low levels of contamination. For example, statistical evaluations indicate that the USP sterility test sampling plan has been described by USP as "only enabling the detection of contamination in a lot in which 10% of the units are contaminated about nine times out of ten in making the test." (Price, 1998) To further illustrate, if a 10,000-unit lot with a 0.1% contamination level is sterility tested using 20 units, there is a 98% chance that the batch will pass the test. This limited sensitivity makes it necessary to ensure that for batch release purposes, an appropriate number of units are tested and that the samples uniformly represent the following:

- *Entire batch*. Samples should be taken at the beginning, middle, and end of the aseptic processing operation.
- *Batch processing circumstances*. Samples should be taken in conjunction with processing interventions or excursions. Because of the limited sensitivity of the test, any positive result is considered a serious cGMP issue and should be thoroughly investigated.

5. Investigation of Sterility Positives

Care should be taken in the performance of the sterility test to preclude any activity that allows for possible sample contamination. When microbial growth is observed, the lot should be considered to be nonsterile. It is inappropriate to attribute a positive result to laboratory error on the basis of a retest that exhibits no growth. [Underscoring this regulatory standard, USP XXV, Section <71>, states that an initial positive test is invalid only in an instance in which "microbial growth can be without a doubt ascribed to" laboratory error (as described in the monograph).]

The evaluation of a positive sterility test result should include an investigation to determine whether the growth observed in the test arose from product contamination or from laboratory error. Although it is recognized that such a determination may not be reached with absolute certainty, it is usually possible to acquire persuasive evidence showing that causative laboratory error is absent. When available evidence is inconclusive, batches should be rejected as not conforming to sterility requirements.

It would be difficult to support invalidation of a positive sterility test. Only if conclusive and documented evidence clearly shows that the contamination occurred as part of testing should a new test be performed.

After considering all relevant factors concerning the manufacture of the product and testing of the samples, the comprehensive written investigation should include specific conclusions and identify corrective actions. The investigation's persuasive evidence of the origin of the contamination should be based on at least the following factors.

a. Identification (Speciation) of the Organism in the Sterility Test

Identification of the sterility test isolate(s) should be to the species level. Microbiological monitoring data should be reviewed to determine whether the organism is also found in laboratory and production environments, personnel, or product bioburden.

b. Record of Laboratory Tests and Deviations

Review of trends in laboratory findings can help to eliminate or implicate the laboratory as the source of contamination. If the organism is seldom found in the laboratory environment, then product contamination is likely. If the organism is

found in laboratory and production environments, it can indicate product contamination. Proper handling of deviations is an essential aspect of laboratory control. When a deviation occurs during sterility testing, it should be documented, investigated, and remedied. If any deviation is considered to have compromised the integrity of the sterility test, the test should be invalidated immediately without incubation.

Deviation and sterility test positive trends should be evaluated periodically (e.g., quarterly, annually) to provide an overview of operations. A sterility positive result can be viewed as indicative of production or laboratory problems and should be investigated globally because such problems often can extend beyond a single batch.

To more accurately monitor potential contamination sources, it is useful to keep separate trends by product, container type, filling line, and personnel. If the degree of sterility test sample manipulation is similar for a terminally sterilized product and an aseptically processed product, a higher rate of initial sterility failures for the latter should be taken as indicative of aseptic processing production problems.

Microbial monitoring of the laboratory environment and personnel over time can also reveal trends that are informative. Upward trends in the microbial load in the laboratory should be promptly investigated as to cause, and corrected. In some instances, such trends can appear to be more indicative of laboratory error as a possible source of a sterility test failure.

A good error record can help eliminate a laboratory as a source of contamination because chances are higher that the contamination arose from production. However, the converse is not true. Specifically, if the laboratory has a poor track record, it should not be automatically assumed that the contamination is more attributable to an error in the laboratory and consequently overlook a genuine production problem. Accordingly, all sterility positives should be thoroughly investigated.

c. Monitoring of Production Area Environment
Of particular importance is trend analysis of microorganisms in the critical and immediately adjacent area. Trends are an important tool in investigating the product as the possible source of a sterility failure. Consideration of environmental microbial loads should not be limited to results of monitoring the production environment for the lot, day, or shift associated with the suspect lot. For example, results showing little or no recovery of microorganisms can be misleading, especially when preceded or followed by a finding of an adverse trend or atypically high microbial counts. It is therefore important to look at both short- and long-term trend analysis.

d. Monitoring of Personnel
Daily personnel monitoring data and associated trends should be reviewed and can in some cases strongly indicate a route of contamination. The adequacy of personnel practices and training should also be considered.

e. Product Presterilization Bioburden
Trends in product bioburden should be reviewed (counts and identity). Adverse bioburden trends occurring during the time period of the test failure should be considered in the investigation.

f. Production Record Review
Complete batch and production control records should be reviewed to detect any signs of failures or anomalies that could have a bearing on product sterility. For example, the investigation should evaluate batch and trending data that indicate whether utility or support systems (e.g., HVAC, WFI) are functioning properly. Records of air quality monitoring for filling lines should show a time at which there was improper air balance, an unusual high particulate count, etc.

g. Manufacturing History
The manufacturing history of the product or similar products should be reviewed as part of the investigation. Past deviations, problems, or changes (e.g., process, components, equipment) are among the factors that can provide an indication of the origin of the problem.

J. Batch Record Review: Process Control Documentation

Sections 211.100, 211.186, and 211.188 address documentation of production and control of a batch, including recording various production and process control activities at the time of performance. Section 211.100(b) requires a documented record and evaluation of any deviation from written procedures. Section 211.192 states

> All drug product production and control records, including those for packaging and labeling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow-up.

Maintaining process and environmental control is a daily necessity for an aseptic processing operation. The requirement for review of all batch records and data for conformance with written procedures, operating parameters, and product specifications prior to arriving at the final release decision for an aseptically processed batch calls for an overall review of process and system performance for that given cycle of manufacture. All in-process data must be included with the batch record documentation per Section 211.188. Review of environmental monitoring data as well as other data relating to the acceptability of output from support systems (e.g., HEPA/HVAC, WFI, steam generator) and proper functioning of equipment (e.g., batch alarms report, integrity of various filters), should be viewed as essential elements of the batch release decision.

While interventions or stoppages are normally recorded in the batch record, the manner of documenting these occurrences varies. In particular, line stoppages and any unplanned interventions should be sufficiently documented in batch records with the associated time and duration of the event. In general, there is a correlation between product (or container/closure) dwell time in the aseptic processing zone and the probability of contamination. Sterility failures can be attributed to atypical or extensive interventions that have occurred as a response to an undesirable event during the aseptic process. Written procedures describing the need for line clearances in the event of certain interventions, such as machine adjustments and any repairs, should be established. Such interventions should be documented with more detail than minor events. Interventions that result in substantial activity near exposed product or container/closures or that last beyond a reasonable exposure time should, where appropriate, result in a local or full line clearance. Any disruption in

power supply, however momentary, during aseptic processing is a manufacturing deviation and must be included in batch records (sections 211.100 and 211.192).

IV. PROCESSING PRIOR TO FILLING AND SEALING OPERATIONS

The following aseptic processing activities that take place prior to the filling and sealing of the finished drug product require special consideration.

A. Aseptic Processing from Early Manufacturing Steps

Because of their nature, some products undergo aseptic processing at some or all manufacturing steps preceding the final product closing step. There is a point in the process after which a product can no longer be rendered sterile by filtration, and the product is handled aseptically in all subsequent steps. Some products are formulated aseptically because the formulated product cannot be sterilized by filtration. For example, products containing aluminum adjuvant are formulated aseptically because once they are alum-adsorbed, they cannot be sterile filtered. When a product is processed aseptically from early steps, the product and all components or other additions are rendered sterile prior to entering the manufacturing process. It is critical that all transfers, transports, and storage stages be carefully controlled at each step of the process to maintain sterility of the product.

Procedures that expose the product or product contact equipment surfaces to the environment, such as aseptic connections, should be performed under unidirectional airflow in a Class 100 environment. The environment of the room surrounding the Class 100 environment should be Class 10,000 or better. Microbiological and particulate monitoring should be performed during operations. Microbial surface monitoring should be performed at the end of operations but prior to cleaning. Personnel monitoring should be performed in association with operations.

Process simulation studies should be designed to incorporate all conditions, product manipulations, and interventions that could impact on the sterility of the product during manufacturing. The process simulation, from early process steps, should demonstrate that controls over the process are adequate to protect the product during manufacturing. These studies should incorporate all product manipulations, additions, and procedures involving exposure of product contact surfaces to the environment. The studies should include worst-case conditions such as maximum duration of open operations and maximum number of participating operators. However, process simulations do not need to mimic total manufacturing time if the manipulations that occur during manufacturing are adequately represented.

It is also important that process simulations incorporate storage of product or transport to other manufacturing areas. For instance, there should be assurance of bulk vessel integrity for specified holding times. The transport of bulk tanks or other containers should be simulated as part of the media fill. Process simulation studies for the formulation stage should be performed at least twice per year.

B. Aseptic Processing of Cell-Based Therapy Products (or of Products Intended for Use as Cell-Based Therapies)

Cell-based therapy products represent a subset of the products for which aseptic manipulations are used throughout the process. Where possible, closed systems should be used during production of this type of products. Cell-based therapy products often have short processing times at each manufacturing stage, even for the final product. Often, it is appropriate for these products to be administered to patients before final product sterility testing results are available. In situations where results of final sterility testing are not available before the product is administered, additional controls and testing should be considered. For example, additional sterility tests can be performed at intermediate stages of manufacture, especially after the last manipulation of the product prior to administration. Other tests that may indicate microbial contamination, such as microscopic examination, Gram stains, and endotoxin testing should be performed prior to product release.

V. ASEPTIC PROCESSING ISOLATORS

An emerging aseptic processing technology uses isolation systems to minimize the extent of personnel involvement and to separate the external clean-room environment from the aseptic processing line. A well-designed positive pressure barrier isolator, supported by adequate procedures for its maintenance, monitoring, and control, appears to offer an advantage over classical aseptic processing, including fewer opportunities for microbial contamination during processing. However, users should not adopt a false sense of security with these systems. Manufacturers should be also aware of the need to establish new procedures addressing issues unique to these systems.

A. Maintenance

1. General

Isolator systems have a number of special maintenance requirements. Although no isolator unit forms an absolute seal, very high integrity can be achieved in a well-designed unit. However, a leak in any of certain components of the system can constitute a significant breach of integrity. The integrity of gloves, half-suits, seams, gaskets, and seals require daily attention and a comprehensive preventative maintenance program. Replacement frequencies should be established in written procedures that require changing parts before they break down or degrade.

2. Glove Integrity

A faulty glove or sleeve (gauntlet) assembly represents a route of contamination and a critical breach of isolator integrity. The choice of durable glove materials coupled with a well-justified replacement frequency are two aspects of good manufacturing practice that should be addressed. With every use, gloves should be visually evaluated for any macroscopic physical defect. Mechanical integrity tests should also be performed routinely. This attentive preventative maintenance program is necessary to prevent use of gloves lacking integrity that would place the sterile product at risk. When such a breach is discovered, the operation should be terminated. Because of the potential for microbial migration through microscopic holes in gloves and the lack of a highly sensitive glove integrity test, the inner part of the installed glove should be sanitized regularly and the operator should also wear a second pair of thin gloves.

B. Design

1. Airflow

The design of an aseptic processing isolator normally employs unidirectional airflow that sweeps over and away from exposed sterile materials, avoiding any turbulence or stagnant airflow in the area of exposed sterilized materials,

product, and container/closures. In most sound designs, air showers over the critical zone once, and is then systematically exhausted. Air-handling systems should employ HEPA or ULPA filters, or both, in series.

2. Materials of Construction

As in any aseptic processing design, suitable materials should be chosen based on durability as well as ease of cleaning and sterilization. For example, rigid wall construction incorporating stainless steel and glass materials is widely used.

3. Pressure Differential

Isolators that include an open exit portal represent a potential compromise in achieving complete physical separation from the external environment. A positive air pressure differential adequate to achieve this full separation should be employed and supported by qualification studies. Positive air pressure differentials from the isolator to the surrounding environment have largely ranged from ca. 0.07 to 0.2 in water gauge. The appropriate minimum pressure differential specification established will be dependent on the system's design and, when applicable, its exit port. Air balance between the isolator and other direct interfaces (e.g., dry-heat tunnel) should also be qualified. The positive pressure differential should be coupled with appropriate protection at the product egress point(s) in order to overcome the potential for ingress of any airborne particles from the external environment by induction. Induction can result from local turbulent flow causing air swirls or pressure waves that can push extraneous particles into the isolator. Local Class 100 protection at an opening can provide a further barrier to induction of outside air into the isolator.

4. Clean-Area Classifications

The interior of the isolator should, at minimum, meet Class 100 standards. The classification of the environment surrounding the isolator should be based on the design of the product interfaces, such as transfer ports and discharge points, as well as the number of transfers into and out of the isolator. A Class 10,000 or Class 100,000 background is appropriate, depending on isolator design and manufacturing situations. The area surrounding the isolator should be justified. An isolator should not be located in an unclassified room.

C. Transfer of Materials and Supplies

The ability to maintain integrity and sterility of an isolator is impacted by the design of transfer ports. Various adaptations of differing capabilities allow for the transfer of supplies into and out of the isolator.

1. Introduction

Multiple material transfers are generally made during the processing of a batch. Frequently, transfers are performed via direct interface with a decontaminating transfer isolator or dry-heat depyrogenation tunnel with balanced airflow. Such provisions, if well designed, help ensure that microbiological ingress does not result from the introduction of supplies. Properly operated RTPs (rapid transfer ports) are also generally considered to be an effective transfer mechanism. The number of transfers should be kept to a minimum because the risk of ingress of contaminants increases with each successive material transfer.

Some transfer ports can have significant limitations, including marginal decontaminating capability [e.g., ultraviolet (UV)] or a design that would compromise isolation by allowing ingress of air from the surrounding room. In the latter case, localized HEPA-filtered laminar airflow cover in the area of such a port should be implemented.

2. Discharge

Isolators often include a "mousehole" or other exit port through which product is discharged, opening the isolator to the outside environment. The mousehole represents a potential route of contamination. Sufficient overpressure should be supplied and monitored on a continuous basis at this location to ensure that isolation is maintained.

D. Decontamination

1. Surface Exposure

Written procedures for decontamination of the isolator should be established. The decontamination process should provide full exposure of all isolator surfaces to the chemical agent. For example, to facilitate contact with the sterilant, the glove apparatus should be fully extended with glove fingers separated during the decontamination cycle.

2. Efficacy

A decontamination method should be developed that renders the inner surfaces of the isolator free of viable microorganisms. Decontamination can be accomplished by a number of vaporized agents, although these agents possess limited capability to penetrate obstructed or covered surfaces. Process development and validation studies should include a thorough determination of cycle capability. The characteristics of these agents generally preclude the use of reliable statistical methods (e.g., fraction negative) to determine process lethality. An appropriate, quantified BI challenge should be placed on various materials and in many locations throughout the isolator, including difficult-to-reach areas. Cycles should be developed with an appropriate margin of extra kill to provide confidence in the robustness of the decontamination processes. For most production applications, demonstration of a 6-log reduction of the challenge BI is recommended. The uniform distribution of the defined concentration of decontaminating agent should also be evaluated concurrently with these studies. Chemical indicators may also be useful as a qualitative tool to show that the decontaminating agent reached a given location.

3. Frequency

Although isolators vary widely in design, their interior and content should be designed to be frequently decontaminated. If an isolator is to be used for multiple days between decontamination cycles, the frequency adopted should include a built-in safety margin and be well justified. This frequency, established during validation studies, should be reevaluated and increased if production data indicate any deterioration of the microbiological quality of the isolator environment.

A breach of isolator integrity (e.g., power failure, glove or seam tear, other air leaks, valve failure, out-of-specification pressure) should lead to a decontamination cycle. Breaches of integrity should be investigated and any product that may have been impacted by the breach rejected.

E. Filling Line Sterilization

To ensure sterility of product contact surfaces from the start of each operation, the entire path of the sterile liquid stream should be sterilized. In addition, loose materials or equipment to be used within the isolator should be chosen based on their ability to withstand steam sterilization (or equivalent

method). It is expected that any materials that can be subjected to a steam sterilization cycle will, in fact, be autoclaved.

F. Environmental Monitoring

An appropriate environmental monitoring program should be established that routinely ensures acceptable microbiological quality of air, surfaces, and gloves (or half-suits) as well as particulate levels within the isolator. Air quality should be monitored periodically during each shift. As an example, the exit port should be monitored for particulates to detect any unusual results.

G. Personnel

Although clean-room apparel requirements are generally reduced, the contribution of human factor to contamination should not be overlooked. Isolation processes generally include periodic or even frequent use of one or more gloves for aseptic manipulations and handling of component transfers into and out of the isolator. Contaminated gloves can lead to product nonsterility. This concern is heightened because locations on gloves, sleeves, or half-suits can be among the more difficult-to-reach places during surface sterilization. Meticulous aseptic technique standards must be observed (section 211.113).

VI. BLOW-FILL-SEAL TECHNOLOGY

Blow-fill-seal (BFS) technology is an automated process by which containers are formed, filled, and sealed in a continuous operation. This manufacturing technology includes economies in container/closure processing and reduced human intervention, and is often used for filling and packaging of ophthalmics and less frequently for injectables. This section discusses some of the critical control points of this technology. Except where otherwise noted later, the aseptic processing standards discussed elsewhere in this document should be applied to the BFS technology.

A. Equipment Design and Air Quality

A BFS machine operates by (1) heating a plastic polymer resin, (2) extruding it to form a parison (a tubular form of the hot resin), (3) cutting the parison with a high temperature knife, (4) moving the parison under the blow-fill needle (mandrel), (5) inflating it to the shape of the mold walls, (6) filling the formed container with the liquid product, (7) removing the mandrel, and (8) sealing. Throughout this operation sterile air is used, for example, to form the parison and inflate it prior to filling. In most operations, the three steps that pose greatest potential for exposure to particle contamination or surrounding air are those in which the parison is cut, the parison is moved under the blow-fill mandrel, and the mandrel is removed (just prior to sealing).

BFS machinery and its surrounding barriers should be designed to prevent potential for extraneous contamination. As with any aseptic processing operation, it is critical that contact surfaces be sterile. A validated steam-in-place cycle should be used to sterilize the equipment path through which the product is conveyed. In addition, any other surface (e.g., above or nearby) that has potential to contaminate the sterile product needs to be sterile.

The classified environment surrounding BFS machinery should generally meet Class 10,000 standards, but special design provisions (e.g., isolation technology) can justify an alternative classification. HEPA-filtered or sterile air provided by membrane filters is necessary in the critical zone in which sterile product or materials are exposed (e.g., parison formation, container molding or filling steps). Air in the critical zone should meet Class 100 microbiological standards. A well-designed BFS system should also normally achieve Class 100 particulate levels. Equipment design should incorporate specialized measures to reduce particulate levels. In contrast to nonpharmaceutical applications that use BFS machinery, control of air quality (i.e., particulates) is critical for sterile drug product manufacture. Particles generated during the plastic extrusion, cutting, and sealing processes provide a potential means of transport for microorganisms into open containers prior to sealing. Provisions for carefully controlled airflow can protect the product by forcing generated particles outward while preventing any ingress from the adjacent environment. Furthermore, designs separating the filling zone from the surrounding environment are important in ensuring product protection. Barriers, pressure vacuums, microenvironments, and appropriately directed high velocities of sterile air have been found useful in preventing contamination (United States Pharmacopoeia). Smoke studies and multilocation particulate data are vital when performing qualification studies to assess whether proper particulate control dynamics have been achieved throughout the critical area.

In addition to suitable design, an adequate preventative maintenance program should be established. For example, because of its potential to contaminate the sterile drug product, the integrity of the boiling system (e.g., mold plates, gaskets) should be carefully monitored and maintained.

B. Validation and Qualification

Advantages of BFS processing are known to include rapid container/closure processing and minimized interventions. However, a properly functioning process is necessary to realize these advantages. Equipment qualification or requalification and personnel practices should be given special attention. Equipment sterilization, media fills, polymer sterilization, endotoxin removal, product–plastic compatibility, forming and sealing integrity, and unit weight variation are among the key issues that should be covered by validation and qualification studies.

Appropriate data should ensure that BFS containers are sterile and nonpyrogenic. This can generally be achieved by validating that time–temperature conditions of the extrusion process destroy the worst-case endotoxin load on the polymeric material.

The plastic polymer material chosen should be pharmaceutical grade, safe, pure, and pass USP criteria for plastics. Polymer suppliers should be qualified and monitored for raw material quality.

C. Batch Monitoring and Control

In-process monitoring should include various control parameters (e.g., container weight variation, fill weight, leakers, or air pressure) to ensure ongoing process control. Environmental monitoring is particularly important. Samples should be taken during each shift at specified locations under dynamic conditions. Because of the generation of high levels of particles near the exposed drug product, continuous monitoring of particles can provide valuable data relative to the control of a BFS operation. Container/closure defects can be a major problem in control of a BFS operation. It is necessary for the operation to be designed and set up to uniformly manufacture leakproof units. As a final measure, inspection of each unit of a batch should employ a reliable, sensitive final product examination capable of detecting a defective unit

(e.g., leakers). Significant defects due to heat or mechanical problems, such as mold thickness, container/closure interface deficiencies, poorly formed closure, or other deviations should be investigated in accord with sections 211.100 and 211.192.

VII. LYOPHILIZATION OF PARENTERALS

A. Introduction

Lyophilization or freeze-drying is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through the liquid phase. The process consists of three separate, unique, and interdependent processes: freezing, primary drying (sublimation), and secondary drying (desorption). The advantages of lyophilization include the following:

- Ease of processing a liquid, which simplifies aseptic handling
- Enhanced stability of a dry powder
- Removal of water without excessive heating of the product
- Enhanced product stability in a dry state
- Rapid and easy dissolution of reconstituted product

Disadvantages of lyophilization include the following:

- Increased handling and processing time
- Need for sterile diluent on reconstitution
- Cost and complexity of equipment

The lyophilization process generally includes the following steps:

- Dissolving the drug and excipients in a suitable solvent, generally WFI
- Sterilizing the bulk solution by passing it through a 0.22-mm bacteria-retentive filter
- Filling into individual sterile containers and partially stoppering the containers under aseptic conditions
- Transporting the partially stoppered containers to the lyophilizer and loading into the chamber under aseptic conditions
- Freezing the solution by placing the partially stoppered containers on cooled shelves in a freeze-drying chamber or prefreezing in another chamber
- Applying a vacuum to the chamber and heating the shelves in order to evaporate the water from the frozen state
- Complete stoppering of the vials usually by hydraulic or screw rod stoppering mechanisms installed in the lyophilizers

Many new parenteral products, including anti-infectives, biotechnology-derived products, and in vitro diagnostics, are manufactured as lyophilized products. Numerous potency, sterility, and stability problems are associated with the manufacture and control of lyophilized products. It is recognized that there is complex technology associated with the manufacture and control of a lyophilized pharmaceutical dosage form. Some of the important aspects of these operations include the formulation of solutions, filling of vials, and validation of the filling operation, sterilization and engineering aspects of the lyophilizer, scale-up and validation of the lyophilization cycle, and testing of the end product. This discussion will address some of the problems associated with the manufacture and control of a lyophilized dosage form.

B. Product Type and Formulation

Products are manufactured in the lyophilized form due to their instability when in solution. Many antibiotics, such as some of the semisynthetic penicillins, cephalosporins, and some of the salts of erythromycin, doxycycline, and chloramphenicol, are made by the lyophilization process. Because they are antibiotics, low bioburden of these formulations would be expected at the time of batching. However, some of the other dosage forms that are lyophilized, such as hydrocortisone sodium succinate, methylprednisolone sodium succinate, and many of the biotechnology-derived products, have no antibacterial effect when in solution.

For these types of products, bioburden should be minimal; the bioburden should be determined prior to sterilization of these bulk solutions prior to filling. Obviously, the batching or compounding of these bulk solutions should be controlled to prevent any increase in microbiological levels that may occur up to the time the bulk solutions are filtered (sterilized). The concern with any microbiological level is the possible increase in endotoxins. Good practice for the compounding of lyophilized products would also include batching in a controlled environment and in sealed tanks, particularly if the solution is to be held for any length of time prior to sterilization.

In some cases, manufacturers have performed bioburden testing on bulk solutions after prefiltration and prior to final filtration. Although the testing of such solutions may be meaningful in determining the bioburden for sterilization, it does not provide any information regarding the potential formation or presence of endotoxins. The testing of 0.1-mL samples by LAL methods of bulk solution for endotoxins is of value, but testing of at least 100-mL size samples prior to prefiltration, particularly for the presence of gram-negative organisms, would be of greater value in evaluating the process. For example, the presence of *Pseudomonas* species in the bioburden of a bulk solution has been identified as an objectionable condition.

C. Filling

The filling of vials that are to be lyophilized has some problems that are somewhat unusual. The stopper is placed on top of the vial and is ultimately seated in the lyophilizer. As a result, the contents of the vial are subject to contamination until they are actually sealed. Validation of filling operations should include media fills and the sampling of critical surfaces and air during active filling (dynamic conditions).

Because of the active involvement of people in filling and aseptic manipulations, an environmental program should also include an evaluation of microbiological levels on people working in aseptic processing areas. One method of evaluating the training of operators working in aseptic processing facilities is the surface monitoring of gloves and gowns on a daily basis. Manufacturers are actively sampling the surfaces of personnel working in aseptic processing areas. A reference that provides for this type of monitoring is the USP discussion of the interpretation of sterility test results. It states under the heading of "Interpretation of Quality Control Tests" that review consideration should be paid to environmental control data, including microbial monitoring, records of operators, gowns, gloves, and garbing practices. In those situations wherein manufacturers have failed to perform some type of personnel monitoring or monitoring has shown unacceptable levels of contamination, regulatory situations have resulted.

Typically, vials to be lyophilized are partially stoppered by machine. However, some filling lines have been noted in which an operator places each stopper on top of the vial by hand. At this time, it would seem difficult for a manufacturer to justify a hand-stoppering operation, even if sterile forceps are employed, in any type of operation other than filling a clinical batch or a very small number of units. Significant regulatory situations have resulted from this practice. Again, the concern is the immediate avenue of contamination offered by the operator. It is well recognized that people are the major source of contamination in an aseptic processing filling operation. The longer a person works in an aseptic operation, the more the microorganisms shed and the greater the probability of contamination.

Once filled and partially stoppered, vials are transported and loaded into the lyophilizer. The transfer and handling, such as loading of the lyophilizer, should take place under primary barriers, such as the laminar flow hoods under which the vials were filled. Validation of this handling should also include the use media fills.

Regarding the filling of sterile media, there are some manufacturers who carry out a partial lyophilization cycle and freeze the media. Although this could seem to greater mimic the process, the freezing of media could reduce microbial levels of some contaminants. Because the purpose of the media fill is to evaluate and justify the aseptic capabilities of the process, the people, and the system, the possible reduction of microbiological levels after aseptic manipulation by freezing would not be warranted. The purpose of a media fill is not to determine the lethality of freezing and its effect on any microbial contaminants that might be present.

In an effort to identify the particular sections of filling and aseptic manipulation that might introduce contamination, several manufacturers have resorted to expanded media fills. That is, they have filled ca. 9000 vials during a media fill and segmented the fill into three stages: the first stage of filling 3000 vials and stoppering on line; the second stage of filling 3000 vials, transporting to the lyophilizer, and then stoppering; and a third stage of filling 3000 vials, loading in the lyophilizer, and exposure to a portion of the nitrogen flush and then stoppering. Because sterilization of lyophilizer and sterilization of the nitrogen system used to backfill require separate validation, media fills should primarily validate the filling, transporting, and loading aseptic operations.

The question of the number of units needed for media fills when the capacity of the process is less than 3000 units is frequently asked, particularly for clinical products. Again, the purpose of the media fill is to assure that the product can be aseptically processed without contamination under operating conditions. It would seem, therefore, that the maximum number of units of media filled be equivalent to the maximum batch size if it is less than 3000 units.

In the transport of vials to the lyophilizer, because they are not sealed, there is concern for the potential for contamination. During inspections and in the review of new facilities, the failure to provide laminar flow coverage or a primary barrier for the transport and loading areas of a lyophilizer has been regarded as an objectionable condition. The solutions include use of laminar flow carts or locating filling lines close to the lyophilizer to minimize exposure. The use of laminar flow units should validate that the air turbulence created in the area does not itself produce a contamination problem. The media fills and smoke studies should be done to identify and correct these problems. Typically, the lyophilization process includes the stoppering of vials in the chamber.

Another major concern with the filling operation is assurance of fill volumes. Obviously, a low fill would represent a subpotency in the vial. Unlike a powder or liquid fill, a low fill would not be readily apparent after lyophilization, particularly for a biopharmaceutical drug product in which the active ingredient may be only a milligram. Because of the clinical significance, subpotency in a vial can be a very serious situation.

On occasion, it has been seen that production operators monitoring fill volumes record these fill volumes only after adjustments are made. Therefore, good practice and a good quality assurance program would include the frequent monitoring of the volume of fill, such as every 15 minutes. Good practice would also include provision for the isolation of particular sections of filling operations when low or high fills are encountered.

Some atypical filling operations have not been discussed. For example, there have also been some situations in which lyophilization is performed on trays of solution rather than in vials. Based on the current technology available, it would seem that for a sterile product, it would be difficult to justify this procedure.

The dual chamber vial also presents additional requirements for aseptic manipulations. Media fills should include the filling of media in both chambers. Also, the diluent in these vials should contain a preservative. (Without a preservative, the filling of diluent would be analogous to the filling of media. In such cases, a 0% level of contamination would be expected.)

D. Lyophilization Cycle and Controls

After sterilization of the lyophilizer and aseptic loading, the initial step is freezing the solution. In some cycles, the shelves are at the temperature needed for freezing, whereas for other cycles, the product is loaded and then the shelves are taken to the freezing temperature necessary for product freeze. In those cycles wherein the shelves are precooled prior to loading, there is concern for any ice formation on shelves prior to loading. Ice on shelves prior to loading can cause partial or complete stoppering of vials prior to lyophilization of the product. It is noteworthy that even 100% vial inspection can fail to identify defective vials. Typically, the product is frozen at a temperature well below the eutectic point.

The scale-up and change of lyophilization cycles, including the freezing procedures, have presented some problems. Studies have shown the rate and manner of freezing may affect the quality of the lyophilized product. For example, slow freezing leads to the formation of larger ice crystals. This results in relatively large voids, which aid in the escape of water vapor during sublimation. On the other hand, slow freezing can increase concentration shifts of components. Also, the rate and manner of freezing have been shown to have an effect on the physical form (polymorph) of the drug substance.

It is desirable after freezing and during primary drying to hold the drying temperature (in the product) at least 4°C to 5°C below the eutectic point. Obviously, the manufacturer should know the eutectic point and have the necessary instrumentation to assure the uniformity of product temperatures. The lyophilizer should also have the necessary instrumentation to control and record the key process parameters. These include shelf temperature, product temperature, condenser temperature, chamber pressure, and condenser pressure. The manufacturing directions should provide for time, temperature, and pressure limits necessary for a lyophilization cycle for a product. The monitoring

of product temperature is particularly important for those cycles for which there are atypical operating procedures, such as power failures or equipment breakdown.

Electromechanical control of a lyophilization cycle has utilized cam-type recorder-controllers. However, newer units provide for microcomputer control of the freeze–drying process. A very basic requirement for a computer-controlled process is a flow chart or logic. Typically, operator involvement in a computer-controlled lyophilization cycle primarily occurs at the beginning. It consists of loading the chamber, inserting temperature probes in product vials, and entering cycle parameters such as shelf temperature for freezing, product freeze temperature, freezing soak time, primary drying shelf temperature and cabinet pressure, product temperature for establishment of fill vacuum, secondary drying shelf temperature, and secondary drying time.

In cases where manufacturers continuously make adjustments in cycles as they are being run, the lyophilization process would be nonvalidated.

Validation of the software program of a lyophilizer follows the same criteria as those for other processes. Basic concerns include software development, modifications, and security. The "Guide to Inspection of Computerized Systems in Drug Processing" contains a discussion of potential problem areas relating to computer systems. The "Guide to the Inspection of Software Development Activities" is a reference that provides a more detailed review of software requirements.

Leakage into a lyophilizer may originate from various sources. As in any vacuum chamber, leakage can occur from the atmosphere into the vessel itself. Other sources are media employed within the system to perform the lyophilizing task. These would be the thermal fluid circulated through the shelves for product heating and cooling, the refrigerant employed inside the vapor condenser cooling surface, and oil vapors that may migrate back from the vacuum pumping system.

Any one source, or a combination of all, can contribute to the leakage of gases and vapors into the system. It is necessary to monitor the leak rate periodically to maintain the integrity of the system. It is also necessary, should the leak rate exceed specified limits, to determine the actual leak site for purposes of repair.

Thus, it would be beneficial to perform a leak test at some time after sterilization, possibly at the beginning of the cycle or prior to stoppering. The time and frequency for performing the leak test will vary and will depend on the data developed during the cycle validation. The pressure rise found acceptable at validation should be used to determine the acceptable pressure rise during production. A limit and what action is to be taken if excessive leakage is found should be addressed in some type of operating document.

To minimize oil vapor migration, some lyophilizers are designed with a tortuous path between the vacuum pump and chamber. For example, one fabricator installed an oil trap in the line between the vacuum pump and chamber in a lyophilizer with an internal condenser. Leakage can also be identified by sampling surfaces in the chamber after lyophilization for contaminants. One could conclude that if contamination is found on a chamber surface after lyophilization, then dosage units in the chamber could also be contaminated. It is a good practice, as part of the validation of cleaning of the lyophilization chamber, to sample the surfaces both before and after cleaning.

Because of the lengthy cycle runs and strain on machinery, it is not unusual to see equipment malfunction or fail during a lyophilization cycle. There should be provisions in place for the corrective action to be taken when these atypical situations occur. In addition to documentation of the malfunction, there should be an evaluation of the possible effects on the product (e.g., partial or complete meltback; refer to subsequent discussion). Merely testing samples after the lyophilization cycle is concluded may be insufficient to justify the release of the remaining units. For example, the leakage of chamber shelf fluid into the chamber or a break in sterility would be cause for rejection of the batch.

E. Cycle Validation

Many manufacturers file (in applications) their normal lyophilization cycles and validate the lyophilization process based on these cycles. Unfortunately, such data would be of little value to substantiate shorter or abnormal cycles. In some cases, manufacturers are unaware of the eutectic point. It would be difficult for a manufacturer to evaluate partial or abnormal cycles without knowing the eutectic point and the cycle parameters needed to facilitate primary drying.

Scale-up for the lyophilized product requires knowledge of the many variables that can affect the product. Some of the variables include freezing rate and temperature ramping rate. As with the scale-up of other drug products, there should be a development report that discusses the process and logic for the cycle. Probably more so than any other product, scale-up of the lyophilization cycle is very difficult.

Some manufacturers market multiple strengths, vial sizes, and different batch sizes. Separate validation should be performed for each product and extrapolation from one cycle to another is not proper.

F. Lyophilizer Sterilization and Design

The sterilization of the lyophilizer is one of the more frequently encountered problems noted during inspections. Some of the older lyophilizers cannot tolerate steam under pressure, and sterilization is marginal at best. These lyophilizers can only have their inside surfaces wiped with a chemical agent that may be a sterilant but usually has been found to be a sanitizing agent. Unfortunately, piping such as that for the administration of inert gas (usually nitrogen) and sterile air for backfill or vacuum break is often inaccessible to such surface "sterilization" or treatment. It would seem very difficult for a manufacturer to demonstrate satisfactory validation of sterilization of a lyophilizer by chemical "treatment."

Another method of sterilization that has been practiced is the use of gaseous ethylene oxide. As with any ethylene oxide treatment, humidification is necessary. Providing a method of introducing the sterile moisture with uniformity has been found to be difficult.

To employ WFI as a final wash or rinse of the lyophilizer and while the chamber is wet, sterilizing by ethylene oxide gas may be satisfactory for the chamber but inadequate for associated plumbing. Another problem associated with ethylene oxide is the residue. A common ethylene oxide and nitrogen supply line to a number of lyophilizers connected in parallel to the system may result in some ethylene oxide in the nitrogen supply line during the backfilling step. Obviously, this type of system is objectionable.

A generally recognized, acceptable method of sterilizing the lyophilizer is through the use of moist steam under pressure. Sterilization procedures should parallel that of an autoclave, and a typical system should include two independent temperature-sensing systems, one to control and record temperatures of the cycle as with sterilizers and the other in the cold spot of the chamber. As with autoclaves, lyophilizers

should have drains with atmospheric breaks to prevent back siphonage.

As discussed, there should also be provisions for sterilizing the inert gas or air and the supply lines. Some manufacturers have chosen to locate the sterilizing filters in a port of the chamber. The port is steam sterilized when the chamber is sterilized, and then the sterilizing filter, previously sterilized, is aseptically connected to the chamber. Some manufacturers have chosen to sterilize the filter and downstream piping to the chamber in place. Typical sterilization-in-place of filters may require steaming of both to obtain sufficient temperatures. In this type of system, there should be provision for removing or draining condensate. The failure to sterilize nitrogen and air filters and the piping downstream leading into the chamber has been identified as a problem on a number of inspections.

Because these filters are used to sterilize inert gas or air, or both, there should be some assurance of their integrity. Some inspections have disclosed a lack of integrity testing of the inert gas or air filter. The question frequently asked is how often the vent filter should be tested for integrity. As with many decisions made by manufacturers, there is a level of risk associated with the operation, process, or system, which only the manufacturer can determine. If the sterilizing filter is found to pass the integrity test after several uses or batches, then one can claim its integrity for the previous batches. However, if the filter is tested only after several batches have been processed and if found to fail the integrity test, then one can question the sterility of all of the previous batches processed. To minimize this risk, some manufacturers have resorted to redundant filtration.

For most cycles, stoppering occurs within the lyophilizer. Typically, the lyophilizer has some type of rod or rods (ram), which enter the immediate chamber at the time of stoppering. Once the rod enters the chamber, there is the potential for contamination of the chamber. However, because the vials are stoppered, there is no avenue for contamination of the vials in the chamber, which are now stoppered. Generally, lyophilizers should be sterilized after each cycle because of the potential for contamination of the shelf support rods. Additionally, the physical act of removing vials and cleaning the chamber can increase levels of contamination.

In some of the larger units, the shelves are collapsed after sterilization to facilitate loading. Obviously, the portions of the ram entering the chamber to collapse the shelves enter from a nonsterile area. Attempts to minimize contamination have included wiping the ram with a sanitizing agent prior to loading. Control aspects have included testing the ram for microbiological contamination, testing it for residues of hydraulic fluid, and testing the fluid for its bacteriostatic effectiveness. One practice is to provide a flexible "skirt" to cover the ram. In addition to microbiological concerns with hydraulic fluid, there is also the concern with product contamination.

During steam sterilization of the chamber, there should be space between shelves that permit passage of free-flowing steam. Some manufacturers have placed "spacers" between shelves to prevent their total collapse. Others have resorted to a two-phase sterilization of the chamber. The initial phase provides for sterilization of the shelves when they are separated. The second phase provides for sterilization of the chamber and piston with the shelves collapsed.

Typically, BIs are used in lyophilizers to validate the steam sterilization cycle. One manufacturer of a biopharmaceutical product was found to have a positive BI after sterilization at 121°C for 45 minutes. During the chamber sterilization, trays used to transport vials from the filling line to the chamber were also sterilized. The trays were sterilized in an inverted position on shelves in the chamber. It is believed that the positive BI is the result of poor steam penetration under these trays.

The sterilization of condensers is also a major issue that warrants discussion. Most of the newer units provide for the capability of sterilization of the condenser along with the chamber, even if the condenser is external to the chamber. This provides a greater assurance of sterility, particularly in those situations in which there is some equipment malfunction and the vacuum in the chamber is deeper than in the condenser.

Malfunctions that can occur, indicating that sterilization of the condenser is warranted, include vacuum pump breakdown, refrigeration system failures, and the potential for contamination by the large valve between the condenser and chamber. This is particularly true for units that have separate vacuum pumps for both the condenser and chamber. When there are problems with the systems in the lyophilizer, contamination could migrate from the condenser back to the chamber. It is recognized that it is not possible to sterilize the condenser in many of the older units, and this represents a major problem, particularly in those cycles in which there is some equipment or operator failure.

As referenced previously, leakage during a lyophilization cycle can occur, and the door seal or gasket presents an avenue of entry for contaminants. If steam leaks from a unit during sterilization, air could possibly enter the chamber during lyophilization.

Some of the newer lyophilizers have double doors, one for loading and the other for unloading. The typical single-door lyophilizer opens in the clean area only, and contamination between loads is minimal. This clean area, as previously discussed, represents a critical processing area for a product made by aseptic processing. In most units, only the piston raising or lowering shelves is the source of contamination. For a double-door system, unloading the lyophilizer in a nonsterile environment, other problems may occur. The nonsterile environment presents a direct avenue of contamination of the chamber when unloading, and door controls similar to double-door sterilizers should be in place.

Obviously, the lyophilizer chamber is to be sterilized between batches because of the direct means of contamination. A significant problem is that of leakage through the door seal. For the single-door unit, leakage before stoppering around the door seal is not a major problem from a sterility standpoint because single-door units open only into sterile areas. However, leakage from a door gasket or seal from a nonsterile area will present a significant microbiological problem. To minimize the potential for contamination, it is recommended that the lyophilizers be unloaded in a cleanroom area to minimize contamination. After steam sterilization, there is often some condensate remaining on the floor of the chamber. Some manufacturers remove this condensate through the drain line while the chamber is still pressurized after sterilization. Nonsterile air could contaminate the chamber through the drain line. Some manufacturers attempt to dry the chamber by blowing sterile nitrogen gas through the chamber at a pressure above atmospheric pressure. Residual of condensate in the chamber is often a cause of *Pseudomonas* contamination.

G. Finished Product Testing

Several aspects of finished product testing are of concern to the lyophilized dosage form. These include dose uniformity testing, moisture and stability testing, and sterility testing.

1. Dose Uniformity

The USP includes two types of dose uniformity testing: content uniformity and weight variation. It states that weight variation may be applied to solids, with or without added substances that have been prepared from true solutions and freeze-dried in final containers. However, when other excipients or other additives are present, weight variation may be applied, provided there is correlation with the sample weight and potency results. For example, in the determination of potency, it is sometimes common to reconstitute and assay the entire contents of a vial without knowing the weight of the sample. Performing the assay in this manner will provide information on the label claim of a product, but without knowing the sample weight, one has no information about dose uniformity. One should correlate the potency result obtained from the assay with the weight of the sample tested.

2. Stability Testing

An obvious concern with the lyophilized product is the amount of moisture present in vials. The manufacturer's data for the establishment of moisture specifications for both product release and stability should be reviewed. As with other dosage forms, the expiration date and moisture limit should be established based on worst-case data. That is, a manufacturer should have data that demonstrate adequate stability at the moisture specification.

As with immediate release potency testing, stability testing should be performed on vials with a known weight of sample. For example, testing a vial (sample) which had a higher fill weight (volume) than the average fill volume of the batch would provide higher potency results and not represent the potency of the batch. Also, the expiration date and stability should be based on those batches with the higher moisture content. Such data should also be considered in the establishment of a moisture specification.

For products showing a loss of potency due to aging, there are generally two potency specifications. There is a higher limit for the dosage form at the time of release. This limit is generally higher than the official USP or filed specification that is official throughout the entire expiration date period of the dosage form. The USP points out that compendial standards apply at any time in the life of the article.

Stability testing should also include provision for the assay of aged samples and subsequent reconstitution of these aged samples for the maximum amount of time specified in the labeling. On some occasions, manufacturers have established expiration dates without performing label claim reconstitution potency assays at the various test intervals and particularly the expiration date test interval. Additionally, this stability testing of reconstituted solutions should include the most concentrated and the least concentrated reconstituted solutions. The most concentrated reconstituted solution will usually exhibit degradation at a faster rate than less concentrated solutions.

3. Sterility Testing

With respect to sterility testing of lyophilized products, there is concern with the solution used to reconstitute the lyophilized product. Although products may be labeled for reconstitution with bacteriostatic WFI, sterile WFI should be used to reconstitute products. Because of the potential toxicities associated with bacteriostatic WFI, many hospitals use WFI only. Bacteriostatic WFI may kill some of the vegetative cells if present as contaminants, and thus mask the true level of contamination in the dosage form. As with other sterile products, sterility test results that show contamination on the initial test should be identified and reviewed.

H. Finished Product Inspection—Meltback

The USP points out that it is good pharmaceutical practice to perform 100% inspection of parenteral products. This includes sterile lyophilized powders. Critical aspects include the presence of correct volume of cake and the cake appearance. With regard to cake appearance, one of the major concerns is *meltback*.

Meltback is a form of cake collapse and is caused by the change from the solid to liquid state; that is, there is incomplete sublimation (change from the solid to vapor state) in the vial. Associated with this problem is a change in the physical form of the drug substance or a pocket of moisture, or both. These may result in greater instability and increased product degradation.

Another problem may be poor solubility. Increased time for reconstitution at the user stage may result in partial loss of potency if the drug is not completely dissolved, because it is common to use in-line filters during administration to the patient.

Manufacturers should be aware of the stability of lyophilized products that exhibit partial or complete meltback. Literature shows that for some products, such as the cephalosporins, the crystalline form is more stable than the amorphous form of lyophilized product. The amorphous form may exist in the meltback portion of the cake where there is incomplete sublimation.

VIII. HIGH-PURITY WATER SYSTEMS

High-purity water systems are used for the manufacture of many types of pharmaceutical products, particularly parenteral and ophthalmic products. The pharmacopoeia describes several specifications for water such as WFI, purified water, and potable water. Because adequate controls in the supply of water systems are considered critical, along with other environmental factors, a detailed description of high-purity water systems is provided here.

A. System Design

One of the basic considerations in the design of a system is the type of product that is to be manufactured. For parenteral products where there is a concern for pyrogens, it is expected that WFI will be used. This applies to the formulation of products, as well as to the final washing of components and equipment used in their manufacture. Distillation and reverse osmosis (RO) filtration are the only acceptable methods listed in the USP for producing WFI. However, in the bulk pharmaceutical and biotechnology industries and some foreign companies, ultra filtration (UF) is employed to minimize endotoxins in those drug substances that are administered parenterally.

It is expected that WFI be used in the formulation of some ophthalmic products such as the ophthalmic irrigating solution and some inhalation products such as sterile water for inhalation, where there are pyrogen specifications. However, purified water is used in the formulation of most inhalation and ophthalmic products. This also applies to topicals, cosmetics, and oral products.

Another design consideration is the temperature of the system. It is recognized that hot (65°C–80°C) systems are self-sanitizing. Although the cost of other systems may be less

expensive for a company, the cost of maintenance, testing, and potential problems may be higher than the cost of energy saved. Whether a system is circulating or one-way is also an important design consideration. Obviously, water in constant motion is less liable to have high levels of contaminant. A one-way water system is basically a "dead-leg."

The final, and possibly the most important, consideration is the risk assessment or level of quality that is desired. It should be recognized that different products require different quality waters. Parenterals require very pure water with no endotoxins. Topical and oral products require less pure water and do not have a requirement for endotoxins. Even with topical and oral products there are factors that dictate different qualities for water. For example, preservatives in antacids are marginally effective, so more stringent microbial limits have to be set. The quality control department should assess each product manufactured with the water from their system and determine the microbial action limits based on the most microbial sensitive product. In lieu of stringent water action limits in the system, the manufacturer can add a microbial reduction step in the manufacturing process for the sensitive drug product(s).

B. System Validation

A basic reference used for the validation of high-purity water systems is the Parenteral Drug Association Technical Report No. 4, "Design Concepts for the Validation of a Water for Injection System."

The introduction provides guidance and states that validation often involves the use of an appropriate challenge. In this situation, it would be undesirable to introduce microorganisms into an on-line system; therefore, reliance is placed on periodic testing for microbiological quality and on the installation of monitoring equipment at specific checkpoints to ensure that the total system is operating properly and continuously fulfilling its intended function.

In the review of a validation report or in the validation of a high-purity water system, several aspects should be considered. Documentation should include a description of the system along with a print. The drawing needs to show all equipment in the system from the water feed to points of use. It should also show all sampling points and their designations. If a system has no print, it is usually considered an objectionable condition. The thinking is that if there is no print, it is not possible for the system to be validated. How can a quality control manager or microbiologist know where to sample? In facilities observed without updated prints, serious problems have been identified in these systems. The print should be compared with the actual system annually to ensure its accuracy, to detect unreported changes, and confirm reported changes to the system.

After all the equipment and piping has been verified as installed correctly and working as specified, the initial phase of the water system validation can begin. During this phase, the operational parameters and the cleaning and sanitization procedures and frequencies will be developed. Sampling should be daily after each step in the purification process and at each point of use for 2 to 4 weeks. The sampling procedure for point-of-use sampling should reflect how the water is to be drawn; for example, if a hose is usually attached, the sample should be taken at the end of the hose. If the SOP calls for the line to be flushed before use of the water from that point, then the sample is taken after the flush.

The second phase of the system validation is to demonstrate that the system will consistently produce the desired water quality when operated in conformance with the SOPs. The sampling is performed as in the initial phase and for the same time period. At the end of this phase, the data should demonstrate that the system will consistently produce the desired quality of water.

The third phase of validation is designed to demonstrate that when the water system is operated in accordance with the SOPs over a long period of time, it will consistently produce water of the desired quality. Any variations in the quality of the feedwater that could affect the operation and ultimately the water quality will be picked up during this phase of the validation. Sampling is performed according to routine procedures and frequencies. For WFI systems, the samples should be taken daily from a minimum of one point of use, with all points of use tested weekly. The validation of the water system is completed when there is at least a full year's worth of data.

Although the above validation scheme is not the only way a system can be validated, it contains the necessary elements for validation of a water system. First, there must be data to support the SOPs. Second, there must be data demonstrating that the SOPs are valid and that the system is capable of consistently producing water that meets the desired specifications. Finally, there must be data to demonstrate that seasonal variations in the feedwater do not adversely affect the operation of the system or the water quality.

The last part of the validation is the compilation of the data, with any conclusions into the final report. The final validation report must be signed by the appropriate people responsible for operation and quality assurance of the water system.

A typical problem is the failure of operating procedures to preclude contamination of the system with nonsterile air remaining in a pipe after drainage. A typical problem occurs when a washer or hose connection is flushed and then drained at the end of the operation. After draining, this valve (the second off of the system) is closed. If, on the next day or start-up of the operation, the primary valve off the circulating system is opened, then the nonsterile air remaining in the pipe after drainage will contaminate the system. The solution is to provide for operational procedures that provide for opening the secondary valve before the primary valve to flush the pipe prior to use.

Another major consideration in the validation of high-purity water systems is the acceptance criteria. Consistent results throughout the system over a period of time constitute the primary element.

C. Microbial Limits

1. WFI Systems

Regarding microbiological results for WFI, it is expected that they be essentially sterile. Because sampling frequently is performed in nonsterile areas and is not truly aseptic, occasional low-level counts due to sampling errors may occur. The U.S. FDA policy is that less than 10 CFU/100 mL is an acceptable action limit. None of the limits for water are pass or fail limits; all limits are action limits. When action limits are exceeded, the cause of the problem must be investigated. Action must be taken to correct the problem and assess the impact of the microbial contamination on products manufactured with the water. The results of the investigation must then be documented.

With regard to sample size, 100 to 300 mL is preferred when sampling WFI systems. Sample volumes less than 100 mL are unacceptable.

The real concern in WFI is endotoxins. Because WFI can pass the LAL endotoxin test and still fail the above microbial action limit, it is important to monitor WFI systems for both endotoxins and microorganisms.

2. Purified Water Systems

For purified water systems, microbiological specifications are not as clear. The USP specifications, that it complies with federal Environmental Protection Agency (EPA) regulations for drinking water, are recognized as being minimal specifications. There have been attempts by some to establish meaningful microbiological specifications for purified water. The CFTA proposed a specification of not more than 500 organisms/mL. The USP has an action guideline of not greater than 100 organisms/mL. Although microbiological specifications have been discussed, none (other than EPA standards) have been established. The U.S. FDA policy is that any action limit over 100 CFU/mL for a purified water system is unacceptable.

The purpose of establishing any action limit or level is to assure that the water system is under control. Any action limit established will depend on the overall purified water system and further processing of the finished product and its use. For example, purified water used to manufacture drug products by cold processing should be free of objectionable organisms. Objectionable organisms are any organisms that can cause infections when the drug product is used as directed or any organism capable of growth in the drug product—the specific contaminant rather than the number is generally more significant.

Organisms exist in a water system either as freely floating in the water or attached to the walls of the pipes and tanks. When they are attached to the walls, they are known as biofilm, which continuously sloughs off organisms. Thus, contamination is not uniformly distributed in a system, and the sample may not be representative of the type and level of contamination. A count of 10 CFU/mL in one sample and 100 or even 1000 CFU/mL in a subsequent sample would not be unrealistic.

Thus, establishing the level of contamination allowed in a high-purity water system used in the manufacture of a nonsterile product requires an understanding of the use of the product, the formulation (preservative system), and manufacturing process. For example, antacids, which do not have an effective preservative system, require an action limit below the 100 CFU/mL maximum.

The USP gives some guidance in their monograph, *Microbiological Attributes of Non-Sterile Products*. It points out that, "The significance of microorganisms in nonsterile pharmaceutical products should be evaluated in terms of the use of the product, the nature of the product, and the potential harm to the user." Thus, not just the indicator organisms listed in some of the specific monographs present problems. It is up to manufacturers to evaluate their product and the way it is manufactured, and establish an acceptable action level of contamination, not to exceed the maximum, for the water system, based on the highest risk product manufactured with the water.

D. WFI Systems

In establishing a validated WFI system, there are several concerns. Pretreatment of feedwater is recommended by most manufacturers of distillation equipment and is definitely required for RO units. The incoming feedwater quality may fluctuate during the life of the system depending on seasonal variations and other external factors beyond the control of the pharmaceutical facility. For example, in the spring (at least in the northeast United States), increases in gram-negative organisms have been known. Also, new construction or fires can deplete water stores in old mains, causing an influx of water heavily contaminated with different flora.

A water system should be designed to operate within these anticipated extremes. Obviously, the only way to know the extremes is to periodically monitor feedwater. If the feedwater is from a municipal water system, reports from the municipality testing can be used in lieu of in-house testing.

E. Still

Most of the new systems now use multieffect stills. Endotoxins find their way into the system through many channels, such as when there is a malfunction of the feedwater valve and level control in the still, which results in droplets of feedwater being carried over in the distillate or water lying in the condenser for several days (i.e., over the weekend). This may produce unacceptable levels of endotoxins. More common, however, is the failure to adequately treat feedwater to reduce levels of endotoxins. Many of the still fabricators will only guarantee a 2.5-log to 3-log reduction in the endotoxin content. Therefore, it is not surprising that in systems in which the feedwater occasionally spikes to 250 EU/mL, unacceptable levels of endotoxins may occasionally appear in the distillate (WFI). This requires having a satisfactory pretreatment system to assure validity of system. Typically, conductivity meters are used on water systems to monitor chemical quality but have no meaning regarding microbiological quality.

Petcocks or small sampling ports between each piece of equipment, such as after the still and before the holding tank, are placed in the system to isolate major pieces of equipment. This is necessary for the qualification of the equipment and to enable easy investigation of any problems that might occur due to these petcocks and sampling ports.

F. Heat Exchangers

One principal component of the still is the heat exchanger. Because of the similar ionic quality of distilled and deionized water, conductivity meters cannot be used to monitor microbiological quality. Positive pressure such as in vapor compression or double-tubesheet design should be employed to prevent possible feedwater-to-distillate contamination in a leaky heat exchanger.

There are potential design-related problems associated with heat exchangers. There are two methods to prevent contamination by leakage: one is to provide gauges to constantly monitor pressure differentials to ensure that the higher pressure is always on the clean fluid side, and the other is to use the double-tubesheet type of heat exchanger.

In some systems, heat exchangers are used to cool water at use points. For the most part, cooling water is not circulated through them when not in use. In a few situations, pinholes have formed in the tubing after they were drained (on the cooling waterside) and not in use. A small amount of moisture remaining in the tubes when combined with air can corrode the stainless steel tubes on the cooling waterside. Thus, it is recommended that, when not in use, heat exchangers not be drained of the cooling water.

G. Holding Tank

In hot systems, temperature is usually maintained by applying heat to a jacketed holding tank or by placing a heat exchanger in the line prior to an insulated holding tank. The one component of the holding tank that requires great attention is the vent filter. It is expected that there be some program for

integrity-testing this filter to assure that it is intact. Typically, filters are now jacketed to prevent condensate or water from blocking the hydrophobic vent filter. If the vent filter becomes blocked, possibly either the filter will rupture or the tank will collapse. There are methods for integrity testing of vent filters in place. It is expected, therefore, that the vent filter be located in a position on the holding tank where it is readily accessible. Just because a WFI system is relatively new and distillation is employed, it is not necessarily problem free. Other considerations such as how it is integrated with the rest of the system are equally important.

H. Pumps

Pumps burn out and parts wear. Also, if pumps are static and not continuously in operation, their reservoir can be a static area where water will lie. A drain from the low point in a pump housing may become a source of contamination if the pump is only periodically operational.

I. Piping

Piping in WFI systems usually consists of highly polished stainless steel. In a few cases, manufacturers have begun to use PVDF (polyvinylidene fluoride) piping. It is purported that this piping can tolerate heat with no extractables being leached. A major problem with PVDF tubing is that it requires considerable support. When this tubing is heated, it tends to sag and may stress the weld (fusion) connection and result in leakage. Additionally, initially at least, fluoride levels are high. This piping is of benefit in product delivery systems wherein low-level metal contamination may accelerate the degradation of drug product, such as in the biotech industry.

One common problem with piping is that of "dead-legs," which are defined as "not having an unused portion greater in length than six diameters of the unused pipe measured from the axis of the pipe in use." It should be pointed out that this was developed for hot (75°C–80°C), circulating systems. With colder systems (65°C–75°C), any drops or unused portion of any length of piping has the potential of forming a biofilm and should be eliminated, if possible, or have special sanitizing procedures. There should be no threaded fittings in a pharmaceutical water system. All pipe joints must use sanitary fittings or be butt-welded. Sanitary fittings are usually used where the piping meets valves, tanks, and other equipment that must be removed for maintenance or replacement. Therefore, the procedures for sanitization, as well as the actual piping, should be established and well documented.

J. Reverse Osmosis

Another acceptable method for manufacturing WFI is RO. However, because these systems are cold, and because RO filters are not absolute, microbiological contamination is not unusual. Because RO filters are not absolute, the filter manufacturers recommend that at least two be in series. There may be an UV light in the system downstream from the RO units to control microbiological contamination.

The ball valves in these systems are not considered sanitary valves because the center of the valve can have water in it when the valve is closed. This is a stagnant pool of water that can harbor microorganisms and provide a starting point for biofilm.

As an additional comment on RO systems, with the recognition of microbiological problems, some manufacturers have installed heat exchangers immediately after the RO filters to heat the water to 75°C to 80°C to minimize microbiological contamination.

With the development of biotechnology products, many small companies are using RO and UF systems to produce high-purity water. Most of these systems employ PVC or some type of plastic tubing. Because the systems are typically cold, the many joints in the system are subject to contamination. Another potential problem with PVC tubing is extractables. Without demonstration to the contrary, it is not possible to evaluate from the design of the system whether the extractables would pose any problem.

The systems also contain 0.2-mm point-of-use filters that can mask the level of microbiological contamination in the system. Although it is recognized that endotoxins are the primary concern in such a system, a filter will reduce microbiological contamination but not necessarily endotoxin contamination. If filters are used in a water system, there should be a stated purpose for the filter, for example, particulate removal or microbial reduction, and an SOP stating the frequency with which the filter is to be changed, which is based on data generated during the validation of the system.

As previously discussed, because of the volume of water actually tested (1 mL for endotoxins vs. 100 mL for WFI), the microbiological test offers a good index of the level of contamination in a system. Therefore, unless the water is sampled before the final 0.2-mm filter, microbiological testing has little meaning.

The FDA strongly recommends that the nonrecirculating water systems be drained daily and water not be allowed to sit in the system, as this practice is bound to produce highly erratic contamination levels.

K. Purified Water Systems

Many of the comments regarding equipment for WFI systems are applicable to purified water systems. One type system that has been used to control microbiological contamination uses ozone. For optimum effectiveness, it is required that dissolved ozone residual remain in the system. This presents both employee safety problems and use problems when drugs are formulated. Problems arise once the ozone generator is turned off or ozone is removed prior to placing the water in the recirculating system, particularly if the levels fall below 0.45 mg/L; also, if sampling is performed immediately after sanitization, results cannot be meaningful.

Purified water systems can be problematic if there is a one-way and not a recirculating system. Even if a heat exchanger is used to heat the water on a weekly basis and sanitize the system, this system shall be classified as "dead."

If a 0.2-mm in-line filter is used to sanitize the purified water on a daily basis, the filter housing provides a good environment for microbiological contamination; a typical problem is water hammer that can cause "ballooning" of the filter. If a valve downstream from the filter is shut too fast, the water pressure will reverse and can cause ballooning. Pipe vibration is a typical, visible sign of high back pressure while passage of upstream contaminants on the filter face is a real problem. Further problems arise where there are several vertical drops at use points. During sanitization, it is important to "crack" the terminal valves so that all of the elbows and bends in the piping are full of water and thus get complete exposure to the sanitizing agent.

It should be pointed out that simply because a system is a one-way system, it is not inadequate. With good SOPs, based on validation data, and routine hot flushings of this system, it could be acceptable. Long system (over 200 yards) with numerous outlets (e.g., over 50 outlets) can be acceptable, for example, with daily flushing of all outlets with 80°C water.

In one-way systems that employ a UV light to control microbiological contamination, it turns on only when water is needed. Thus, there are times when water is allowed to remain in the system. Systems containing flexible hose are very difficult to sanitize. UV lights must be properly maintained to work. The glass sleeves around the bulb(s) must be kept clean or their effectiveness will decrease. In multibulb units there must be a system to determine that each bulb is functioning. It must be remembered that, at best, UV light will kill only 90% of the organisms entering the unit.

L. Process Water

Currently, the USP, in the "General Notices" section, allows drug substances to be manufactured from potable water. It comments that any dosage form must be manufactured from purified water, WFI, or one of the forms of sterile water. There is some inconsistency in these two statements, because purified water has to be used for the granulation of tablets, yet potable water can be used for the final purification of the drug substance.

The FDA "Guide to Inspection of Bulk Pharmaceutical Chemicals" comments on the concern for the quality of the water used for the manufacture of drug substances, particularly those used in parenteral manufacture. Excessive levels of microbiological or endotoxin contamination have been found in drug substances, with the source of contamination being the water used in purification. At this time, WFI does not have to be used in the finishing steps of synthesis and purification of drug substances for parenteral use. However, such water systems should be validated to assure minimal endotoxin or microbiological contamination.

In the bulk drug substance industry, particularly for parenteral-grade substances, it is common to see UF and RO systems in use in water systems. Although UF may not be as efficient at reducing pyrogens, it reduces the high–molecular-weight endotoxins that are a contaminant in water systems. As with RO, UF is not absolute, but it reduces numbers. Additionally, as previously discussed with other cold systems, considerable maintenance is required to maintain the system.

For the manufacture of drug substances that are not for parenteral use, there is still a microbiological concern, although not to the degree as for parenteral-grade drug substances. In some areas of the world, potable (chlorinated) water may not present a microbiological problem. However, there may be other issues. For example, chlorinated water will generally increase chloride levels. In some areas, process water can be obtained directly from neutral sources.

M. Evaluation Strategy

Manufacturers should have some way of presenting their water quality data, which should be thoroughly reviewed to contain any investigation reports when values exceed limits.

Because microbiological test results from a water system are not usually obtained until after the drug product is manufactured, results exceeding limits should be reviewed with regard to the drug product formulated from such water. Consideration with regard to the further processing or release of such a product will depend on the specific contaminant, the process, and the end use of the product. Such situations are usually evaluated on a case-by-case basis. It is a good practice in such situations to include an investigation report with the logic for release or rejection. End-product microbiological testing, while providing some information, should not be relied on as the sole justification for the release of the drug product. The limitations of microbiological sampling and testing should be recognized. Manufacturers should also have maintenance records or logs for equipment, such as the still.

RELEVANT GUIDANCE DOCUMENTS (FDA)

1. Guidance for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Product, 1994.
2. Guideline for Validation of Limulus Amebocyte Lysate Test as an End Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices, 1987.
3. Guide to Inspections of Lyophilization of Parenterals, 1993.
4. Guide to Inspections of High-Purity Water Systems, 1993.
5. Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories, 1993.
6. Guide to Inspections of Sterile Drug Substance Manufacturers, 1994.
7. Pyrogens: Still a Danger, 1979 (Inspection Technical Guide); Bacterial Endotoxins/Pyrogens, 1985 (Inspection Technical Guide).
8. Heat Exchangers to Avoid Contamination, 1979 (Inspection Technical Guide).
9. Guidance for Industry: Container and Closure Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products, 1999.
10. Compliance Policy Guide 7132a.13: Parametric Release of Terminally Heat Sterilized Drug Products, 1987.
11. Compliance Policy Guide 7150.16: Status and Responsibilities of Contract Sterilizers Engaged in the Sterilization of Drugs and Devices, 1995.
12. Compliance Program CP7346.832: Pre-Approval Inspections/Investigations, 1994.
13. Compliance Program CP7346.843: Post-Approval Audit Inspections, 1992.
14. Compliance Program CP7346.002A: Sterile Drug Process Inspections, Foreign Inspection Guide, 1992.
15. Laboratory Inspection Guide, 1993.
16. Cleaning Validation Inspection Guide, 1993.

GLOSSARY

Action Limit—An established microbial or particulate level which, when exceeded, should trigger appropriate investigation and corrective action based on the investigation.

AirLock—A small room with interlocked doors, constructed to maintain air pressure control between adjoining rooms (generally with different air cleanliness standards). The intent of an aseptic processing airlock is to preclude ingress of particulate matter and microorganism contamination from a lesser-controlled area.

Alert Limit—An established microbial or particulate level giving early warning of potential drift from normal operating conditions and triggering appropriate scrutiny and follow-up to address the potential problem. Alert limits are always lower than action limits.

Asepsis—State of control attained by using an aseptic work area and performing activities in a manner that

precludes microbiological contamination of the exposed sterile product.

Aseptic Processing Facility—Building containing clean rooms in which air supply, materials, and equipment are regulated to control microbial and particulate contamination.

Aseptic Processing Room—A room in which one or more aseptic activities or processes are performed.

Atmosphere, The Earth's—The envelope of gases surrounding the earth, exerting under gravity a pressure at the earth's surface, which includes by volume 78% nitrogen, 21% oxygen, and small quantities of hydrogen, carbon dioxide, noble gases, water vapor, pollutants, and dust.

Atmospheric Pressure—The pressure exerted at the earth's surface by the atmosphere. For reference purposes a standard atmosphere is defined as 760 torr or mm Hg, or 760,000 mm.

Backstreaming—A process that occurs at low chamber pressures wherein hydrocarbon vapors from the vacuum system can enter the product chamber.

Barrier—Physical partition that affords aseptic manufacturing zone protection by partially separating it from the surrounding area.

Bioburden—Total number of microorganisms associated with a specific item prior to sterilization.

Biological Indicator (BI)—A population of microorganisms inoculated onto a suitable medium (e.g., solution, container/closure) and placed within appropriate sterilizer load locations to determine the sterilization cycle efficacy of a physical or chemical process. The challenged microorganism is selected based on its resistance to the given process. Incoming lot *D*-value and microbiological count define the quality of the BI.

Blank-Off Pressure—The ultimate pressure the pump or system can attain.

Blower—This pump is positioned between the mechanical pump and the chamber. It operates by means of two lobes turning at high speed. It is used to reduce the chamber pressure to less than 20 mm. See Mechanical Booster Pump.

Breaking Vacuum—Admitting air or a selected gas to an evacuated chamber, while isolated from a vacuum pump, to raise the pressure toward, or up to, atmospheric.

Circulation Pump—A pump for conveying the heat transfer fluid.

Clean Area—An area with defined particulate and microbiological cleanliness standards (e.g., Class 100, Class 10,000, or Class 100,000).

Clean Zone—See Clean Area.

Clean Room—A room designed, maintained, and controlled to prevent particulate and microbiological contamination of drug products. Such a room is assigned and must meet an appropriate air cleanliness classification.

Colony-Forming Unit (CFU)—A microbiological term that describes the formation of a single macroscopic colony after the introduction of one or more microorganism(s) into microbiological growth media. One colony-forming unit is expressed as 1 CFU.

Component—Any ingredient intended for use in the manufacture of a drug product, including one that may not appear in the final drug product.

Conax Connection—A device to pass thermocouple wires through and maintain a vacuum-tight vessel.

Condenser (Cold Trap)—In terms of the lyophilization process, the vessel that collects the moisture on plates and holds it in the frozen state. Protects the vacuum pump from water vapor contaminating the vacuum pump oil.

Condenser/Receiver—In terms of refrigeration, the unit that condenses (changes) the hot refrigerant gas into a liquid and stores it under pressure to be reused by the system.

Contamination—In the vacuum system, the introduction of water vapor into the oil in the vacuum pump, which then causes the pump to lose its ability to attain its ultimate pressure.

Cooling—Lowering the temperature in any part of the temperature scale.

Critical Areas—Areas designed to maintain sterility of sterile materials. Sterilized product, container/closures, and equipment may be exposed in critical areas.

Critical Surfaces—Surfaces that may come into contact with or directly impact on sterilized product or containers/closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained throughout processing.

***D*-Value**—The time (minutes) of exposure to a given temperature that causes a one-log or 90% reduction in the population of a specific microorganism.

Decontamination—A process that eliminates viable bioburden via use of sporicidal chemical agents.

Defrosting—The removal of ice from a condenser by melting or mechanical means.

Degree of Crystallization—The ratio of the energy released during the freezing of a solution to that of an equal volume of water.

Degree of Supercooling—The number of degrees below the equilibrium freezing temperature where ice first starts to form.

Depyrogenation—A process used to destroy or remove pyrogens (e.g., endotoxin).

Desiccant—A drying agent.

Dry—Free from liquid or moisture, or both.

Drying—The removal of moisture and other liquids by evaporation.

Dynamic—Conditions relating to clean-area classification under conditions of normal production.

Endotoxin—A pyrogenic product (e.g., lipopolysaccharide) present in the bacterial cell wall. Endotoxin can lead to reactions ranging from fever to death in patients receiving injections.

Equilibrium Freezing Temperature—The temperature at which ice will form in the absence of supercooling.

Eutectic Temperature—A point of a phase diagram at which all phases are present and the temperature and composition of the liquid phase cannot be altered without one of the phases disappearing.

Expansion Tank—This tank is located in the circulation system and is used as a holding and expansion tank for the transfer liquid.

Filter or Filter/Drier—Two systems have their systems filtered or filter/dried: the circulation and refrigeration systems. In the newer dryers, this filter or filter/dryer is the same and can be replaced with a new core.

Free Water—Water that is absorbed on the surfaces of a product and must be removed to limit further biological and chemical reactions.

Freezing—The absence of heat. A controlled change of the product temperature as a function of time, during the

freezing process, so as to ensure a completely frozen form.

Gas Ballast—Used in the vacuum system on the vacuum pump to decontaminate small amounts of moisture in the vacuum pump oil.

Gas Bleed (Vacuum Control)—To control the pressure in the chamber during the cycle to help the drying process. In freeze-drying, the purpose is to improve heat transfer to the product.

Gowning Qualification—Program that establishes, both initially and on a periodic basis, the capability of an individual to don the complete sterile gown in an aseptic manner.

Heat Exchanger—The exchanger located in circulation and refrigeration systems that transfers heat from the circulation system to the refrigeration system.

Heat Transfer Fluid—A liquid of suitable vapor pressure and viscosity range for transferring heat to or from a component, for example, a shelf or condenser in a freeze-dryer. The choice of such a fluid may depend on safety considerations. Diathermic fluid.

HEPA filter—High-efficiency particulate air filter with minimum 0.3-μm particle-retaining efficiency of 99.97%.

Hot Gas Bypass—A refrigeration system to control the suction pressure of the big four (20–30 hp) compressors during the refrigeration operation.

Hot Gas Defrost—A refrigeration system to defrost the condenser plates after the lyophilization cycle is complete.

HVAC—Heating, ventilation, and air conditioning.

Ice—The solid, crystalline form of water.

Inert Gas—Any gas of a group including helium, radon, and nitrogen, formerly considered chemically inactive.

Interstage—In a two-stage compressor system, the crossover piping on top of the compressor that connects the low side to the high side. One could also think of it as low side, intermediate, and high side.

Interstage Pressure Regulating Valve—Valve that prevents the interstage pressure from exceeding 80 to 90 psi. This valve opens to suction as the interstage pressure rises above 80 to 90 psi.

Intervention—An aseptic manipulation or activity that occurs at the critical zone.

Isolator—A decontaminated unit, supplied with HEPA- or ULPA-filtered air, that provides uncompromised, continuous isolation of its interior from the external environment (e.g., surrounding clean-room air and personnel).

Laminarity—Unidirectional airflow at a velocity sufficient to uniformly sweep particulate matter away from a critical processing or testing area.

Lexsol—A heat transfer fluid (high grade kerosene).

Liquid Subcooler Heat Exchanger—The liquid refrigerant leaving the condenser/receiver at cooling water temperature is subcooled to a temperature of +15°F (–10°C) to –15°F (–25°C); see Subcooled Liquid.

Lyophilization—A process in which the product is first frozen and then, while still in the frozen state, the major portion of the water and solvent system is reduced by sublimation and desorption so as to limit biological and chemical reactions at the designated storage temperature.

Main Vacuum Valve—This valve between the chamber and external condenser to isolate the two vessels after the process is finished. This valve protects the finished product. See Vapor Valve.

Matrix—In terms of the lyophilization process, a system of ice crystals and solids that is distributed throughout the product.

Mechanical Booster Pump—A roots pump with a high displacement for its size but a low compression ratio. When backed by an oil-seal rotary pump, the combination is an economical alternative to a two-stage, oil-sealed rotary pump, with the advantage of obtaining a high vacuum. See Blower.

Mechanical Vacuum Pump—The mechanical pumping system that lowers the pressure in the chamber to below atmospheric pressure so that sublimation can occur.

Melting Temperature (Meltback)—That temperature at which mobile water first becomes evident in a frozen system.

Micron—A unit of pressure used in the lyophilization process. 1 mm = 1 Mtorr or 25,400 mm = 1 in Hg, or 760,000 mm = 1 atm. See Torr.

Noncondensables—A mixture of gases such as nitrogen, hydrogen, chlorine, and hydrocarbons, which may be drawn into the system through leaks when part of the system is under a vacuum. Presence of the gases reduces the operating efficiency of the system by increasing the condensing pressure.

Nucleation—The formation of ice crystals on foreign surfaces or as a result of the growth of water clusters.

Oil-Mist Filter—In vacuum terminology, a filter attached to the discharge (exhaust) of an oil-sealed rotary pump to eliminate most of the "smoke" of suspended fine droplets of oil that would be discharged into the environment.

Oil-Sealed Rotary Pump—A standard type of mechanical vacuum pump used in freeze-drying with a high compression ratio but a relatively low displacement (speed) for its size. A two-stage pump is effectively two such pumps in series and can obtain an ultimate vacuum.

Oil Separator—Separates the oil from the compressor discharge gas and returns the oil through the oil float trap and piping to the compressor crankcase.

Operator—Any individual participating in the aseptic processing operation, including line setup, filler, maintenance, or other personnel associated with aseptic line activities.

Overkill Sterilization Process—A process that is sufficient to provide at least a 12-log reduction of microorganisms having a minimum *D*-value of 1 minute.

Pyrogen—Substance that induces a febrile reaction in a patient.

Real Leak—A source of atmospheric gases resulting from a penetration through the chamber.

Reconstitute—Dissolving of the dried product into a solvent or diluent.

Relief Valve—Used for safety purposes to prevent damage in case excessive pressure is encountered.

Rotary Vane Pump—A mechanical pumping system with sliding vanes as the mechanical seal. Can be single or two stages.

Self-Liquid Heat Exchanger—Transfer of heat from the shelf fluid to the refrigeration system through tubes in the exchanger causing compressor suction gas to warm.

Shelf Compressor (Controlling Compressor)—For controlling shelf temperature, either by cooling or by preventing overheating.

Shelves—In terms of the lyophilization process, a form of heat exchanger within the chamber that has a

serpentine liquid flow through it, entering one side and flowing to the other side. Located in the circulation system.

Silicone Oil—A heat-transfer fluid.

Single-Stage Compressor—A normal type compressor used in refrigeration. In the lyophilization process, used to control the shelf temperature, both for cooling and keeping the shelf temperature from overheating by using a temperature controller.

Sterilization—The use of steam and pressure to kill any bacteria that could contaminate that environment or vessel.

Sterilizing-Grade Filter—A filter which, when appropriately validated, removes all microorganisms from a fluid stream, producing a sterile effluent.

Subcooled Liquid—The liquid refrigerant cooled through an exchanger so that it increases the refrigerating effect as well as reduces the volume of gas flashed from the liquid refrigerant passing through the expansion valve. See Liquid Subcooler Heat Exchanger.

Sublimation—Conversion of a material from a solid phase directly to a vapor phase, without passing through the liquid phase. Referred to as the primary drying stage.

Suction Line Accumulator—To prevent refrigerant liquid slug (droplets of liquid refrigerant) from returning to the compressor and damaging it.

Temperature—The degree of hotness or coldness of a body.

Terminal Sterilization—The application of a lethal agent to sealed, finished drug products to achieve a predetermined sterility assurance level of usually less than 10^6 (i.e., a probability of a nonsterile unit of greater than one in a million).

Thermocouple—A metal-to-metal contact between wires of two dissimilar metals that produces a small voltage across the free ends of the wires.

Thermostatic Expansion Valve—An automatic variable device controlling the flow of liquid refrigerant.

Torr—A unit of measure equivalent to the amount of pressure in 1000 mm. See Micron.

Trichloroethylene (TCE)—A heat-transfer fluid.

Two-Stage Compressor—A specially built compressor that attains low temperatures by being able to operate at low pressures. It is two compressors built into one: a low stage connected internally and a high stage connected externally with piping, called interstage. See Interstage

ULPA Filter—Ultra-low penetration air filter with a minimum 0.3-mm particle-retaining efficiency of 99.999%.

Unloading Valve—The valve that connects the interstage with suction to equalize both pressures during pumpdown.

Vacuum—Strictly speaking, a space in which the total pressure is less than atmospheric.

Vacuum Control (Gas Bleed)—To assist in the rate of sublimation by controlling the pressure in the lyophilizer.

Vacuum Pump—A mechanical way of reducing the pressure in a vessel below atmospheric pressure at which sublimation can occur. There are three types of pumps: rotary vane, rotary piston, and mechanical booster.

Vacuum Valves—Ball- or disk-type valves that can seal without leaking. The ball types are used for services to the chamber and condenser and also for drains and isolation applications. The disk types are used in the vacuum line system and are connected to the vacuum pump, chamber, and condenser.

Validation—Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Vapor Baffle—A target-shaped object placed in the condenser to direct vapor flow and to promote an even distribution of condensate.

Vapor Valve—The vacuum valve between the chamber and external condenser. When this valve is closed, the chamber is isolated from the external condenser. Also known as the main vapor valve. See Main Vacuum Valve.

Vial—A small glass bottle with a flat bottom, short neck, and flat flange designed for stoppering.

Virtual Leak—In the vacuum system, the passage of gas into the chamber from a source that is located internally in the chamber.

Worst Case—A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure (when compared to ideal conditions). Such conditions do not necessarily induce product or process failure.

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4

New Drug Application for Sterilized Products

I. INTRODUCTION

The efficacy of a given sterilization process for a specific drug product is evaluated on the basis of a series of protocols and scientific experiments designed to demonstrate that the sterilization process and associated control procedures can reproducibly deliver a sterile product. Data derived from experiments and control procedures allow conclusions to be drawn about the probability of nonsterile product units (sterility assurance level). Whether a drug product is sterilized by a terminal sterilization process or by an aseptic filling process, the efficacy of the sterilization process may be validated without the manufacture of three production batches. Sterilization process validation data, however, should be generated by procedures and conditions that are fully representative and descriptive of the procedures and conditions proposed for manufacture of the product in the application.

II. TERMINAL HEAT STERILIZATION

A. Description of the Process and Product

1. *Drug product and container/closure system.* Descriptions of the drug product and the container/closure system(s) to be sterilized (e.g., size(s), fill volume, or secondary packaging) should be provided.
2. *Sterilization process.* The sterilization process used to sterilize the drug product in its final container/closure system, as well as a description of any other sterilization process(es) used to sterilize delivery sets, components, packaging, bulk drug substance or bulk product, and related items, should be described. Information and data in support of the efficacy of these processes should also be submitted.
3. *Autoclave process and performance specifications*. The autoclave process, including pertinent information such as cycle type (e.g., saturated steam, water immersion, and water spray); cycle parameters; and performance specifications, including temperature, pressure, time, and minimum and maximum F_0, should be described. The autoclave(s) to be used for production sterilization, including manufacturer and model, should be identified.
4. *Autoclave loading patterns*. A description of representative autoclave loading patterns should be provided.
5. *Methods and controls to monitor production cycles.* Methods and controls used to monitor routine production cycles (e.g., thermocouples, pilot bottles, and biological indicators) should be described, including the number and location of each as well as acceptance and rejection specifications.
6. *Requalification of production autoclaves.* A description of the program for routine and unscheduled requalification of production autoclaves, including frequency, should be provided.
7. *Reprocessing*. A description and validation summary of any program that provides for reprocessing (e.g., additional thermal processing) of product should be provided.

B. Thermal Qualification of the Cycle

1. *Heat distribution and penetration studies.* Heat distribution and penetration study protocols and data summaries that demonstrate the uniformity, reproducibility, and conformance to specifications of the production sterilization cycle should be provided. Results from a minimum of three consecutive successful cycles should be provided to ensure that the results are consistent and meaningful.
2. *Thermal monitors.* The number of thermal monitors used and their location in the chamber should be described. A diagram is helpful.
3. *Effects of loading on thermal input.* Data should be generated with minimum and maximum load to demonstrate the effects of loading on thermal input to product. Additional studies may be necessary if different fill volumes are used in the same container line. Data summaries are acceptable for these purposes. A summary should consist of, for example, high and low temperatures (range), average temperature during the dwell period, minimum and maximum F_0 values, dwell time, run date and time, and identification of the autoclave(s) used. These data should have been generated from studies carried out in production autoclave(s) that will be used for sterilization of the product that is the subject of the application.
4. *Information included in the batch record.* The batch record supplied with the chemistry, manufacturing, and controls section of the application should identify the validated processes to be used for sterilization and for depyrogenation of any container/closure components. This information can be included in the batch record by reference to the validation protocol or standard operating procedure (SOP). Validation information should be provided as described previously.

C. Microbiological Efficacy of the Cycle

Validation studies that demonstrate the efficacy (lethality) of the production cycle should be provided. A sterility assurance of 10^{-6} or better should be demonstrated for any terminal sterilization process. This level of sterility assurance should be demonstrated for all parts of the drug product (including the container and closure, if applicable), which are claimed to be sterile. The specific type of study and the methods used to carry out the study (or studies) are product and process specific and may vary from manufacturer to manufacturer. In general, the following types of information and data should be provided.

1. *Identification and characterization of bioburden organisms.* The methods and results from studies used to identify and characterize bioburden organisms should be described. The amount and type of information supplied may depend on the validation strategy chosen. For example, more information may be needed for bioburden-based autoclave

processes than for overkill processes. Information concerning the number, type, and resistance of bioburden organisms may be necessary, including those organisms associated with the product solution and the container and closure. It may be necessary to identify the most heat-resistant bioburden organisms.

2. *Specifications for bioburden.* Specifications (alert and action levels) for bioburden should be provided. A description should be included of the program for routinely monitoring bioburden to ensure that validated and established limits are not exceeded (e.g., frequency of analysis and methods used in bioburden screening). The methods provided should be specific.
3. *Identification, resistance, and stability of biological indicators*. Information and data concerning the identification, resistance (D and Z values), and stability of biological indicators used in the biological validation of the cycle should be provided. If biological indicators are purchased from a commercial source, it may be necessary to corroborate the microbial count and resistance, and provide performance specifications.
4. *Resistance of the biological indicator relative to that of bioburden*. Studies characterizing the resistance of the biological indicator relative to that of bioburden may be necessary. Resistance in or on the product (i.e., in the product solution or on the surface of container or closure parts or interfaces) should be determined as necessary. If spore carriers are used (e.g., spore strips), the resistance of spores on the carrier relative to that of directly inoculated product should be determined, if necessary.
5. *Microbiological challenge studies*. Microbiological validation studies should be submitted that demonstrate the efficacy of the minimum cycle to provide a sterility assurance of 10^{-6} or better to the product under the most difficult to sterilize conditions (e.g., the most difficult to sterilize load with biological indicators at microbiological master sites or in master product or both). Use of a microbiological master product or site should be supported by scientific data. Microbiological master sites or solutions are those sites or solutions in which it is most difficult to kill the biological indicator under sterilization cycles that simulate production conditions.

D. Microbiological Monitoring of the Environment

Section 211.160 of the CFR requires, in part, the establishment of scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to ensure that components, drug product containers, closures, in-process materials, and drug products conform to appropriate quality standards. Therefore, a microbiological monitoring program for production areas along with a bioburden monitoring program for product components and process water should be established. Process water includes autoclaved cooling water. Applicants should provide information concerning this program. Frequency, methods used, action levels, and data summaries should be included. A description of the actions taken when specifications are exceeded should be provided.

E. Container/Closure and Package Integrity

An applicant should provide scientific validation studies (and data) in support of the microbial integrity of the drug packaging components. The following types of information should be included

1. *Simulation of the stresses from processing*. Experimental designs should simulate the stresses of the sterilization process, handling, and storage of the drug and their effects on the container/closure system. Physical, chemical, and microbiological challenge studies may be necessary.
2. *Demonstrate integrity following maximum exposure*. Container-closure integrity should be demonstrated on product units that have been exposed to the maximum sterilization cycle(s). If a product is exposed to more than one process, then exposure to the maximum cycle of all processes should be incorporated into the study design.
3. *Multiple barriers*. Each barrier that separates areas of the drug product claimed to be sterile should be separately evaluated and validated.
4. *Sensitivity of the test.* The sensitivity of the experimental method used for container/closure integrity testing should be specified and provided.
5. *Integrity over product shelf life.* Microbial integrity of the container/closure system should be demonstrated over the shelf life of the product.

F. Bacterial Endotoxins Test and Method

The bacterial endotoxins test used for the product should be described. The description should include qualification of the laboratory, inhibition and enhancement testing and results, determination of noninhibitory concentration, and maximum valid dilution. For further information, see the agency guidance entitled "Guideline on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endo-toxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices."

G. Sterility Testing Methods and Release Criteria

Sterility test methods should be described and should include the protocol for selecting representative units during production. When test methods differ significantly from compendial test methods, a demonstration of the equivalency to the compendial method should be provided. Testing performed within barrier systems should be described, and information concerning validation of the barrier system may be necessary.

H. Evidence of Formal Written Procedures

Section 211.113(b) of the CFR requires that written procedures designed to prevent microbiological contamination of drug products purporting to be sterile be established and followed. Such procedures should include validation of any sterilization process. Therefore, evidence should be provided that there are formal written procedures describing the elements listed previously and that these procedures are followed. Such evidence may consist of SOPs, listing of SOPs, and protocols submitted as part of these elements.

III. OTHER TERMINAL STERILIZATION PROCESSES

Although the information provided previously directly addresses moist heat processes, the same type of information will pertain to other terminal sterilization processes used singly or in combination to sterilize a drug product. The types of information outlined are, in general, also applicable to ethylene oxide and radiation (gamma and electron beam). These other processes should be addressed as each applies to the drug product, sterile packaging, and in-process sterilization of components. Examples of such information might include descriptions of loading configurations; qualification

and validation of master load configurations; determination and validation of the efficacy of the minimum cycle to provide sterility assurance at the product master sites; requalification of the cycle; provisions for resterilization, specifications, and monitoring program for product bioburden; and container/closure integrity. Specific examples are provided to demonstrate the application of these concepts to other sterilization processes. Additional information relating to the effects of the sterilization process on the chemical and physical attributes of the drug substance or drug product may be applicable and should be supplied to the chemistry, manufacturing, and controls section of the application.

A. Ethylene Oxide

1. *Description of the sterilizer*. The sterilizer(s) and controlled site(s) for prehumidification and aeration of the product load should be described.
2. *Cycle parameters*. The parameters and limits for all phases of the cycle, such as prehumidification, gas concentration, vacuum and gas pressure cycles, exposure time and temperature, humidity, degassing, aeration, and determination of residuals, should be specified. Specific procedures used to monitor and control routine production cycles to assure that performance is within validated limits should be provided.
3. *Microbiological methods*. The microbiological methods (growth medium, incubation temperature, and time interval) for cultivating spores from inoculated samples during validation experiments should be described as well as the microbiological methods used as part of routine production cycles.
4. *Stability.* The program for monitoring the stability of packaging and the integrity of the container/closure system barrier over the claimed shelf life should be described.

B. Radiation

1. *Facility and process.* The radiation facility should be identified. The radiation source, method of exposure (i.e., movement through the irradiator), and the type and location of dosimeters used to monitor routine production loads should be described. If the low-dose site is not used for routine monitoring, data that show the dose relationship between the two sites should be provided.
2. *Packaging of the product*. The packaging of the drug product within the shipping carton and within the carrier should be described.
3. *Multiple-dose mapping studies*. Multiple-dose mapping studies for identification of low- and high-dose sites and demonstration of uniformity and reproducibility of the process should be described.
4. *Microbiological methods and controls*. The microbiological methods and controls used to establish, validate, and audit the efficacy of the cycle should be described.
5. *Monitoring stability*. The program for monitoring the stability of packaging and the integrity of the container/closure system barrier over the claimed shelf life should be described.

IV. ASEPTIC FILL MANUFACTURING PROCESSES

The following types of information should be submitted in support of sterility assurance for products manufactured by aseptic processing.

A. Buildings and Facilities

A brief description of the manufacturing building and facilities should be provided. The following information should be included

1. *Floor plan*. A floor plan of the areas holding the aseptic filling facilities, including preparation and holding areas, filtering and filling areas, and gowning rooms, should be included. The air cleanliness class of each area should be identified (e.g., class 100, class 10,000, class 100,000). Isolators or barrier systems should be identified.
2. *Location of equipment*. The placement of all critical equipment, including, but not limited to, laminar flow hoods, autoclaves, lyophilizers, and filling heads, should be identified. Equipment within barrier or isolation systems should be noted.

B. Overall Manufacturing Operation

The overall manufacturing operation including, for example, material flow, filling, capping, and aseptic assembly, should be described. The normal flow (movement) of product and components from formulation to finished dosage form should be identified and indicated on the floor plan described above. The following information should be considered when describing the overall manufacturing operation.

1. *Drug product solution filtration.* The specific bulk drug product solution filtration processes, including tandem filter units, prefilters, and bacterial retentive filters, should be described. A summary should be provided containing information and data concerning the validation of the retention of microbes and compatibility of the filter used for the specific product. Any effects of the filter on the product formulation should be described (e.g., adsorption of preservatives or active drug substance, or extractables).
2. *Specifications concerning holding periods.* Section 211.111 of the CFR requires, in part, when appropriate, the establishment of time limits for completing each phase of production to ensure the quality of the drug product. Therefore, specifications concerning any holding periods between the compounding of the bulk drug product and its filling into final containers should be provided. These specifications should include, holding tanks, times, temperatures, and conditions of storage. Procedures used to protect microbiological quality of the bulk drug during these holding periods should be indicated. Maintenance of the microbiological quality during holding periods may need verification.
3. *Critical operations.* The critical operations that expose product or product contact surfaces to the environment (such as transfer of sterilized containers or closures to the aseptic filling areas) should be described. Any barrier or isolation systems should be described.

C. Containers and Closures

The sterilization and depyrogenation processes used for containers, closures, equipment, components, and barrier systems should be described. A description of the validation of these processes should be provided including, where applicable, heat distribution and penetration summaries, biological challenge studies (microbiological indicators and endotoxins), and routine monitoring procedures. Validation information for sterilization processes other than moist heat should also be included. Methods and data (including controls) demonstrating distribution and penetration of the sterilant and microbiological efficacy of each process

should be submitted. The section of this guidance concerning terminal sterilization contains information that may be of further assistance.

1. *Bulk drug solution components sterilized separately.* If the bulk drug solution is aseptically formulated from components that are sterilized separately, information and data concerning the validation of each of these separate sterilization processes should be provided.
2. *Sterilization information in batch records*. The completed batch record supplied with the chemistry, manufacturing, and controls section of the application should identify the validated processes to be used for sterilization and depyrogenation of any container/closure components. This information may be included in the batch record by reference to the validation protocol or SOP.

D. Procedures and Specifications for Media Fills

The procedures and specifications used for media fills and summaries of results for validation using the same container/closure system and filling process that is to be used for the product should be described. The microbiological testing method(s) used should be described. Any procedural differences between the media fill and the production process should be indicated. A summary of recent media fill results, including failures, should be provided. These data should be obtained by the same filling line(s) that is to be used for the drug product. The following are recommended to be included with the data summary for each media fill run described.

1. *The filling room*. The aseptic filling area used should be identified and related to the floor plan.
2. Container-closure type and size.
3. Volume of medium used in each container.
4. Type of medium used.
5. Number of units filled.
6. Number of units incubated.
7. Number of units positive.
8. *Incubation parameters*. The incubation time and temperature for each group of units incubated and specifications for any group of units subjected to two (or more) different temperatures should be specified.
9. Date of each media fill.
10. *Simulations*. The procedures used to simulate any steps of a normal production fill should be described. This might include, for example, slower line speed, personnel shift changes, equipment failure and repair, mock lyophilization, and substitution of vial headspace gas.
11. *Microbiological monitoring*. The microbiological monitoring data obtained during the media fill runs should be provided.
12. *Process parameters*. The parameters used for production filling and for media fills (e.g., line speed, fill volume, number of containers filled, or duration of fill) should be compared.

E. Actions Concerning Product When Media Fills Fail

The disposition of product made before and after a failed media fill should be described. The description should include details of investigations, reviews, and how decisions are made to reject or release product.

F. Microbiological Monitoring of the Environment

The microbiological monitoring program used during routine production and media fills should be described. The frequency of monitoring, type of monitoring, sites monitored, alert and action level specifications, and precise descriptions of the actions taken when specifications are exceeded should be included.

1. *Microbiological methods.* The microbiological materials and methods used in the environmental monitoring program should be described. Methods may include sample collection, transport, neutralization of sanitizers, incubation, and calculation of results. The following are sources of microbial contamination and their monitoring that should be addressed, including specifications:
   - Airborne microorganisms
   - Microorganisms on inanimate surfaces
   - Microorganisms on personnel
   - Water systems
   - Product component bioburden
2. *Yeasts, molds, and anaerobic microorganisms.* A description of periodic or routine monitoring methods used for yeasts, molds, and anaerobes should be provided.
3. *Exceeded limits*. A description of the actions taken when specifications are exceeded should be provided.

G. Container/Closure and Package Integrity

The methods and results demonstrating the integrity of the microbiological barrier of the container/closure system should be summarized. This should include testing for initial validation. The procedures used for the stability protocol also should be described. For initial validation of microbiological integrity of container/closure systems, product sterility testing is not normally considered sufficient. The sensitivity of the experimental method used for container/closure integrity testing should be specified and provided.

H. Sterility Testing Methods and Release Criteria

Sterility test methods should be described and should include the protocol for selecting representative units during production. For a drug product represented to be a drug recognized in an official compendium, when test methods differ significantly from official compendial test methods, a demonstration of the equivalency to the official compendial method should be provided. Testing performed within barrier systems should be discussed, and information concerning validation of the barrier system may be necessary.

I. Bacterial Endotoxins Test and Method

The bacterial endotoxins test used for the product should be described, if applicable. This description should include qualification of the laboratory, inhibition and enhancement testing and results, determination of noninhibitory concentration, and maximum valid dilution. For further information see the agency guidance entitled "Guidance on Validation of the Limulus Amebocyte Lysate Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices."

J. Evidence of Formal Written Procedures

Evidence should be provided that there are formal written procedures describing the elements listed previously and that these procedures are followed. Such evidence may consist of SOPs or a listing of SOPs or protocols submitted as part of the elements listed previously.

V. MAINTENANCE OF MICROBIOLOGICAL CONTROL AND QUALITY: STABILITY CONSIDERATIONS

A. Container/Closure Integrity

The ability of the container/closure system to maintain the integrity of its microbial barrier and hence the sterility of a drug product throughout its shelf life should be demonstrated. As previously stated, sterility testing at the initial time point is not considered sufficient to demonstrate the microbial integrity of a container/closure system. Documentation of the sensitivity of the container/closure integrity test should be provided.

B. Preservative Effectiveness

The efficacy of preservative systems to control bacteria and fungi inadvertently introduced during drug product use should be demonstrated at the minimum concentration specified for drug product release or at the minimum concentration specified for the end of the expiration dating period, whichever is less. Because the efficacy of preservative systems is judged by their effect on microorganisms, microbial challenge assays should be performed. The United States Pharmacopoeia (USP) provides a microbial challenge assay under the title "Antimicrobial Preservatives—Effectiveness." For purposes of the stability protocol, the first three production lots should be tested with a microbial challenge assay at the beginning and end of the stability period. Chemical assays to monitor the concentration of preservatives should be performed at all test intervals. For subsequent lots placed on stability, chemical assays may be adequate to demonstrate the presence of specified concentrations of preservatives, and such testing should be carried out according to the approved stability study protocol.

C. Pyrogen or Endotoxin Testing

For drug products purporting to be pyrogen-free, it is recommended that pyrogen or endotoxin tests be carried out at the beginning and end of the stability period as part of the approved stability study protocol.

5

Validation of Cleaning Process

I. INTRODUCTION

Validation of cleaning procedures has generated considerable discussion since FDA documents, including the *Inspection Guide for Bulk Pharmaceutical Chemicals* and *Biotechnology Inspection Guide*, have briefly addressed this issue. These FDA documents clearly establish the expectation that cleaning procedures (processes) must be validated. It is recognized that for cleaning validation, as with validation of other processes, more than one way might exist to validate a process. In the end, the test of any validation process is whether or not scientific data show that the system consistently does as expected and produces a result that consistently meets predetermined specifications. The discussion in this chapter is intended to cover equipment cleaning for chemical residues only. While cleaning validation in the manufacture of over-the-counter (OTC) products may not be as great a concern as for the manufacture of other drugs, it is an important component of current good manufacturing practices (cGMPs) that requires reiteration, which is why this chapter has been included in a book dealing with OTC drugs.

II. BACKGROUND

For the FDA to require that equipment be clean prior to use is nothing new. The 1963 GMP Regulations (part 133.4) stated as follows: "Equipment shall be maintained in a clean and orderly manner." A similar section on equipment cleaning (211.67) was included in the 1978 cGMP regulations. Of course, the main rationale for requiring clean equipment is to prevent contamination or adulteration of drug products. Historically, FDA investigators have looked for gross insanitation due to inadequate cleaning and maintenance of equipment and/or poor dust-control systems. Also, historically speaking, the FDA was more concerned about contamination of nonpenicillin drug products with penicillins or cross-contamination of drug products with potent steroids or hormones. A number of products have been recalled over the past decade due to actual or potential penicillin cross-contamination.

One event that increased FDA awareness of the potential for cross-contamination due to inadequate procedures was the 1988 recall of a finished drug product, cholestyramine resin USP. The bulk pharmaceutical chemical used to produce the product had become contaminated with low levels of intermediates and degradants from the production of agricultural pesticides. The FDA instituted an import alert in 1992 on a foreign bulk pharmaceutical manufacturer that manufactured potent steroid products as well as nonsteroidal products using common equipment. This firm was a multiuse bulk pharmaceutical facility. The FDA considered the potential for cross-contamination to be significant and to pose a serious health risk to the public. The firm had only recently started a cleaning validation program at the time of the inspection, and it was considered inadequate by the FDA. One of the reasons why it was considered inadequate was that the firm was only looking for evidence of the absence of the previous compound. The firm had evidence, from TLC tests on the rinse water, of the presence of residues of reaction byproducts and degradants from the previous process.

III. GENERAL REQUIREMENTS

- The FDA expects firms to have written SOPs detailing the cleaning processes used for various pieces of equipment. If firms have one cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, the FDA expects the written procedures to address these different scenarios. Similarly, if firms have one process for removing water-soluble residues and another process for non-water-soluble residues, the written procedure should address both scenarios and make it clear when a given procedure is to be followed. Bulk pharmaceutical firms may decide to dedicate certain equipment for particular chemical manufacturing process steps that produce tarry or gummy residues that are difficult to remove from the equipment. Fluid-bed dryer bags are another example of equipment that is difficult to clean and is often dedicated to a specific product. Any residues from the cleaning process itself (detergents, solvents, and so on) also have to be removed from the equipment.
- The FDA expects firms to have written general procedures on how cleaning processes will be validated.
- The FDA expects the general validation procedures to address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required.
- The FDA expects firms to prepare specific written validation protocols in advance for the studies to be performed on each manufacturing system or piece of equipment, which should address such issues as sampling procedures and analytical methods to be used, including the sensitivity of those methods.
- The FDA expects firms to conduct the validation studies in accordance with the protocols and to document the results of studies.
- The FDA expects a final validation report that is approved by management and states whether or not the cleaning process is valid. The data should support a conclusion that residues have been reduced to an "acceptable level."

IV. EVALUATION OF CLEANING VALIDATION

The first step is to focus on the objective of the validation process; some companies fail to develop such objectives prior to establishing all sorts of protocols and detailed investigations.

It is not unusual to see manufacturers use extensive sampling and testing programs following the cleaning process without ever really evaluating the effectiveness of the steps used to clean the equipment. Several questions need to be addressed when evaluating the cleaning process. For example, at what point does a piece of equipment or system become clean? Does it have to be scrubbed by hand? What is accomplished by hand scrubbing rather than just a solvent wash? How variable are manual cleaning processes from batch to batch and product to product? The answers to these questions are obviously important to the evaluation of the cleaning process because one must determine the overall effectiveness of the process. Answers to these questions may also identify steps that can be eliminated for more effective measures and result in resource savings for the company.

Ideally, a piece of equipment or system will have one process for cleaning; however, this will depend on the products being produced and whether the cleanup occurs between batches of the same product (as in a large campaign) or between batches of different products. When the cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process), the manufacturer must only meet a criterion of "visibly clean" for the equipment; such between-batch cleaning processes do not require validation.

A. Equipment Design

The design of equipment, particularly in large systems that may employ semiautomatic or fully automatic clean-in-place (CIP) systems, is important. For example, a sanitary type of piping without ball valves should be used. When such ball valves are used, as is common in the bulk drug industry, the cleaning process is more difficult. When such systems are identified, it is important that operators performing cleaning operations be aware of problems and have special training in cleaning these systems and valves. The cleaning operators must have knowledge of these systems and the level of training and experience required for cleaning these systems. Also, the written and validated cleaning process must be properly identified and validated.

In larger systems, such as those employing long transfer lines or piping, flow charts and piping diagrams must be available for the identification of valves, as well as written cleaning procedures. Piping and valves should be tagged and easily identifiable by the operator performing the cleaning function. Sometimes, inadequately identified valves, both on prints and physically, have led to incorrect cleaning practices.

The documentation should be complete in regard to the cleaning processes of critical steps and should identify and control the length of time between the end of processing and each cleaning step. This is especially important for topicals, suspensions, and bulk drug operations. In such operations, the drying of residues will directly affect the efficiency of a cleaning process.

Whether or not CIP systems are used for cleaning of processing equipment, the microbiological aspects of equipment cleaning should be considered, largely through taking preventive measures rather than removing contamination once it has occurred. Manufacturers should maintain some evidence that routine cleaning and storage of equipment do not allow microbial proliferation. For example, equipment should be dried before storage, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations.

Subsequent to the cleaning process, equipment may be subjected to sterilization or sanitization procedures when such equipment is used for sterile processing or to nonsterile processing when products may support microbial growth. While such sterilization or sanitization procedures are beyond the scope of this guide, it is important to note that control of the bioburden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary level of sterility. This is also particularly important from the standpoint of the control of pyrogens in sterile processing, as equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

B. Cleaning Process, Written Procedure, and Documentation

The detail and specificity of the procedure for the (cleaning) process being validated and the amount of documentation required to establish it are critical. Some manufacturers use general SOPs, while others use a batch record or log sheet system that requires some type of specific documentation for performing each step. Depending on the complexity of the system and cleaning process and the ability and training of the operators, the amount of documentation necessary for executing various cleaning steps or procedures will vary.

When more complex cleaning procedures are required, it is important to document the critical cleaning steps (e.g., certain bulk drug synthesis processes). In this regard, it is valuable to have specific documentation on the equipment itself that includes information about who cleaned it and when; however, for relatively simple cleaning operations, merely documenting that the overall cleaning process was performed might be sufficient.

Other factors, such as history of cleaning, residue levels found after cleaning, and variability of test results, may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and operator performance. Appropriate evaluations must be made, and when operator performance is deemed a problem more extensive documentation (guidance) and training may be required.

C. Analytical Methods

The specificity and sensitivity of the analytical method used to detect residuals or contaminants should be well established. With advances in analytical technology, residues from the manufacturing and cleaning processes can be detected at very low levels. If levels of contamination or residual are not detected, it does not mean that no residual contaminant is present after cleaning. It only means that levels of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample. The firm should challenge the analytical method in combination with the sampling methods used to show that contaminants can be recovered from the equipment surface and at what level (e.g., 50% or 90% recovery). This is necessary before any conclusions can be made based on the sample results. A negative test may also be the result of poor sampling technique (see below).

D. Sampling

Two general types of sampling have been found to be acceptable. The most desirable is the direct method of sampling the surface of the equipment, and the other method is the use of rinse solutions.

1. Direct Surface Sampling

The type of sampling material used and its impact on the test data must be identified, as the sampling material may interfere with the test; for example, the adhesive used in swabs has been found to interfere with analysis of samples. Therefore, early in the validation program, it is important to ensure that the sampling medium and solvent (used for extraction from the medium) are satisfactory and can be readily used. Advantages of direct sampling are that areas that are the most difficult to clean and which are reasonably accessible can be evaluated, leading to establishment of a level of contamination or residue per given surface area. Additionally, residues that are dried out or are insoluble can be sampled by physical removal.

2. Rinse Samples

Two advantages of using rinse samples are that a larger surface area may be sampled and inaccessible systems or ones that cannot be routinely disassembled can be sampled and evaluated. A disadvantage of rinse samples is that the residue or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is a dirty pot. When evaluating the cleaning of a dirty pot, particularly one with dried-out residue, one does not look at the rinse water to see that it is clean; one looks at the pot. It is important to ensure that a direct measurement of the residue or contaminant is made for the rinse water when it is used to validate the cleaning process. For example, it is not acceptable to simply test rinse water for water quality (does it meet the compendia tests?) rather than test it for potential contaminates.

3. Routine Production In-Process Control Monitoring

Indirect testing, such as conductivity testing, may be of some value for routine monitoring once a cleaning process has been validated. This would be particularly true for bulk drug substance manufacturers whose reactors, centrifuges, and piping between such large equipment can be sampled only using rinse solution samples. Any indirect test method must have been shown to correlate with the condition of the equipment. During validation, a manufacturer should be able to provide documentation that testing the uncleaned equipment gives a not acceptable result for the indirect test.

V. ESTABLISHMENT OF LIMITS

The FDA does not generally set acceptance specifications or methods for determining whether a cleaning process is validated. It is impractical for the FDA to do so due to the wide variation in equipment and products used throughout the bulk and finished dosage form industries. A manufacturer's rationale for the residue limits established should be logical based on the manufacturer's knowledge of the materials involved and should be practical, achievable, and verifiable. It is important to define the sensitivity of the analytical methods in order to set reasonable limits. Some limits that have been mentioned by industry representatives in the literature or in presentations include analytical detection levels (such as 10 ppm), biological activity levels (such as 1/1000 of the normal therapeutic dose), and organoleptic levels such as no visible residue.

The manner in which limits are established should be documented. Unlike finished pharmaceuticals, where the chemical identities of residuals are known (e.g., from actives, inactives, detergents), bulk processes may have partial reactants and unwanted byproducts that may never have been chemically identified. In establishing residual limits, it may not be adequate to focus only on the principal reactant, as other chemical variations may be more difficult to remove. In some circumstances, TLC screening, in addition to chemical analyses, may be needed. In a bulk process, particularly for very potent chemicals such as some steroids, the issue of by products must be considered if equipment is not dedicated.

VI. OTHER ISSUES

A. Placebo Product

In order to evaluate and validate cleaning processes, some manufacturers have processed a placebo batch in the equipment under essentially the same operating parameters used for processing product. A sample of the placebo batch is then tested for residual contamination. One cannot be sure that a contaminant is uniformly distributed throughout the system. For example, if the discharge valve or chute of a blender is contaminated, the contaminant would probably not be uniformly dispersed in the placebo; it would most likely be concentrated in the initial discharge portion of the batch. Additionally, if the contaminant or residue is of a larger particle size, it may not be uniformly dispersed in the placebo. Some firms have made the assumption that a residual contaminant would wear off the equipment surface uniformly, but this is an invalid conclusion. Finally, the analytical power may be greatly reduced by dilution of the contaminate. Because of such problems, rinse and/or swab samples should be used in conjunction with the placebo method.

B. Detergent

If a detergent or soap is used for cleaning, evaluate the difficulty that may arise when attempting to test for residues. A common problem associated with detergent use is its composition. Many detergent suppliers will not provide a specific composition, which makes it difficult for the user to evaluate residues. As with product residues, it is important and it is expected that the manufacturer evaluate the efficiency of the cleaning process for the removal of residues. However, unlike product residues, it is expected that no (or, for ultrasensitive analytical tests, very little) detergent remains after cleaning. Detergents are not part of the manufacturing process and are only added to facilitate cleaning during the cleaning process. Thus, they should be easily removable; otherwise, a different detergent should be selected.

C. Test Until Clean

Evaluate the level of testing and the retest results when using this concept. Test, resample, and retest equipment or systems until an acceptable residue level is attained. For a system or equipment with a validated cleaning process, this practice of resampling should not be utilized and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated, as these retests actually document the presence of unacceptable residue and contaminants from an ineffective cleaning process.

Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

I. INTRODUCTION

This document is concerned with testing and evaluation of the viral safety of biotechnology products derived from characterized cell lines of human or animal origin (i.e., mammalian, avian, insect) and outlines data that should be submitted in the marketing application/registration package. For the purposes of this document, the term virus excludes nonconventional transmissible agents like those associated with bovine spongiform encephalopathy and scrapie. Applicants are encouraged to discuss issues associated with bovine spongiform encephalopathy with the regulatory authorities.

The scope of the document covers products derived from cell cultures initiated from characterized cell banks. It covers products derived from in vitro cell culture, such as interferons, monoclonal antibodies, and recombinant DNA-derived products including recombinant subunit vaccines, and also includes products derived from hybridoma cells grown in vivo as ascites. In the latter case, special considerations apply and additional information on testing cells propagated in vivo is contained in Appendix 1. Inactivated vaccines, all live vaccines containing self-replicating agents, and genetically engineered live vectors are excluded from the scope of this document.

The risk of viral contamination is a feature common to all biotechnology products derived from cell lines. Such contamination could have serious clinical consequences and can arise from the contamination of the source cell lines themselves (cell substrates) or from adventitious introduction of virus during production. To date, however, biotechnology products derived from cell lines have not been implicated in the transmission of viruses. Nevertheless, it is expected that the safety of these products with regard to viral contamination can be reasonably assured only by the application of a virus testing program and assessment of virus removal and inactivation achieved by the manufacturing process, as outlined below.

Three principal, complementary approaches have evolved to control the potential viral contamination of biotechnology products:

(a) selecting and testing cell lines and other raw materials, including media components, for the absence of undesirable viruses which may be infectious and/or pathogenic for humans,
(b) assessing the capacity of the production processes to clear infectious viruses, and
(c) testing the product at appropriate steps of production for absence of contaminating infectious viruses.

All testing suffers from the inherent limitation of quantitative virus assays, that is, that the ability to detect low viral concentrations depends for statistical reasons on the size of the sample. Therefore, no single approach will necessarily establish the safety of a product. Confidence that infectious virus is absent from the final product will in many instances not be derived solely from direct testing for its presence but also from a demonstration that the purification regimen is capable of removing and/or inactivating the viruses.

The type and extent of viral tests and viral clearance studies required at different steps of production will depend on various factors and should be considered on a case-by-case and step-by-step basis. The factors that should be taken into account include the extent of cell bank characterization and qualification, the nature of any viruses detected, culture medium constituents, culture methods, facility and equipment design, the results of viral tests after cell culture, the ability of the process to clear viruses, and the type of product and its intended clinical use.

The purpose of this document is to provide a general framework for virus testing, experiments for the assessment of viral clearance, and a recommended approach for the design of viral tests and viral clearance studies. Related information is described in the appendices and selected definitions are provided in the glossary.

The manufacturers should adjust the recommendations presented here to their specific product and its production process. The approach used by manufacturers in their overall strategy for ensuring viral safety should be explained and justified. In addition to the detailed data which is provided, an overall summary of the viral safety assessment would be useful in facilitating the review by regulatory authorities. This summary should contain a brief description of all aspects of the viral safety studies and strategies used to prevent virus contamination as they pertain to this document.

II. POTENTIAL SOURCES OF VIRUS CONTAMINATION

Viral contamination of biotechnology products may arise from the original source of the cell lines or from adventitious introduction of virus during production processes.

A. Viruses That Could Occur in the Master Cell Bank

Cells may have latent or persistent virus infection (e.g., herpesvirus) or endogenous retrovirus which may be transmitted vertically from one cell generation to the next, since the viral genome persists within the cell. Such viruses may be constitutively expressed or may unexpectedly become expressed as an infectious virus.

Viruses can be introduced into the master cell bank (MCB) by several routes such as (1) derivation of cell lines from infected animals, (2) use of virus to establish the cell line, (3) use of contaminated biological reagents such as animal serum components, and (4) contamination during cell handling.

B. Adventitious Viruses That Could Be Introduced during Production

Adventitious viruses can be introduced into the final product by several routes including, but not limited to, the following: (1) the use of contaminated biological reagents such as animal serum components; (2) the use of a virus for the induction of expression of specific genes encoding a desired protein; (3) the use of a contaminated reagent, such as a monoclonal antibody affinity column; (4) the use of a contaminated excipient during formulation; and (5) contamination during cell and medium handling. Monitoring of cell culture parameters can be helpful in the early detection of potential adventitious viral contamination.

III. CELL LINE QUALIFICATION: TESTING FOR VIRUSES

An important part of qualifying a cell line for use in the production of a biotechnology product is the appropriate testing for the presence of virus.

A. Suggested Virus Tests for MCB, Working Cell Bank, and Cells at the Limit of In Vitro Cell Age Used for Production

Table 1 shows an example of virus tests to be performed once only at various cell levels, including MCB, WCB, and cells at the limit of in vitro cell age used for production.

1. Master Cell Bank

Extensive screening for both endogenous and nonendogenous viral contamination should be performed on the MCB. For heterohybrid cell lines in which one or more partners are human or nonhuman primate in origin, tests should be performed in order to detect viruses of human or nonhuman primate origin as viral contamination arising from these cells may pose a particular hazard.

Table 1 Virus Tests to Be Performed Once at Various Cell Levels

	MCB	WCB[a]	Cells at the Limit[b]
Tests for retroviruses and other endogenous viruses			
Infectivity	+	−	+
Electron microscopy[c]	+[c]	−	+[c]
Reverse transcriptase[d]	+[d]	−	+[d]
Other virus-specific tests[e]	As appropriate[e]	−	As appropriate[e]
Tests for nonendogenous or adventitious viruses			
In vitro assays	+	−[f]	+
In vivo assays	+	−[f]	+
Antibody production tests[g]	+[g]	−	−
Other virus-specific tests[h]	+[h]	−	−

[a] See text—Section III.A.2.
[b] Cells at the limit: cells at the limit of in vitro cell age used for production (see text—Section III.A.3).
[c] May also detect other agents.
[d] Not necessary if positive by retrovirus infectivity test.
[e] As appropriate for cell lines which are known to have been infected by such agents.
[f] For the first WCB, this test should be performed on cells at the limit of in vitro cell age, generated from that WCB; for WCBs subsequent to the first WCB, a single in vitro and in vivo test can be done either directly on the WCB or on cells at the limit of in vitro cell age.
[g] e.g., MAP, RAP, HAP—Usually applicable for rodent cell lines.
[h] e.g., tests for cell lines derived from human, nonhuman primate, or other cell lines as appropriate.

Testing for nonendogenous viruses should include in vitro and in vivo inoculation tests and any other specific tests, including species-specific tests such as the mouse antibody production (MAP) test, that are appropriate, based on the passage history of the cell line, to detect possible contaminating viruses.

2. Working Cell Bank

Each WCB as a starting cell substrate for drug production should be tested for adventitious virus either by direct testing or by analysis of cells at the limit of in vitro cell age, initiated from the WCB. When appropriate nonendogenous virus tests have been performed on the MCB and cells cultured up to or beyond the limit of in vitro cell age have been derived from the WCB and used for testing for the presence of adventitious viruses, similar tests need not be performed on the initial WCB. Antibody production tests are usually not necessary for the WCB. An alternative approach in which full tests are carried out on the WCB rather than on the MCB would also be acceptable.

3. Cells at the Limit of In Vitro Cell Age Used for Production

The limit of in vitro cell age used for production should be based on data derived from production cells expanded under pilot-plant scale or commercial-scale conditions to the proposed in vitro cell age or beyond. Generally, the production cells are obtained by expansion of the WCB; the MCB could also be used to prepare the production cells. Cells at the limit of in vitro cell age should be evaluated once for those endogenous viruses that may have been undetected in the MCB and WCB. The performance of suitable tests (e.g., in vitro and in vivo) at least once on cells at the limit of in vitro cell age used for production would provide further assurance that the production process is not prone to contamination by adventitious virus. If any adventitious viruses are detected at this level, the process should be carefully checked in order to determine the cause of the contamination, and completely redesigned if necessary.

B. Recommended Viral Detection and Identification Assays

Numerous assays can be used for the detection of endogenous and adventitious viruses. Table 2 outlines examples for these assays. They should be regarded as assay protocols recommended for the present, but the list is not all-inclusive or definitive. Since the most appropriate techniques may change with scientific progress, proposals for alternative techniques, when accompanied by adequate supporting data, may be acceptable. Manufacturers are encouraged to discuss these alternatives with the regulatory authorities. Other tests may be necessary depending on the individual case. Assays should include appropriate controls to ensure adequate sensitivity and specificity. Wherever a relatively high possibility of the presence of a specific virus can be predicted from the species of origin of the cell substrate, specific tests and/or approaches may be necessary. If the cell line used for production is of human or nonhuman primate origin, additional tests for human viruses, such as those causing immunodeficiency diseases and hepatitis, should be performed unless otherwise justified. The polymerase chain reaction (PCR) may be appropriate for detection of sequences of these human viruses as well as for other specific viruses. The following is a brief description of a general framework and philosophical

Table 2 Examples of the Use and Limitations of Assays Which May Be Used to Test for Virus

Test	Test Article	Detection Capability	Detection Limitation
Antibody production	Lysate of cells and their culture medium	Specific viral antigens	Antigens not infectious for animal test system
In vivo virus screen	Lysate of cells and their culture medium	Broad range of viruses pathogenic for humans	Agents failing to replicate or produce diseases in the test system
In vitro virus screen for 1. Cell bank characterization 2. Production screen	1. Lysate of cells and their culture medium (for cocultivation, intact cells should be in the test article) 2. Unprocessed bulk harvest or lysate of cells and their cell culture medium from the production reactor	Broad range of viruses pathogenic for humans	Agents failing to replicate or produce diseases in the test system
TEM on 1. Cell substrate 2. Cell culture supernatant	 1. Viable cells 2. Cell-free culture supernatant	Virus and virus-like particles	Qualitative assay with assessment of identity
Reverse transcriptase (RT)	Cell-free culture supernatant	Retroviruses and expressed retroviral RT	Only detects enzymes with optimal activity under preferred conditions. Interpretation may be difficult due to presence of cellular enzymes; background with some concentrated samples
Retrovirus (RV) infectivity	Cell-free culture supernatant	Infectious retroviruses	RV failing to replicate or form discrete foci or plaques in the chosen test system
Cocultivation 1. Infectivity endpoint 2. TEM endpoint 3. RT endpoint	Viable cells	Infectious retroviruses	RV failing to replicate 1. See above under RV infectivity 2. See above under TEM[a] 3. See above under RT
PCR (Polymerase chain reaction)	Cells, culture fluid, and other materials	Specific virus sequences	Primer sequences must be present. Does not indicate whether virus is infectious

[a] In addition, difficult to distinguish test article from indicator cells.

background within which the manufacturer should justify what was done.

1. Tests for Retroviruses

For the MCB and for cells cultured up to or beyond the limit of in vitro cell age used for production, tests for retroviruses, including infectivity assays in sensitive cell cultures and electron microscopy studies, should be carried out. If infectivity is not detected and no retrovirus or retrovirus-like particles have been observed by electron microscopy, reverse transcriptase (RT) or other appropriate assays should be performed to detect retroviruses which may be noninfectious. Induction studies have not been found to be useful.

2. In Vitro Assays

In vitro tests are carried out by the inoculation of a test article (Table 2) into various susceptible indicator cell cultures capable of detecting a wide range of human and relevant animal viruses. The choice of cells used in the test is governed by the species of origin of the cell bank to be tested, but should include a human and/or a nonhuman primate cell line susceptible to human viruses. The nature of the assay and the sample to be tested are governed by the type of virus which may possibly be present based on the origin or handling of the cells. Both cytopathic and hemadsorbing viruses should be sought.

3. In Vivo Assays

A test article (Table 2) should be inoculated into animals, including suckling and adult mice, and in embryonated eggs to reveal viruses that cannot grow in cell cultures. Additional animal species may be used depending on the nature and source of the cell lines being tested. The health of the animals should be monitored and any abnormality should be investigated to establish the cause of the illness.

4. Antibody Production Tests

Species-specific viruses present in rodent cell lines may be detected by inoculating test article (Table 2) into virus-free animals, and by examining the serum antibody level or enzyme activity after a specified period. Examples of such tests are the mouse antibody production (MAP) test, rat antibody production (RAP) test, and hamster antibody production (HAP) test. The viruses currently screened for in the antibody production assays are discussed in Table 3.

C. Acceptability of Cell Lines

It is recognized that some cell lines used for the manufacture of product will contain endogenous retroviruses, other viruses, or viral sequences. In such circumstances, the action plan recommended for manufacture is described in section V of this document. The acceptability of cell lines containing viruses other than endogenous retroviruses will be considered on an individual basis by the regulatory authorities, by taking into account a risk/benefit analysis based on the benefit of the product and its intended clinical use, the nature of the contaminating viruses, their potential for infecting humans or for causing disease in humans, the purification process for the product (e.g., viral clearance evaluation data), and the extent of the virus tests conducted on the purified bulk.

Table 3 Virus Detected in Antibody Production Tests

MAP	HAP	RAP
Ectromelia virus[b,c]	Lymphocytic choriomeningitis virus (LCM)[a,c]	Hantaan virus[a,c]
Hantaan virus[a,c]	Pneumonia virus of mice (PVM)[b,c]	Kilham rat virus (KRV)[b,c]
K virus[b]	Reovirus type 3 (Reo3)[a,c]	Mouse encephalomyelitis virus (Theilers, GDVII)[b]
Lactic dehydrogenase virus (LDM)[a,c]	Sendai virus[a,c]	Pneumonia virus of mice (PVM)[b,c]
	SV5	Rat coronavirus (RCV)[b]
Lymphocytic choriomeningitis virus (LCM)[a,c]		Reovirus type 3 (Reo3)[a,c]
Minute virus of mice [b,c]		Sendai virus[a,c]
Mouse adenovirus (MAV)[b,c]		Sialoacryoadenitis virus (SDAV)[b]
Mouse cytomegalovirus (MCMV)[b,c]		
Mouse encephalomyelitis virus (Theilers, GDVII)[b]		Toolan virus (HI)[b,c]
Mouse hepatitis virus (MHV)[b]		
Mouse rotavirus (EDIM)[b,c]		
Pneumonia virus of mice (PVM)[b,c]		
Polyoma virus[b]		
Reovirus type 3 (Reo3)[a,c]		
Sendai virus[a,c]		
Thymic virus[b]		

[a] Viruses for which there is evidence of capacity for infecting humans or primates.
[b] Viruses for which there is no evidence of capacity for infecting humans.
[c] Virus capable of replicating in vitro in cells of human or primate origin.

IV. TESTING FOR VIRUSES IN UNPROCESSED BULK

The unprocessed bulk constitutes one or multiple pooled harvests of cells and culture media. When cells are not readily accessible (e.g., hollow fiber or similar systems), the unprocessed bulk would constitute fluids harvested from the fermenter. A representative sample of the unprocessed bulk, removed from the production reactor prior to further processing, represents one of the most suitable levels at which the possibility of adventitious virus contamination can be determined with a high probability of detection. Appropriate testing for viruses should be performed at the unprocessed bulk level unless virus testing is made more sensitive by initial partial processing (e.g., unprocessed bulk may be toxic in test cell cultures, whereas partially processed bulk may not be toxic).

In certain instances, it may be more appropriate to test a mixture consisting of both intact and disrupted cells and their cell culture supernatants removed from the production reactor prior to further processing. Data from at least 3 lots of unprocessed bulk at pilot-plant scale or commercial scale should be submitted as part of the marketing application/registration package.

It is recommended that manufacturers develop programs for the ongoing assessment of adventitious viruses in production batches. The scope, extent, and frequency of virus testing on the unprocessed bulk should be determined by taking several points into consideration including the nature of the cell lines used to produce the desired products, the results and extent of virus tests performed during the qualification of the cell lines, and the cultivation method, raw material sources, and results of viral clearance studies. In vitro screening tests, using one or several cell lines, are generally employed to test unprocessed bulk. If appropriate, a PCR test or other suitable methods may be used.

Generally, harvest material in which adventitious virus has been detected should not be used to manufacture the product. If any adventitious viruses are detected at this level, the process should be carefully checked to determine the cause of the contamination, and appropriate actions taken.

V. RATIONALE AND ACTION PLAN FOR VIRAL CLEARANCE STUDIES AND VIRUS TESTS ON PURIFIED BULK

It is important to design the most relevant and rational protocol for virus tests from the MCB level, through the various steps of drug production, to the final product including evaluation and characterization of viral clearance from unprocessed bulk. The evaluation and characterization of viral clearance plays a critical role in this scheme. The goal should be to obtain the best reasonable assurance that the product is free of virus contamination.

In selecting viruses to use for a clearance study, it is useful to distinguish between the need to evaluate processes for their ability to clear viruses that are known to be present and the desire to estimate the robustness of the process by characterizing the clearance of nonspecific "model" viruses (described later). Definitions of "relevant," specific, and nonspecific "model" viruses are given in the glossary. Process evaluation requires knowledge of how much virus may be present in the process, such as the unprocessed bulk, and how much can be cleared in order to assess product safety. Knowledge of the time dependence for inactivation procedures is helpful in assuring the effectiveness of the inactivation process. When evaluating clearance of known contaminants, in-depth time-dependent inactivation studies, demonstration of reproducibility of inactivation/removal, and evaluation of process parameters will be needed. When a manufacturing process is characterized for robustness of clearance using nonspecific "model" viruses, particular attention should be paid to nonenveloped viruses in the study design. The extent of viral clearance characterization studies may be influenced by the results of tests on cell lines and unprocessed bulk. These studies should be performed as described below (section VI).

Table 4 presents an example of an action plan, in terms of process evaluation and characterization of viral clearance as well as virus tests on purified bulk, in response to the results of virus tests on cells and/or the unprocessed bulk. Various cases are considered. In all cases, characterization of clearance using nonspecific "model" viruses should be performed. The most common situations are Cases A and B. Production systems contaminated with a virus other than a

Table 4 Action Plan for Process Assessment of Viral Clearance and Virus Tests on Purified Bulk

	Case A	Case B	Case C[b]	Case D[b]	Case E[b]
Status					
Presence of virus[a]	−	−	+	+	(+)[c]
Virus-like particles[a]	−	−	−	−	(+)[c]
Retrovirus-like particles[a]	−	+	−	−	(+)[c]
Virus identified	Not applicable	+	+	+	−
Virus pathogenic for humans	Not applicable	−[d]	−[d]	+	Unknown
Action					
Process characterization of viral clearance using nonspecific "model" viruses	Yes[e]	Yes[e]	Yes[e]	Yes[e]	Yes[g]
Process evaluation of viral clearance using "relevant" or specific "model" viruses	No	Yes[f]	Yes[f]	Yes[f]	Yes[g]
Test for virus in purified bulk	Not applicable	Yes[h]	Yes[h]	Yes[h]	Yes[h]

[a] Results of virus tests for the cell substrate and/or at the unprocessed bulk level. Cell cultures used for production which are contaminated with viruses will generally be not acceptable. Endogenous viruses (such as retroviruses) or viruses that are an integral part of the MCB may be acceptable if appropriate viral clearance evaluation procedures are followed.

[b] The use of source material which is contaminated with viruses, whether or not they are known to be infectious and/or pathogenic in humans, will only be permitted under very exceptional circumstances.

[c] Virus has been observed by either direct or indirect methods.

[d] Believed to be nonpathogenic.

[e] Characterization of clearance using nonspecific "model" viruses should be performed.

[f] Process evaluation for "relevant" viruses or specific "model" viruses should be performed.

[g] See text under Case E.

[h] The absence of detectable virus should be confirmed for purified bulk by means of suitable methods having high specificity and sensitivity for the detection of the virus in question. For the purpose of marketing authorization, data from at least 3 lots of purified bulk manufactured at pilot-plant scale or commercial scale should be provided. However, for cell lines such as CHO cells for which the endogenous particles have been extensively characterized and adequate clearance has been demonstrated, it is not usually necessary to assay for the presence of the noninfectious particles in purified bulk.

rodent retrovirus are normally not used. Where there are convincing and well-justified reasons for drug production using a cell line from Cases C, D, or E, these should be discussed with the regulatory authorities. With Cases C, D, and E it is important to have validated effective steps to inactivate/remove the virus in question from the manufacturing process.

Case A: Where no virus, virus-like particle, or retrovirus-like particle has been demonstrated in the cells or the unprocessed bulk, virus removal and inactivation studies should be performed with nonspecific "model" viruses as previously stated.

Case B: Where only a rodent retrovirus (or a retrovirus-like particle which is believed to be nonpathogenic, such as rodent A- and R-type particles) is present, process evaluation using a specific "model" virus, such as a murine leukemia virus, should be performed. Purified bulk should be tested using suitable methods having high specificity and sensitivity for the detection of the virus in question. For marketing authorization, data from at least 3 lots of purified bulk at pilot-plant scale or commercial scale should be provided. Cell lines such as CHO, C127, BHK, and murine hybridoma cell lines have frequently been used as substrates for drug production with no reported safety problems related to viral contamination of the products. For these cell lines in which the endogenous particles have been extensively characterized and clearance has been demonstrated, it is not usually necessary to assay for the presence of the noninfectious particles in purified bulk. Studies with nonspecific "model" viruses, as in Case A, are appropriate.

Case C: When the cells or unprocessed bulk are known to contain a virus, other than a rodent retrovirus, for which there is no evidence of capacity for infecting humans, [such as those identified by footnote 2 in Table 3, except rodent retroviruses (Case B)], virus removal and inactivation evaluation studies should use the identified virus. If it is not possible to use the identified virus, "relevant" or specific "model" viruses should be used to demonstrate acceptable clearance. Time-dependent inactivation for identified (or "relevant" or specific "model") viruses at the critical inactivation step(s) should be obtained as part of process evaluation for these viruses. Purified bulk should be tested using suitable methods having high specificity and sensitivity for the detection of the virus in question. For the purpose of marketing authorization, data from at least 3 lots of purified bulk manufactured at pilot-plant scale or commercial scale should be provided.

Case D: Where a known human pathogen, such as those indicated by footnote 1 in Table 3, is identified, the product may be acceptable only under exceptional circumstances. In this instance, it is recommended that the identified virus be used for virus removal and inactivation evaluation studies and specific methods with high specificity and sensitivity for the detection of the virus in question be employed. If it is not possible to use the identified virus, "relevant" and/or specific "model" viruses (described later) should be used. The process should be shown to achieve the removal and inactivation of the selected viruses during the purification and inactivation processes. Time-dependent inactivation data for the critical inactivation step(s) should be obtained as part of process evaluation. Purified bulk should be tested using suitable methods having high specificity and sensitivity for the detection of the virus in question. For the purpose of marketing authorization, data from at least 3 lots of purified bulk manufactured at pilot-plant scale or commercial scale should be provided.

Case E: When a virus, which cannot be classified by currently available methodologies, is detected in the cells or unprocessed bulk, the product is usually considered unacceptable since the virus may prove to be pathogenic. In the very rare case where there are convincing and well-justified reasons for drug production using such a cell line, this should be discussed with the regulatory authorities before proceeding further.

VI. EVALUATION AND CHARACTERIZATION OF VIRAL CLEARANCE PROCEDURES

Evaluation and characterization of the virus removal and/or inactivation procedures play an important role in establishing the safety of biotechnology products. Many instances of contamination in the past have occurred with agents whose presence was not known or even suspected, and though this happened to biological products derived from various source materials other than fully characterized cell lines, assessment of viral clearance will provide a measure of confidence that any unknown, unsuspected, and harmful viruses may be removed. Studies should be carried out in a manner that is well documented and controlled.

The objective of viral clearance studies is to assess process step(s) that can be considered to be effective in inactivating/removing viruses and to estimate quantitatively the overall level of virus reduction obtained by the process. This should be achieved by the deliberate addition ("spiking") of significant amounts of a virus to the crude material and/or to different fractions obtained during the various process steps and demonstrating its removal or inactivation during the subsequent steps. It is not necessary to evaluate or characterize every step of a manufacturing process if adequate clearance is demonstrated by the use of fewer steps. It should be borne in mind that other steps in the process may have an indirect effect on the viral inactivation/removal achieved. Manufacturers should explain and justify the approach used in studies for evaluating virus clearance.

The reduction of virus infectivity may be achieved by removal of virus particles or by inactivation of viral infectivity. For each production step assessed, the possible mechanism of loss of viral infectivity should be described with regard to whether it is due to inactivation or removal. For inactivation steps, the study should be planned in such a way that samples are taken at different times and an inactivation curve constructed (see section VI.B.5).

Viral clearance evaluation studies are performed to demonstrate the clearance of a virus known to be present in the MCB and/or to provide some level of assurance that adventitious virus which could not be detected, or might gain access to the production process, would be cleared. Reduction factors are normally expressed on a logarithmic scale which implies that, while residual virus infectivity will never be reduced to zero, it may be greatly reduced mathematically.

In addition to clearance studies for viruses known to be present, studies to characterize the ability to remove and/or inactivate other viruses should be conducted. The purpose of studies with viruses, exhibiting a range of biochemical and biophysical properties that are not known or expected to be present, is to characterize the robustness of the procedure rather than to achieve a specific inactivation or removal goal. A demonstration of the capacity of the production process to inactivate or remove viruses is desirable (see section VI.C). Such studies are not performed to evaluate a specific safety risk. Therefore, a specific clearance value need not be achieved.

A. The Choice of Viruses for the Evaluation and Characterization of Viral Clearance

Viruses for clearance evaluation and process characterization studies should be chosen to resemble viruses which may contaminate the product and to represent a wide range of physicochemical properties in order to test the ability of the system to eliminate viruses in general. The manufacturer should justify the choice of viruses in accordance with the aims of the evaluation and characterization study and the guidance provided in this guideline.

1. "Relevant" Viruses and "Model" Viruses

A major issue in performing a viral clearance study is to determine which viruses should be used. Such viruses fall into three categories: "relevant" viruses, specific "model" viruses, and nonspecific "model" viruses.

"Relevant" viruses are viruses used in process evaluation of viral clearance studies which are either the identified viruses, or of the same species as the viruses that are known, or likely to contaminate the cell substrate or any other reagents or materials used in the production process. The purification and/or inactivation process should demonstrate the capability to remove and/or inactivate such viruses. When a "relevant" virus is not available or when it is not well adapted to process evaluation of viral clearance studies (e.g., it cannot be grown in vitro to sufficiently high titers), a specific "model" virus should be used as a substitute. An appropriate specific "model" virus may be a virus which is closely related to the known or suspected virus (same genus or family), having similar physical and chemical properties to the observed or suspected virus.

Cell lines derived from rodents usually contain endogenous retrovirus particles or retrovirus-like particles, which may be infectious (C-type particles) or noninfectious (cytoplasmic A- and R-type particles). The capacity of the manufacturing process to remove and/or inactivate rodent retroviruses from products obtained from such cells should be determined. This may be accomplished by using a murine leukemia virus, a specific "model" virus in the case of cells of murine origin. When human cell lines secreting monoclonal antibodies have been obtained by the immortalization of B lymphocytes by Epstein-Barr Virus (EBV), the ability of the manufacturing process to remove and/or inactivate a herpes virus should be determined. Pseudorabies virus may also be used as a specific "model" virus.

When the purpose is to characterize the capacity of the manufacturing process to remove and/or inactivate viruses in general, that is, to characterize the robustness of the clearance process, viral clearance characterization studies should be performed with nonspecific "model" viruses with differing properties. Data obtained from studies with "relevant" and/or specific "model" viruses may also contribute to this assessment. It is not necessary to test all types of viruses. Preference should be given to viruses that display a significant resistance to physical and/or chemical treatments. The results obtained for such viruses provide useful information about the ability of the production process to remove and/or inactivate viruses in general. The choice and number of viruses used will be influenced by the quality and characterization of the cell lines and the production process.

Examples of useful "model" viruses representing a range of physicochemical structures and examples of viruses which have been used in viral clearance studies are given in Appendix 2 and Table A.1.

2. Other Considerations

Additional points to be considered are as follows:

(a) Viruses which can be grown to high titer are desirable, although this may not always be possible.
(b) There should be an efficient and reliable assay for the detection of each virus used, for every stage of manufacturing that is tested.

(c) Consideration should be given to the health hazard which certain viruses may pose to the personnel performing the clearance studies.

B. Design and Implications of Viral Clearance Evaluation and Characterization Studies

1. Facility and Staff

It is inappropriate to introduce any virus into a production facility because of GMP constraints. Therefore, viral clearance studies should be conducted in a separate laboratory equipped for virological work and performed by staff with virological expertise in conjunction with production personnel involved in designing and preparing a scaled-down version of the purification process.

2. Scaled-Down Production System

The validity of the scaling down should be demonstrated. The level of purification of the scaled-down version should represent the production procedure as closely as possible. For chromatographic equipment, column bed-height, linear flow-rate, flow-rate-to-bed-volume ratio (i.e., contact time), buffer and gel types, pH, temperature, and concentration of protein, salt, and product should all be shown to be representative of commercial-scale manufacturing. A similar elution profile should result. For other procedures, similar considerations apply. Deviations which cannot be avoided should be discussed with regard to their influence on the results.

3. Analysis of StepWise Elimination of Virus

When viral clearance studies are being performed, it is desirable to assess the contribution of more than one production step to virus elimination. Steps which are likely to clear virus should be individually assessed for their ability to remove and inactivate virus and careful consideration should be given to the exact definition of an individual step. Sufficient virus should be present in the material of each step to be tested so that an adequate assessment of the effectiveness of each step is obtained. Generally, virus should be added to in-process material of each step to be tested. In some cases, simply adding high titer virus to unpurified bulk and testing its concentration between steps will be sufficient. Where virus removal results from separation procedures, it is recommended that, if appropriate and if possible, the distribution of the virus load in the different fractions be investigated. When virucidal buffers are used in multiple steps within the manufacturing process, alternative strategies such as parallel spiking in less virucidal buffers may be carried out as part of the overall process assessment. The virus titer before and after each step being tested should be determined. Quantitative infectivity assays should have adequate sensitivity and reproducibility and should be performed with sufficient replicates to ensure adequate statistical validity of the result. Quantitative assays not associated with infectivity may be used if justified. Appropriate virus controls should be included in all infectivity assays to ensure the sensitivity of the method. Also, the statistics of sampling virus when at low concentrations should be considered (Appendix 3).

4. Determining Physical Removal Vs. Inactivation

Reduction in virus infectivity may be achieved by the removal or inactivation of virus. For each production step assessed, the possible mechanism of loss of viral infectivity should be described with regard to whether it is due to inactivation or removal. If little clearance of infectivity is achieved by the production process, and the clearance of virus is considered to be a major factor in the safety of the product, specific or additional inactivation/removal steps should be introduced. It may be necessary to distinguish between removal and inactivation for a particular step, for example, when there is a possibility that a buffer used in more than one clearance step may contribute to inactivation during each step; that is, the contribution to inactivation by a buffer shared by several chromatographic steps and the removal achieved by each of these chromatographic steps should be distinguished.

5. Inactivation Assessment

For assessment of viral inactivation, unprocessed crude material or intermediate material should be spiked with infectious virus and the reduction factor calculated. It should be recognized that virus inactivation is not a simple, first-order reaction and is usually more complex, with a fast "phase 1" and a slow "phase 2." The study should, therefore, be planned in such a way that samples are taken at different times and an inactivation curve constructed. It is recommended that studies for inactivation include at least one time point less than the minimum exposure time and greater than zero, in addition to the minimum exposure time. Additional data are particularly important where the virus is a "relevant" virus known to be a human pathogen and an effective inactivation process is being designed. However, for inactivation studies in which nonspecific "model" viruses are used or when specific "model" viruses are used as surrogates for virus particles such as the CHO intracytoplasmic retrovirus-like particles, reproducible clearance should be demonstrated in at least two independent studies. Whenever possible, the initial virus load should be determined from the virus which can be detected in the spiked starting material. If this is not possible, the initial virus load may be calculated from the titer of the spiking virus preparation. Where inactivation is too rapid to plot an inactivation curve using process conditions, appropriate controls should be performed to demonstrate that infectivity is indeed lost by inactivation.

6. Function and Regeneration of Columns

Over time and after repeated use, the ability of chromatography columns and other devices used in the purification scheme to clear virus may vary. Some estimate of the stability of the viral clearance after several uses may provide support for repeated use of such columns. Assurance should be provided that any virus potentially retained by the production system would be adequately destroyed or removed prior to reuse of the system. For example, such evidence may be provided by demonstrating that the cleaning and regeneration procedures do inactivate or remove virus.

7. Specific Precautions

(a) Care should be taken in preparing the high-titer virus to avoid aggregation which may enhance physical removal and decrease inactivation, thus distorting the correlation with actual production.
(b) Consideration should be given to the minimum quantity of virus which can be reliably assayed.
(c) The study should include parallel control assays to assess the loss of infectivity of the virus due to such reasons as the dilution, concentration, filtration, or storage of samples before titration.
(d) The virus "spike" should be added to the product in a small volume so as not to dilute or change the

characteristics of the product. Diluted, test-protein sample is no longer identical to the product obtained at commercial scale.

(e) Small differences in, for example, buffers, media, or reagents can substantially affect viral clearance.

(f) Virus inactivation is time dependent; therefore, the amount of time a spiked product remains in a particular buffer solution or on a particular chromatography column should reflect the conditions of the commercial-scale process.

(g) Buffers and product should be evaluated independently for toxicity or interference in assays used to determine the virus titer, as these components may adversely affect the indicator cells. If the solutions are toxic to the indicator cells, dilution, adjustment of the pH, or dialysis of the buffer-containing spiked virus might be necessary. If the product itself has antiviral activity, the clearance study may need to be performed without the product in a "mock" run, although omitting the product or substituting a similar protein that does not have antiviral activity could affect the behavior of the virus in some production steps. Sufficient controls to demonstrate the effect of procedures used solely to prepare the sample for assay (e.g., dialysis, storage) on the removal/inactivation of the spiking virus should be included.

(h) Many purification schemes use the same or similar buffers or columns repetitively. The effects of this approach should be taken into account when analyzing the data. The effectiveness of virus elimination by a particular process may vary with the stage in manufacture at which it is used.

(i) Overall reduction factors may be underestimated where production conditions or buffers are too cytotoxic or virucidal and should be discussed on a case-by-case basis. Overall reduction factors may also be overestimated due to inherent limitations or inadequate design of viral clearance studies.

C. Interpretation of Viral Clearance Studies

1. Acceptability

The object of assessing virus inactivation/removal is to evaluate and characterize process steps that can be considered to be effective in inactivating/removing viruses and to estimate quantitatively the overall level of virus reduction obtained by the manufacturing process. For virus contaminants, as in Cases B–E, it is important to show that not only is the virus eliminated or inactivated, but that there is excess capacity for viral clearance built into the purification process to assure an appropriate level of safety for the final product. The amount of virus eliminated or inactivated by the production process should be compared to the amount of virus which may be present in unprocessed bulk.

To carry out this comparison, it is important to estimate the amount of virus in the unprocessed bulk. This estimate should be obtained using assays for infectivity or other methods such as transmission electron microscopy (TEM). The entire purification process should be able to eliminate substantially more virus than is estimated to be present in a single-dose-equivalent of unprocessed bulk. See Appendix 4 for calculation of virus reduction factors and Appendix 5 for calculation of estimated particles per dose.

Manufacturers should recognize that clearance mechanisms may differ between virus classes. A combination of factors must be considered when judging the data supporting the effectiveness of virus inactivation/removal procedures. These include

(i) the appropriateness of the test viruses used,
(ii) the design of the clearance studies,
(iii) the log reduction achieved,
(iv) the time dependence of inactivation,
(v) the potential effects of variation in process parameters on virus inactivation/removal,
(vi) the limits of assay sensitivities, and
(vii) the possible selectivity of inactivation/removal procedure(s) for certain classes of viruses.

Effective clearance may be achieved by any of the following: multiple inactivation steps, multiple complementary separation steps, or combinations of inactivation and separation steps. Since separation methods may be dependent on the extremely specific physicochemical properties of a virus which influence its interaction with gel matrices and precipitation properties, "model" viruses may be separated in a different manner from a target virus. Manufacturing parameters influencing separation should be properly defined and controlled. Differences may originate from changes in surface properties such as glycosylation. However, despite these potential variables, effective removal can be obtained by a combination of complementary separation steps or combinations of inactivation and separation steps. Therefore, well-designed separation steps, such as chromatographic procedures, filtration steps, and extractions, can be effective virus removal steps provided that they are performed under appropriately controlled conditions. An effective virus removal step should give reproducible reduction of virus load shown by at least two independent studies.

An overall reduction factor is generally expressed as the sum of the individual factors. However, reduction in virus titer of the order of 1 $\log_{10}$ or less would be considered negligible and would be ignored unless justified.

If little reduction of infectivity is achieved by the production process, and the removal of virus is considered to be a major factor in the safety of the product, a specific, additional inactivation/removal step or steps should be introduced. For all viruses, manufacturers should justify the acceptability of the reduction factors obtained. Results will be evaluated on the basis of the factors listed above.

D. Limitations of Viral Clearance Studies

Viral clearance studies are useful for contributing to the assurance that an acceptable level of safety in the final product is achieved but do not establish safety by themselves. However, a number of factors in the design and execution of viral clearance studies may lead to an incorrect estimate of the ability of the process to remove virus infectivity. These factors include the following:

1. Virus preparations used in clearance studies for a production process are likely to be produced in tissue culture. The behavior of a tissue culture virus in a production step may be different from that of the native virus; for example, if native and cultured viruses differ in purity or degree of aggregation.
2. Inactivation of virus infectivity frequently follows a biphasic curve in which a rapid initial phase is followed by a slower phase. It is possible that virus escaping a first inactivation step may be more resistant to subsequent steps. For example, if the resistant fraction takes the form of virus aggregates, infectivity may be resistant to a range of different chemical treatments and to heating.

3. The ability of the overall process to remove infectivity is expressed as the sum of the logarithm of the reductions at each step. The summation of the reduction factors of multiple steps, particularly of steps with little reduction (e.g., below 1 $\log_{10}$), may overestimate the true potential for virus elimination. Furthermore, reduction values achieved by repetition of identical or near identical procedures should not be included unless justified.
4. The expression of reduction factors as logarithmic reductions in titer implies that, while residual virus infectivity may be greatly reduced, it will never be reduced to zero. For example, a reduction in the infectivity of a preparation containing 8 $\log_{10}$ infectious units per milliliter by a factor of 8 $\log_{10}$ leaves 0 $\log_{10}$ per milliliter or one infectious unit per milliliter, taking into consideration the limit of detection of the assay.
5. Pilot-plant scale processing may differ from commercial-scale processing despite care taken to design the scaled-down process.
6. Addition of individual virus reduction factors resulting from similar inactivation mechanisms along the manufacturing process may overestimate overall viral clearance.

E. Statistics

The viral clearance studies should include the use of statistical analysis of the data to evaluate the results. The study results should be statistically valid to support the conclusions reached (refer to Appendix 3).

F. Reevaluation of Viral Clearance

Whenever significant changes in the production or purification process are made, the effect of that change, both direct and indirect, on viral clearance should be considered and the system reevaluated as needed. For example, changes in production processes may cause significant changes in the amount of virus produced by the cell line; changes in process steps may change the extent of viral clearance.

VII. SUMMARY

This document suggests approaches for the evaluation of the risk of viral contamination and for the removal of virus from product, thus contributing to the production of safe biotechnology products derived from animal or human cell lines and emphasizes the value of many strategies, including

A. thorough characterization/screening of cell substrate starting material in order to identify which, if any, viral contaminants are present,
B. assessment of risk by determination of the human tropism of the contaminants,
C. establishment of an appropriate program of testing for adventitious viruses in unprocessed bulk,
D. careful design of viral clearance studies using different methods of virus inactivation or removal in the same production process in order to achieve maximum viral clearance, and
E. performance of studies which assess virus inactivation and removal.

GLOSSARY

Adventitious Virus—See Virus.
Cell Substrate—Cells used to manufacture product.
Endogenous Virus—See Virus.
Inactivation—Reduction of virus infectivity caused by chemical or physical modification.
In Vitro Cell Age—A measure of the period between thawing of the MCB vial(s) and harvest of the production vessel measured by elapsed chronological time in culture, population doubling level of the cells, or passage level of the cells when subcultivated by a defined procedure for dilution of the culture.
Master Cell Bank (MCB)—An aliquot of a single pool of cells which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers, and stored under defined conditions. The MCB is used to derive all working cell banks. The testing performed on a new MCB (from a previous initial cell clone, MCB, or WCB) should be the same as for the MCB, unless justified.
Minimum Exposure Time—The shortest period for which a treatment step will be maintained.
Nonendogenous Virus—See Virus.
Process Characterization of Viral Clearance—Viral clearance studies in which nonspecific "model" viruses are used to assess the robustness of the manufacturing process to remove and/or inactivate viruses.
Process Evaluation Studies of Viral Clearance—Viral clearance studies in which "relevant" and/or specific "model" viruses are used to determine the ability of the manufacturing process to remove and/or inactivate these viruses.
Production Cells—Cell substrate used to manufacture product.
Unprocessed Bulk—One or multiple pooled harvests of cells and culture media. When cells are not readily accessible, the unprocessed bulk would constitute fluid harvested from the fermenter.
Virus—Intracellularly replicating infectious agents that are potentially pathogenic, possessing only a single type of nucleic acid (either RNA or DNA), are unable to grow and undergo binary fission, and multiply in the form of their genetic material.
Adventitious Virus—Unintentionally introduced contaminant viruses.
Endogenous Virus—Viral entity whose genome is part of the germ line of the species of origin of the cell line and is covalently integrated into the genome of animal from which the parental cell line was derived. For the purposes of this document, intentionally introduced, nonintegrated viruses such as EBV used to immortalize cell substrates or Bovine Papilloma Virus fit in this category.
Nonendogenous Virus—Viruses from external sources present in the Master Cell Bank.
Nonspecific Model Virus—A virus used for characterization of viral clearance of the process when the purpose is to characterize the capacity of the manufacturing process to remove and/or inactivate viruses in general, that is, to characterize the robustness of the purification process.
Relevant Virus—Virus used in process evaluation studies, which is either the identified virus, or of the same species as the virus that is known, or likely to

contaminate the cell substrate or any other reagents or materials used in the production process.

Specific Model Virus—Virus which is closely related to the known or suspected virus (same genus or family), having similar physical and chemical properties to those of the observed or suspected virus.

Viral Clearance—Elimination of target virus by removal of viral particles or inactivation of viral infectivity.

Virus-Like Particles—Structures visible by electron microscopy which morphologically appear to be related to known viruses.

Virus Removal—Physical separation of virus particles from the intended product.

Working Cell Bank (WCB)—The WCB is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the MCB under defined culture conditions.

Appendix 1: Products Derived from Characterized Cell Banks which Were Subsequently Grown In Vivo

For products manufactured from fluids harvested from animals inoculated with cells from characterized banks, additional information regarding the animals should be provided.

Whenever possible, animals used in the manufacture of biotechnological/biological products should be obtained from well-defined, specific pathogen-free colonies. Adequate testing for appropriate viruses, such as those listed in Table 3, should be performed. Quarantine procedures for newly arrived as well as diseased animals should be described, and assurance provided that all containment, cleaning, and decontamination methodologies employed within the facility are adequate to contain the spread of adventitious agents. This may be accomplished through the use of a sentinel program. A listing of agents for which testing is performed should also be included. Veterinary support services should be available on-site or within easy access. The degree to which the vivarium is segregated from other areas of the manufacturing facility should be described. Personnel practices should be adequate to ensure safety.

Procedures for the maintenance of the animals should be fully described. These would include diet, cleaning and feeding schedules, provisions for periodic veterinary care if applicable, and details of special handling that the animals may require once inoculated. A description of the priming regimen(s) for the animals, the preparation of the inoculum and the site and route of inoculation should also be included.

The primary harvest material from animals may be considered an equivalent stage of manufacture to unprocessed bulk harvest from a bioreactor. Therefore, all testing considerations previously outlined in section IV of this document should apply. In addition, the manufacturer should assess the bioburden of the unprocessed bulk, determine whether the material is free of mycoplasma, and perform species-specific assay(s) as well as in vivo testing in adult and suckling mice.

Appendix 2: The Choice of Viruses for Viral Clearance Studies

A. Examples of useful "model" viruses
   1. Nonspecific "model" viruses representing a range of physicochemical structures:
      – SV40 (Polyomavirus maccacae 1), human polio virus 1 (Sabin), animal parvovirus, or some other small, nonenveloped viruses;
      – a parainfluenza virus or influenza virus, Sindbis virus or some other medium-to-large, enveloped, RNA viruses;
      – a herpes virus (e.g., HSV-1 or a pseudorabies virus), or some other medium-to-large, DNA viruses.

   These viruses are examples only and their use is not mandatory.
   2. For rodent cell substrates murine retroviruses are commonly used as specific "model" viruses.

B. Examples of viruses which have been used in viral clearance studies

   Several viruses which have been used in viral clearance studies are listed in Table A.1 However, since these are merely examples, the use of any of the viruses in the table is not mandatory and manufacturers are invited to consider other viruses, especially those which may be more appropriate for their individual production processes. Generally, the process should be assessed for its ability to clear at least three different viruses with differing characteristics.

These viruses are examples only and their use is not mandatory.

Table A.1 Examples of Viruses Which Have Been Used in Viral Clearance Studies

Virus	Family	Genus	Natural host	Genome	Env	Size (nm)	Shape	Resistance[a]
Vesicular stomatitis virus	Rhabdo	*Vesiculovirus*	Equine Bovine	RNA	Yes	70 × 150	Bullet	Low
Parainfluenza virus	Paramyxo	*Paramyxovirus*	Various	RNA	Yes	100–200+	Pleo/Spher	Low
MuLV	Retro	*Type C oncovirus*	Mouse	RNA	Yes	80–110	Spherical	Low
Sindbis virus	Toga	*Alphavirus*	Human	RNA	Yes	60–70	Spherical	Low
BVDV	Flavi	*Pestivirus*	Bovine	RNA	Yes	50–70	Pleo-Spher	Low
Pseudorabies virus	Herpes		Swine	DNA	Yes	120–200	Spherical	Med
Poliovirus Sabin type 1	Picorna	*Enterovirus*	Human	RNA	No	25–30	Icosahedral	Med
Encephalomyo-carditis virus (EMC)	Picorna	*Cardiovirus*	Mouse	RNA	No	25–30	Icosahedral	Med
Reovirus 3	Reo	*Orthoreovirus*	Various	RNA	No	60–80	Spherical	Med
SV40	Papova	*Polyomavirus*	Monkey	DNA	No	40–50	Icosahedral	Very high
Parvoviruses (canine, porcine)	Parvo	*Parvovirus*	Canine Porcine	DNA	No	18–24	Icosahedral	Very high

[a] Resistance to physicochemical treatments based on studies of production processes. Resistance is relative to the specific treatment and it is used in the context of the understanding of the biology of the virus and the nature of the manufacturing process. Actual results will vary according to the treatment.

Appendix 3: Statistical Considerations for Assessing Virus Assays

Virus titrations suffer the problems of variation common to all biological assay systems. Assessment of the accuracy of the virus titrations and reduction factors derived from them and the validity of the assays should be performed to define the reliability of a study. The objective of statistical evaluation is to establish that the study has been carried out to an acceptable level of virological competence.

1. Assay methods may be either quantal or quantitative. Quantal methods include infectivity assays in animals or in tissue-culture-infectious-dose assays, in which the animal or cell culture is scored as either infected or not. Infectivity titers are then measured by the proportion of animals or culture infected. In quantitative methods, the infectivity measured varies continuously with the virus input. Quantitative methods include plaque assays where each plaque counted corresponds to a single infectious unit. Both quantal and quantitative assays are amenable to statistical evaluation.
2. Variation can arise within an assay as a result of dilution errors, statistical effects, and differences within the assay system which are either unknown or difficult to control. These effects are likely to be greater when different assay runs are compared (between-assay variation) than when results within a single assay run are compared (within-assay variation).
3. The 95% confidence limits for results of within-assay variation normally should be on the order of ± 0.5 $\log_{10}$ of the mean. Within-assay variation can be assessed by standard textbook methods. Between-assay variation can be monitored by the inclusion of a reference preparation, the estimate of whose potency should be within approximately 0.5 $\log_{10}$ of the mean estimate established in the laboratory for the assay to be acceptable. Assays with lower precision may be acceptable with appropriate justification.
4. The 95% confidence limits for the reduction factor observed should be calculated wherever possible in studies of clearance of "relevant" and specific "model" viruses. If the 95% confidence limits for the viral assays of the starting material are $+s$, and for the viral assays of the material after the step are $+a$, the 95% confidence limits for the reduction factor are

$$\pm\sqrt{S^2 + a^2} \quad 1$$

Probability of Detection of Viruses at Low Concentrations

At low virus concentrations (e.g., in the range of 10 to 1000 infectious particles per liter), it is evident that a sample of a few milliliters may or may not contain infectious particles. The probability, p, that this sample does not contain infectious viruses is

$$p = \left(\frac{(V - v)}{V}\right)^n$$

where V (liter) is the overall volume of the material to be tested, v (liter) is the volume of the sample and n is the absolute number of infectious particles statistically distributed in V.

If $V \gg v$, this equation can be approximated by the Poisson distribution:

$$p = \mathrm{e}^{-cv}$$

where c is the concentration of infectious particles per liter

$$or, c = \ln \frac{p}{-v}$$

As an example, if a sample volume of 1 mL is tested, the probabilities p at virus concentrations ranging from 10 to 1000 infectious particles per liter are

c	10	100	1000
p	0.99	0.90	0.37

This indicates that for a concentration of 1000 viruses per liter, in 37% of sampling, 1 mL will not contain a virus particle.

If only a portion of a sample is tested for virus and the test is negative, the amount of virus which would have to be present in the total sample in order to achieve a positive result should be calculated and this value taken into account when calculating a reduction factor. Confidence limits at 95% are desirable. However, in some instances, this may not be practical due to material limitations.

Appendix 4: Calculation of Reduction Factors in Studies to Determine Viral Clearance

The virus reduction factor of an individual purification or inactivation step is defined as the $\log_{10}$ of the ratio of the virus load in the prepurification material and the virus load in the postpurification material which is ready for use in the next step of the process. If the following abbreviations are used:

Starting material:

vol v'; titer $10^{a'}$;
virus load: $(v')(10^{a'})$,

Final material:

vol v''; titer $10^{a''}$;
virus load: $(v'')(10^{a''})$,

the individual reduction factors Ri are calculated according to

$$10^{Ri} = \frac{(v')(10^{a'})}{(v'')(10^{a''})}$$

This formula takes into account both the titers and volumes of the materials before and after the purification step.

Because of the inherent imprecision of some virus titrations, an individual reduction factor used for the calculation of an overall reduction factor should be greater than 1.

The overall reduction factor for a complete production process is the sum logarithm of the reduction factors of the individual steps. It represents the logarithm of the ratio of the virus load at the beginning of the first process clearance step and at the end of the last process clearance step. Reduction factors are normally expressed on a logarithmic scale which implies that, while residual virus infectivity will never be reduced to zero, it may be greatly reduced mathematically.

Appendix 5: Calculation of Estimated Particles per Dose

This is applicable to those viruses for which an estimate of starting numbers can be made, such as endogenous retroviruses.

Example:

I. Assumptions

Measured or estimated concentration of virus in cell culture harvest $= 10^6/\text{mL}$
Calculated viral clearance factor $= >10^{15}$
Volume of culture harvest needed to make a dose of product $= 1$ L ($l0^3$ mL)

II. Calculation of Estimated Particles/Dose

$$\frac{(10^6 \text{ virus units/ml}) \times (10^3 \text{ ml/dose})}{\text{Clearance factor} > 10^{15}}$$

$$= \frac{10^9 \text{particles/dose}}{\text{Clearance factor} > 10^{15}}$$

$$= < 10^{-6} \text{ particles/dose}$$

Therefore, less than one particle per million doses would be expected.

7

Analysis of the Expression Construct in Cells Used for Production of rDNA-Derived Protein Products

I. INTRODUCTION

This document presents guidance regarding the characterization of the expression construct for the production of recombinant DNA protein products in eukaryotic and prokaryotic cells. This document is intended to describe the types of information that are considered valuable in assessing the structure of the expression construct used to produce recombinant DNA-derived proteins. This document is not intended to cover the whole quality aspect of rDNA-derived medicinal products.

The expression construct is defined as the expression vector containing the coding sequence of the recombinant protein. Segments of the expression construct should be analyzed using nucleic acid techniques in conjunction with other tests performed on the purified recombinant protein for assuring the quality and consistency of the final product. Analysis of the expression construct at the nucleic acid level should be considered as part of the overall evaluation of quality, taking into account that this testing only evaluates the coding sequence of a recombinant gene and not the translational fidelity nor other characteristics of the recombinant protein, such as secondary structure, tertiary structure, and posttranslational modifications.

II. RATIONALE FOR ANALYSIS OF THE EXPRESSION CONSTRUCT

The purpose of analyzing the expression construct is to establish that the correct coding sequence of the product has been incorporated into the host cell and is maintained during culture to the end of production. The genetic sequence of recombinant proteins produced in living cells can undergo mutations that could alter the properties of the protein with potential adverse consequences to patients. No single experimental approach can be expected to detect all possible modifications to a protein. Protein analytical techniques can be used to assess the amino acid sequence of the protein and structural features of the expressed protein due to posttranslational modifications such as proteolytic processing, glycosylation, phosphorylation, and acetylation. Data from nucleic acid analysis may be useful since protein analytical methods may not detect all changes in protein structure resulting from mutations in the sequence coding for the recombinant protein. The relative importance of nucleic acid analysis and protein analysis will vary from product to product.

Nucleic acid analysis can be used to verify the coding sequence and the physical state of the expression construct. The nucleic acid analysis is performed to ensure that the expressed protein will have the correct amino acid sequence but is not intended to detect low levels of variant sequences. Where the production cells have multiple integrated copies of the expression construct, not all of which may be transcriptionally active, examination of the transcription product itself by analysis of mRNA or cDNA may be more appropriate than analysis of genomic DNA. Analytical approaches that examine a bulk population of nucleic acids, such as those performed on pooled clones or material amplified by the polymerase chain reaction, may be considered as an alternative to approaches that depend on selection of individual DNA clones. Other techniques could be considered that allow for rapid and sensitive confirmation of the sequence coding for the recombinant protein in the expression construct.

The following sections describe information that should be supplied regarding the characterization of the expression construct during the development and validation of the production system. Analytical methodologies should be validated for the intended purpose of confirmation of sequence. The validation documentation should at a minimum include estimates of the limits of detection for variant sequences. This should be performed for either nucleic acid or protein sequencing methods. The philosophy and recommendations for analysis expressed in this document should be periodically reviewed to take advantage of new advances in technology and scientific information.

III. CHARACTERIZATION OF THE EXPRESSION SYSTEM

A. Expression Construct and Cell Clone Used to Develop the Master Cell Bank

The manufacturer should describe the origin of the nucleotide sequence coding for the protein. This should include identification and source of the cell from which the nucleotide sequence was originally obtained. Methods used to prepare the DNA coding for the protein should be described.

The steps in the assembly of the expression construct should be described in detail. This description should include the source and function of the component parts of the expression construct, for example, origins of replication, antibiotic resistance genes, promoters, enhancers, whether or not the protein is being synthesized as a fusion protein. A detailed component map and a complete annotated sequence of the plasmid should be given, indicating those regions that have been sequenced during the construction and those taken from the literature. Other expressed proteins encoded by the plasmid should be indicated. The nucleotide sequence of the coding region of the gene of interest and associated flanking regions that are inserted into the vector, up to and including the junctions of insertion, should be determined by DNA sequencing of the construct.

A description of the method of transfer of the expression construct into the host cell should be provided. In addition, methods used to amplify the expression construct and criteria used to select the cell clone for production should be described in detail.

B. Cell Bank System

Production of the recombinant protein should be based on well-defined Master and Working Cell Banks. A cell bank is a collection of ampoules of uniform composition stored under defined conditions each containing an aliquot of a single pool of cells. The Master Cell Bank (MCB) is generally derived from the selected cell clone containing the expression construct. The Working Cell Bank (WCB) is derived by expansion of one or more ampoules of the MCB. The cell line history and production of the cell banks should be described in detail, including methods and reagents used during culture, in vitro cell age, and storage conditions. All cell banks should be characterized for relevant phenotypic and genotypic markers which could include the expression of the recombinant protein or presence of the expression construct.

The expression construct in the MCB should be analyzed as described below. If the testing cannot be carried out on the MCB, it should be carried out on each WCB.

Restriction endonuclease mapping or other suitable techniques should be used to analyze the expression construct for copy number, for insertions or deletions, and for the number of integration sites. For extrachromosomal expression systems, the percent of host cells retaining the expression construct should be determined.

The protein coding sequence for the recombinant protein product of the expression construct should be verified. For extrachromosomal expression systems, the expression construct should be isolated and the nucleotide sequence encoding the product should be verified without further cloning. For cells with chromosomal copies of the expression construct, the nucleotide sequence encoding the product could be verified by recloning and sequencing of chromosomal copies. Alternatively, the nucleic acid sequence encoding the product could be verified by techniques such as sequencing of pooled cDNA clones or material amplified by the polymerase chain reaction. The nucleic acid sequence should be identical, within the limits of detection of the methodology, to that determined for the expression construct as described in section III.A. and should correspond to that expected for the protein sequence.

C. Limit for In Vitro Cell Age for Production

The limit for in vitro cell age for production should be based on data derived from production cells expanded under pilot plant scale or full scale conditions to the proposed in vitro cell age or beyond. Generally, the production cells are obtained by expansion of the WCB; the MCB could be used to prepare the production cells with appropriate justification.

The expression construct of the production cells should be analyzed once for the MCB as described in section III.B., except that the protein coding sequence of the expression construct in the production cells could be verified by either nucleic acid testing or analysis of the final protein product. Increases in the defined limit for in vitro cell age for production should be supported by data from cells which have been expanded to an in vitro cell age which is equal to or greater than the new limit for in vitro cell age.

IV. CONCLUSION

The characterization of the expression construct and the final purified protein are both important to ensure the consistent production of a recombinant DNA-derived product. As described above, it is considered that analytical data derived from both nucleic acid analysis and evaluation of the final purified protein should be evaluated to ensure the quality of a recombinant protein product.

GLOSSARY

Expression Construct—The expression vector which contains the coding sequence of the recombinant protein and the elements necessary for its expression.

Flanking Control Regions—Noncoding nucleotide sequences that are adjacent to the 5′ and 3′ end of the coding sequence of the product which contain important elements that affect the transcription, translation, or stability of the coding sequence. These regions include, for example, promoter, enhancer, and splicing sequences and do not include origins of replication and antibiotic resistance genes.

Integration Site—The site where one or more copies of the expression construct is integrated into the host cell genome.

In vitro Cell Age—Measure of time between thaw of the MCB vial(s) to harvest of the production vessel measured by elapsed chronological time in culture, by population doubling level of the cells, or by passage level of the cells when subcultivated by a defined procedure for dilution of the culture.

Master Cell Bank (MCB)—An aliquot of a single pool of cells, which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers, and stored under defined conditions. The MCB is used to derive all working cell banks. The testing performed on a new MCB (from a previous initial cell clone, MCB, or WCB) should be the same as for the MCB unless justified.

Pilot Plant Scale—The production of a recombinant protein by a procedure fully representative of and simulating that to be applied on a full commercial manufacturing scale. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

Relevant Genotypic and Phenotypic Markers—Those markers permitting the identification of the strain of the cell line which should include the expression of the recombinant protein or presence of the expression construct.

Working Cell Bank (WCB)—The WCB is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the MCB under defined culture conditions.

8

Stability Testing of Biotechnological/Biological Products

I. PREAMBLE

The guidance stated in the ICH harmonized tripartite guideline "Stability Testing of New Drug Substances and Products" (October 27, 1993) applies in general to biotechnological/biological products. However, biotechnological/biological products do have distinguishing characteristics to which consideration should be given in any well-defined testing program designed to confirm their stability during the intended storage period. For such products, in which the active components are typically proteins and/or polypeptides, maintenance of molecular conformation and, hence of biological activity, is dependent on noncovalent as well as covalent forces. The products are particularly sensitive to environmental factors such as temperature changes, oxidation, light, ionic content, and shear. In order to ensure maintenance of biological activity and to avoid degradation, stringent conditions for their storage are usually necessary.

The evaluation of stability may necessitate complex analytical methodologies. Assays for biological activity, where applicable, should be part of the pivotal stability studies. Appropriate physicochemical, biochemical, and immunochemical methods for the analysis of the molecular entity and the quantitative detection of degradation products should also be part of the stability program whenever purity and molecular characteristics of the product permit use of these methodologies.

With the above concerns in mind, the applicant should develop the proper supporting stability data for a biotechnological/biological product and consider many external conditions which can affect the product's potency, purity, and quality. Primary data to support a requested storage period for either drug substance or drug product should be based on long-term, real-time, and real-condition stability studies. Thus, the development of a proper long-term stability program becomes critical to the successful development of a commercial product. The purpose of this document is to give guidance to applicants regarding the type of stability studies that should be provided in support of marketing applications. It is understood that during the review and evaluation process, continuing updates of initial stability data may occur.

II. SCOPE OF THE ANNEX

The guidance stated in this Annex applies to well-characterized proteins and polypeptides, their derivatives and products of which they are components, and which are isolated from tissues, body fluids, cell cultures, or produced using rDNA technology. Thus, the document covers the generation and submission of stability data for products such as cytokines (interferons, interleukins, colony-stimulating factors, tumour necrosis factors), erythropoietins, plasminogen activators, blood plasma factors, growth hormones and growth factors, insulins, monoclonal antibodies, and vaccines consisting of well-characterized proteins or polypeptides. In addition, the guidance outlined in the following sections may apply to other types of products, such as conventional vaccines, after consultation with the appropriate regulatory authorities. The document does not cover antibiotics, allergenic extracts, heparins, vitamins, whole blood, or cellular blood components.

III. TERMINOLOGY

For the basic terms used in this Annex, the reader is referred to the "Glossary" in the ICH harmonized tripartite guideline "Stability Testing of New Drug Substances and Products" (October 27, 1993). However, since manufacturers of biotechnological/biological products sometimes use traditional terminology, traditional terms are specified in parentheses to assist the reader. A supplemental glossary is also included that explains certain terms used in the production of biotechnological/biological products.

IV. SELECTION OF BATCHES

A. Drug Substance (Bulk Material)

Where bulk material is to be stored after manufacture but prior to formulation and final manufacturing, stability data should be provided on at least three batches for which manufacture and storage are representative of the manufacturing scale of production. A minimum of 6 months stability data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested. For drug substances with storage periods of less than 6 months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis. Data from pilot-plant scale batches of drug substance produced at a reduced scale of fermentation and purification may be provided at the time the dossier is submitted to the regulatory agencies with a commitment to place the first three manufacturing scale batches into the long-term stability program after approval.

The quality of the batches of drug substance placed into the stability program should be representative of the quality of the material used in preclinical and clinical studies and of the quality of the material to be made at manufacturing scale. In addition, the drug substance (bulk material) made at pilot-plant scale should be produced by a process and stored under conditions representative of that used for the manufacturing scale. The drug substance entered into the stability program should be stored in containers which properly represent the actual holding containers used during manufacture. Containers of reduced size may be acceptable for drug substance stability testing provided that they are constructed of

the same material and use the same type of container/closure system that is intended to be used during manufacture.

B. Intermediates

During manufacture of biotechnological/biological products, the quality and control of certain intermediates may be critical to the production of the final product. In general, the manufacturer should identify intermediates and generate in-house data and process limits that assure their stability within the bounds of the developed process. While the use of pilot-plant scale data is permissible, the manufacturer should establish the suitability of such data using the manufacturing scale process.

C. Drug Product (Final Container Product)

Stability information should be provided on at least three batches of final container product representative of that which will be used at manufacturing scale. Where possible, batches of final container product included in stability testing should be derived from different batches of bulk material. A minimum of 6 months data at the time of submission should be submitted in cases where storage periods greater than 6 months are requested. For drug products with storage periods of less than 6 months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis. Product expiration dating will be based upon the actual data submitted in support of the application. Since dating is based upon the real-time/real-temperature data submitted for review, continuing updates of initial stability data should occur during the review and evaluation process. The quality of the final container product placed on stability studies should be representative of the quality of the material used in the preclinical and clinical studies. Data from pilot-plant scale batches of drug product may be provided at the time the dossier is submitted to the regulatory agencies with a commitment to place the first three manufacturing scale batches into the long-term stability program after approval. Where pilot-plant scale batches were submitted to establish the dating for a product and, in the event that product produced at manufacturing scale does not meet those long-term stability specifications throughout the dating period or is not representative of the material used in preclinical and clinical studies, the applicant should notify the appropriate regulatory authorities to determine a suitable course of action.

D. Sample Selection

Where one product is distributed in batches differing in fill volume (e.g., 1 mL), 2 mL, or 10 mL), unitage (e.g., 10 units, 20 units, or 50 units), or mass (e.g., 1 mg, 2 mg, or 5 mg) samples to be entered into the stability program may be selected on the basis of a matrix system and/or by bracketing.

Matrixing, that is, the statistical design of a stability study in which different fractions of samples are tested at different sampling points, should only be applied when appropriate documentation is provided that confirms that the stability of the samples tested represents the stability of all samples. The differences in the samples for the same drug product should be identified as, for example, covering different batches, different strengths, different sizes of the same closure, and possibly, in some cases, different container/closure systems. Matrixing should not be applied to samples with differences that may affect stability, such as different strengths and different containers/closures, where it cannot be confirmed that the products respond similarly under storage conditions.

Where the same strength and exact container/closure system is used for three or more fill contents, the manufacturer may elect to place only the smallest and largest container size into the stability program, that is, bracketing. The design of a protocol that incorporates bracketing assumes that the stability of the intermediate condition samples are represented by those at the extremes. In certain cases, data may be needed to demonstrate that all samples are properly represented by data collected for the extremes.

V. STABILITY-INDICATING PROFILE

On the whole, there is no single stability-indicating assay or parameter that profiles the stability characteristics of a biotechnological/biological product. Consequently, the manufacturer should propose a stability-indicating profile that provides assurance that changes in the identity, purity, and potency of the product will be detected.

At the time of submission, applicants should have validated the methods that comprise the stability-indicating profile and the data should be available for review. The determination of which tests should be included will be product-specific. The items emphasized in the following subsections are not intended to be all-inclusive, but represent product characteristics that should typically be documented to adequately demonstrate product stability.

A. Protocol

The dossier accompanying the application for marketing authorization should include a detailed protocol for the assessment of the stability of both drug substance and drug product in support of the proposed storage conditions and expiration dating periods. The protocol should include all necessary information which demonstrates the stability of the biotechnological/biological product throughout the proposed expiration dating period including, for example, well-defined specifications and test intervals. The statistical methods that should be used are described in the tripartite guideline on stability.

B. Potency

When the intended use of a product is linked to a definable and measurable biological activity, testing for potency should be part of the stability studies. For the purpose of stability testing of the products described in this guideline, potency is the specific ability or capacity of a product to achieve its intended effect. It is based on the measurement of some attribute of the product and is determined by a suitable quantitative method. In general, potencies of biotechnological/biological products tested by different laboratories can be compared in a meaningful way only if expressed in relation to that of an appropriate reference material. For that purpose, a reference material calibrated directly or indirectly against the corresponding national or international reference material should be included in the assay.

Potency studies should be performed at appropriate intervals as defined in the stability protocol and the results should be reported in units of biological activity calibrated, whenever possible, against nationally or internationally recognized standard. Where no national or international reference standards exist, the assay results may be reported in in-house derived units using a characterized reference material.

In some biotechnological/biological products, potency is dependent upon the conjugation of the active ingredient(s) to a second moiety or binding to an adjuvant. Dissociation of the active ingredient(s) from the carrier used in conjugates or adjuvants should be examined in real-time/real-temperature studies (including conditions encountered during shipment). The assessment of the stability of such products may be difficult since, in some cases, in vitro tests for biological activity and physicochemical characterization are impractical or provide inaccurate results. Appropriate strategies (e.g., testing the product prior to conjugation/binding, assessing the release of the active compound from the second moiety, in vivo assays) or the use of an appropriate surrogate test should be considered to overcome the inadequacies of in vitro testing.

C. Purity and Molecular Characterization

For the purpose of stability testing of the products described in this guideline, purity is a relative term. Because of the effect of glycosylation, deamidation, or other heterogeneities, the absolute purity of a biotechnological/biological product is extremely difficult to determine. Thus, the purity of a biotechnological/biological product should be typically assessed by more than one method and the purity value derived is method-dependent. For the purpose of stability testing, tests for purity should focus on methods for determination of degradation products.

The degree of purity, as well as individual and total amounts of degradation products of the biotechnological/biological product entered into the stability studies, should be reported and documented whenever possible. Limits of acceptable degradation should be derived from the analytical profiles of batches of the drug substance and drug product used in the preclinical and clinical studies.

The use of relevant physicochemical, biochemical, and immunochemical analytical methodologies should permit a comprehensive characterization of the drug substance and/or drug product (e.g., molecular size, charge, hydrophobicity) and the accurate detection of degradation changes that may result from deamidation, oxidation, sulfoxidation, aggregation, or fragmentation during storage. As examples, methods that may contribute to this include electrophoresis (SDS-PAGE, immunoelectrophoresis, Western blot, isoelectrofocusing), high-resolution chromatography (e.g., reversed-phase chromatography, gel filtration, ion exchange, affinity chromatography), and peptide mapping.

Wherever significant qualitative or quantitative changes indicative of degradation product formation are detected during long-term, accelerated, and/or stress stability studies, consideration should be given to potential hazards and to the need for characterization and quantification of degradation products within the long-term stability program. Acceptable limits should be proposed and justified, taking into account the levels observed in material used in preclinical and clinical studies.

For substances that cannot be properly characterized or products for which an exact analysis of the purity cannot be determined through routine analytical methods, the applicant should propose and justify alternative testing procedures.

D. Other Product Characteristics

The following product characteristics, though not specifically relating to biotechnological/biological products, should be monitored and reported for the drug product in its final container:

- Visual appearance of the product (color and opacity for solutions/suspensions; color, texture, and dissolution time for powders), visible particulates in solutions or after the reconstitution of powders or lyophilized cakes, pH, and moisture level of powders and lyophilized products.
- Sterility testing or alternatives (e.g., container/closure integrity testing) should be performed at a minimum initially and at the end of the proposed shelf life.
- Additives (e.g., stabilizers, preservatives) or excipients may degrade during the dating period of the drug product. If there is any indication during preliminary stability studies that reaction or degradation of such materials adversely effect the quality of the drug product, these items may need to be monitored during the stability program.
- The container/closure has the potential to adversely affect the product and should be carefully evaluated (see below).

VI. STORAGE CONDITIONS

A. Temperature

Since most finished biotechnological/biological products need precisely defined storage temperatures, the storage conditions for the real-time/real-temperature stability studies may be confined to the proposed storage temperature.

B. Humidity

Biotechnological/biological products are generally distributed in containers protecting them against humidity. Therefore, where it can be demonstrated that the proposed containers (and conditions of storage) afford sufficient protection against high and low humidity, stability tests at different relative humidities can usually be omitted. Where humidity-protecting containers are not used, appropriate stability data should be provided.

C. Accelerated and Stress Conditions

As previously noted, the expiration dating should be based on real-time/real-temperature data. However, it is strongly suggested that studies be conducted on the drug substance and drug product under accelerated and stress conditions. Studies under accelerated conditions may provide useful support data for establishing the expiration date, provide product stability information for future product development (e.g., preliminary assessment of proposed manufacturing changes such as change in formulation, scale-up), assist in validation of analytical methods for the stability program, or generate information which may help elucidate the degradation profile of the drug substance or drug product. Studies under stress conditions may be useful in determining whether accidental exposures to conditions other than those proposed (e.g., during transportation) are deleterious to the product and also for evaluating which specific test parameters may be the best indicators of product stability. Studies of the exposure of the drug substance or drug product to extreme conditions may help to reveal patterns of degradation; if so, such changes should be monitored under proposed storage conditions. While the tripartite guideline on stability describes the conditions of the accelerated and stress study, the applicant should note that those conditions may not be appropriate for biotechnological/biological products. Conditions should be carefully selected on a case-by-case basis.

D. Light

Applicants should consult the appropriate regulatory authorities on a case-by-case basis to determine guidance for testing.

E. Container/Closure

Changes in the quality of the product may occur due to the interactions between the formulated biotechnological/biological product and container/closure. Where the lack of interactions cannot be excluded in liquid products (other than sealed ampoules), stability studies should include samples maintained in the inverted or horizontal position (i.e., in contact with the closure), as well as in the upright position, to determine the effects of the closure on product quality. Data should be supplied for all different container/closure combinations that will be marketed.

In addition to the standard data necessary for a conventional single-use vial, the applicant should demonstrate that the closure used with a multiple-dose vial is capable of withstanding the conditions of repeated insertions and withdrawals so that the product retains its full potency, purity, and quality for the maximum period specified in the instructions-for-use on containers, packages, and/or package inserts. Such labeling should be in accordance with relevant national/regional requirements.

F. Stability After Reconstitution of Freeze-Dried Product

The stability of freeze-dried products after their reconstitution should be demonstrated for the conditions and the maximum storage period specified on containers, packages, and/or package inserts. Such labeling should be in accordance with relevant national/regional requirements.

VII. TESTING FREQUENCY

The shelf lives of biotechnological/biological products may vary from days to several years. Thus, it is difficult to draft uniform guidelines regarding the stability study duration and testing frequency that would be applicable to all types of biotechnological/biological products. With only a few exceptions, however, the shelf lives for existing products and potential future products will be within the range of 0.5 to 5 years. Therefore, the guidance is based upon expected shelf lives in that range. This takes into account the fact that degradation of biotechnological/biological products may not be governed by the same factors during different intervals of a long storage period.

When shelf lives of 1 year or less are proposed, the real-time stability studies should be conducted monthly for the first 3 months and at 3-month intervals thereafter.

For products with proposed shelf lives of greater than 1 year, the studies should be conducted every 3 months during the first year of storage, every 6 months during the second year, and annually thereafter.

While the testing intervals listed above may be appropriate in the preapproval or prelicence stage, reduced testing may be appropriate after approval or licensure where data are available that demonstrate adequate stability. Where data exist that indicate the stability of a product is not compromised, the applicant is encouraged to submit a protocol, which supports elimination of specific test intervals (e.g., 9-month testing) for postapproval/postlicensure and long-term studies.

VIII. SPECIFICATIONS

Although biotechnological/biological products may be subject to significant losses of activity, physicochemical changes, or degradation during storage, international and national regulations have provided little guidance with respect to distinct release and end of shelf life specifications. Recommendations for maximum acceptable losses of activity, limits for physicochemical changes, or degradation during the proposed shelf life have not been developed for individual types or groups of biotechnological/biological products but are considered on a case-by-case basis. Each product should retain its specifications within established limits for safety, purity, and potency throughout its proposed shelf life. These specifications and limits should be derived from all available information using the appropriate statistical methods. The use of different specifications for release and expiration should be supported by sufficient data to demonstrate that clinical performance is not affected as discussed in the tripartite guideline on stability.

IX. LABELING

For most biotechnological/biological drug substances and drug products, precisely defined storage temperatures are recommended. Specific recommendations should be stated, particularly for drug substances and drug products that cannot tolerate freezing. These conditions, and where appropriate, recommendations for protection against light and/or humidity, should appear on containers, packages, and/or package inserts. Such labeling should be in accordance with relevant national/regional requirements.

GLOSSARY

Conjugated Product—A conjugated product is made up of an active ingredient (e.g., peptide, carbohydrate) bound covalently or noncovalently to a carrier (e.g., protein, peptide, inorganic mineral) with the objective of improving the efficacy or stability of the product.

Degradation Product—A molecule resulting from a change in the drug substance (bulk material) brought about overtime. For the purpose of stability testing of the products described in this guideline, such changes could occur as a result of processing or storage (e.g., by deamidation, oxidation, aggregation, proteolysis). For biotechnological/biological products, some degradation products may be active.

Impurity—Any component of the drug substance (bulk material) or drug product (final container product) which is not the chemical entity defined as the drug substance, an excipient, or other additives to the drug product.

Intermediate—For biotechnological/biological products, a material produced during a manufacturing process which is not the drug substance or the drug product but whose manufacture is critical to the successful production of the drug substance or the drug product. Generally, an intermediate will be quantifiable and specifications will be established to determine the successful completion of the manufacturing step prior to continuation of the manufacturing process. This includes

material which may undergo further molecular modification or be held for an extended period of time prior to further processing.

Manufacturing Scale Production—Manufacture at the scale typically encountered in a facility intended for product production for marketing.

Pilot-Plant Scale—The production of the drug substance or drug product by a procedure fully representative of and simulating that to be applied at manufacturing scale. The methods of cell expansion, harvest, and product purification should be identical except for the scale of production.

Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products

I. INTRODUCTION

A. Objective

The objective of this guideline is to provide broad guidance on appropriate standards for the derivation of human and animal cell lines and microbial cells to be used to prepare biotechnological/biological products defined in section 1.3, Scope, and for the preparation and characterization of cell banks to be used for production. The document, therefore, provides recommendations on the information in these areas that should be presented in market applications for these products.

B. Rationale

Historically, some quality concerns for cell-derived biological products have originated from the presence of adventitious contaminants or from the properties of the cells used to prepare the product. Recombinant DNA (rDNA)-derived products also carry quality concerns regarding the expression construct contained in the cell substrate. Thus, it is well established that the properties of the cell substrate and events linked to the cell substrate can affect resultant product quality and safety and, further, that effective quality control of these products requires appropriate controls on all aspects of handling the cell substrate.

This document complements other guidelines to provide a comprehensive approach to quality issues arising from biological aspects of processing products from metazoan and microbial cell culture.

C. Scope

This guideline covers cell substrates having a cell banking system. In this document, "cell substrate" refers to microbial cells or cell lines derived from human or animal sources that possess the full potential for generation of the desired biotechnological/biological products for human in vivo or ex vivo use. Reagents for in vitro diagnostic use are outside the scope of this document. Animal sources of cell lines include all those of metazoan origin. Both continuous cell lines of indefinite in vitro life span and diploid cells of finite in vitro life span are included. Microbial sources include bacteria, fungi, yeast, and other unicellular life forms.

"Biotechnological/biological products" refers to any products prepared from cells cultivated from cell banks with the exception of microbial metabolites such as, for example, antibiotics, amino acids, carbohydrates, and other low-molecular-weight substances. Cell banks used to prepare gene therapy products or vaccines should follow the recommendations presented in this document. Some biological products, such as certain viral vaccines, are prepared in primary cell cultures derived directly from animal tissues or organs. Primary cells are not banked and therefore are not addressed by this document. However, other considerations which may apply to primary cells are discussed further in Appendix 1 of this document.

II. GUIDELINES

A. Source, History, and Generation of the Cell Substrate

1. Introduction

It is important to provide supportive documentation which describes the history of the cell substrate that is used in the manufacture of a biotechnological/biological product, as well as any parental cell line from which it was totally or partially derived. Events during the research and development phases of the cell substrate may contribute significantly to assessment of the risks associated with the use of that particular cell substrate for production. The information supplied in this regard is meant to facilitate an overall evaluation, which will ensure the quality and safety of the product.

Careful records of the manipulation of the cell substrate should be maintained throughout its development. Description of cell history is only one tool of many used for cell substrate characterization. In general, deficiencies in documented history may not, by itself, be an impediment to product approval, but extensive deficiencies will result in increased reliance on other methods to characterize the cell substrate.

2. Origin, Source, and History of Cells

The source of cells (laboratory or culture collection) from which the cell substrate was derived should be stated, and relevant references from the scientific literature should be cited. Information obtained directly from the source laboratory is preferred. When this is not available, literature references may be utilized.

For human cell lines, it is relevant to describe the following characteristics of the original donor: Tissue or organ of origin, ethnic and geographical origin, age, sex, and general physiological condition. If known, the state of health or medical history of the donor should be reported along with the results of any tests of the donor for pathogenic agents. Specifically for human diploid fibroblasts, the age of the donor may influence the in vitro life span of the cell line and this information should be provided if available. For animal cell lines, relevant descriptions of the source include species, strains, breeding conditions, tissue or organ of origin, geographical origin, age and sex, the results of tests for pathogenic agents, and general physiological condition of the original donor.

For microbes, manufacturers should describe the species, strain, and known genotypic and phenotypic characteristics of the organism from which the cell substrate was derived. Manufacturers should also describe the pathogenicity, toxin production, and other biohazard information, if any.

The cultivation history of the cells should be documented. The method originally used for the isolation of the cells should be described as well as the procedures used in the culturing of the cells in vitro and any procedures used to establish cell lines (e.g., use of any physical, chemical, or biological procedure, or added nucleotide sequences). A description of any genetic manipulation or selection should be provided. All available information regarding the identification, characteristics, and results of testing of these cells for endogenous and adventitious agents should be provided.

For continuous cell lines of metazoan origin, it is usually adequate to quantitate culture duration by estimation of either number of population doublings, or number of subcultivations at defined dilution ratio, or time in days. For diploid cell lines possessing finite in vitro life span, accurate estimation of the number of population doublings during all stages of research, development, and manufacturing is important. For microbial cells, documentation of subcultivation frequency after cell substrate generation is considered adequate.

Regarding the generation of cell substrates, applicants should provide a thorough discussion of procedures which would provide exposure to infectious agents. Constituents of the culture medium should be described, in particular, information regarding exposure of the cells to materials of human or animal origin such as serum, enzymes, hydrolysates, or other living cells. The description should include the source, method of preparation and control, test results, and quality assurance. Relevant literature on these points may be referenced when available. This information will allow a detailed analysis of potential entry routes for adventitious agents from these sources, and will be part of the risk–benefit analysis of the product.

3. Generation of the Cell Substrate

A crucial step is the choice of a suitable parental cell line. For recombinant products, a parental cell line is typically the untransfected recipient cell line. The use of characterized parental cell banks is suggested, but is not considered essential. A characterized parental cell bank may be of benefit, especially when multiple cell substrates are generated from the same parental cell type, by providing a set of information on which the quality assessment of the Master Cell Bank (MCB) can be based. For example, the myeloma cell line may be banked as a parental cell line for hybridomas.

During the generation of the cell substrate, one or more specific procedures may be utilized in the ultimate development of the desired characteristics. These may include, for example, cell fusion, transfection, selection, colony isolation, cloning, gene amplification, and adaptation to specific culture conditions or media. Information regarding the methodologies utilized in developing the cell substrate can help to provide a clear understanding of the history of the cell substrate. Some cell substrates such as human diploid fibroblasts may not need extensive manipulation or cloning prior to cell banking.

For recombinant products, the cell substrate is the transfected cell containing the desired sequences, which has been cloned from a single cell progenitor. For further information on generation of rDNA-modified cell substrates, consult other relevant (e.g., regional or international) guidelines. For nonrecombinant products or nonrecombinant vaccines, the cell substrate is the cell from the parental cell line chosen for preparation of the MCB without further modification. For products derived from hybridomas, the cell substrate is the hybridoma cell line derived by fusion of the parental myeloma cell line with other parental cells, for example, immune spleen cells.

B. Cell Banking

One of the most important advantages of using serially subcultivated cells to produce biotechnological/biological products is the ability to have a characterized common starting source for each production lot, that is, the preserved bank of cells. Manufacturers may prepare their own cell banks, or may obtain them from external sources. Manufacturers are responsible for ensuring the quality of each cell bank and of the testing performed on each bank.

1. Cell Banking System

The concept of a two-tiered cell bank, in which the MCB which is used to generate Working Cell Banks (WCBs), is generally accepted as the most practical approach to providing a supply of cell substrate for continued manufacture of the product. Manufacturers should describe their strategy for providing a continued supply of cells from their cell bank(s), including the anticipated utilization rate of the cell bank(s) for production, the expected intervals between generation of new cell bank(s), and the criteria for qualification of cell bank(s).

Generally, the MCB is made first, usually directly from an initial clone or from a preliminary cell bank derived from an initial clone. It is not considered necessary to prepare cell banks from clones for certain types of cells (e.g., diploid cells, where limited in vitro life span or other technical factors make cell cloning impractical) or where the uncloned cell population is already adequately homogeneous for the intended use.

A WCB is derived from one or more containers of the MCB. It is the WCB which is typically used to directly provide cells for the manufacturing process. Additional WCBs are generated from the MCB as needed. A newly prepared WCB should be appropriately qualified by characterization and testing.

It should be noted that the MCB and WCB may differ from each other in certain respects, for example, culture components and culture conditions. Similarly, the culture conditions used to prepare the MCB and WCB may differ from those used for the production process. If changes in cell culture process do not affect product quality, it is not considered necessary to reclone the cells or to rebank the MCB or WCB. It is important that a characterized bank provides a consistent product.

A single-tiered banking system consisting only of the MCB but no WCBs could be used in principle, for example, if relatively few containers were needed each year to produce the desired product.

In some microbial expression systems, a new transformation is performed for each new cell substrate container lot, based upon using aliquots of thoroughly tested host cell banks and plasmid banks for each new transformation and on testing of each transformed cell substrate bank. This transformed cell substrate bank is considered the MCB, and it is used as the source of cell substrate for production. Host cell banks, plasmid banks, and MCBs are maintained by appropriate preservation methods. This alternative system is considered adequate because the transformation of bacteria and yeast is generally a very reproducible and easily performed process, unlike the events needed for transfection of metazoan cells. Manufacturers should provide information on the host cells, rDNA molecules (such

as plasmids), method of transformation and of cell banking, and the results of characterization studies.

2. Cell Banking Procedures

It is important to prevent a contaminated cell substrate (or bank) from being used in production and to avoid a loss of product availability or development time resulting from the need to recreate a cell bank found to be unusable due to contamination. It is recognized that no cell bank testing regimen is able to detect all potential contaminants; therefore, use of these preventive principles during cell banking is important to provide reasonable assurance of the absence of contamination and to provide a reliable source of the cell substrate.

Manufacturers should describe the type of banking system used, the size of the cell bank(s), the container (vials, ampoules, or other appropriate vessels) and closure system used, the methods used for preparation of the cell bank(s) including the cryoprotectants and media used, and the conditions employed for cryopreservation and storage.

Manufacturers should describe the procedures used to avoid microbial contamination and cross-contamination by other cell types present in the laboratory, and the procedures that allow the cell bank containers to be traced. This should include a description of the documentation system as well as that of a labeling system, which can withstand the process of preservation, storage, and recovery from storage without loss of labeling information on the container.

Manufacturers should describe their cell banking procedures. Cells are generally prepared for banking by expanding cultures in a progressively greater number or larger size of vessel until a pool of cells can be obtained which is sufficient to generate enough containers for the bank. To ensure the uniform composition of the contents of each container, a single pool of cells for banking should be prepared by combining the cells from all of the culture vessels, if more than one vessel is used.

Cells suspended in preservation medium are aliquoted from the single pool into sterilized containers which are then sealed and stored under appropriate conditions. For example, animal cells in media containing a cryoprotectant are frozen in the sealed containers under defined and controlled conditions, and then transferred to storage in the vapor or liquid phase of liquid nitrogen or at equivalent ultralow temperatures. Other methods of preservation and storage may be adequate depending on the organism used, but they should be capable of maintaining a level of cell viability upon reconstitution which is both consistent and adequate for production use.

To ensure continuous, uninterrupted production of pharmaceuticals, manufacturers should carefully consider the steps that can be taken to provide for protection from catastrophic events that could render the cell bank unusable. Examples of these events include fires, power outages, and human error. Manufacturers should describe their plans for such precautions; for example, these may include redundancy in the storage of bank containers in multiple freezers, use of back-up power, use of automatic liquid nitrogen fill systems for storage units, storage of a portion of the MCB and WCB at remote sites, or regeneration of the MCB.

The starting point of reference for estimates of in vitro cell age during manufacturing should be the thawing of one or more containers of the MCB. For diploid cell lines, in vitro life span should be estimated in terms of population doubling levels. The population doubling level at which senescence occurs should be determined for diploid cells.

C. General Principles of Characterization and Testing of Cell Banks

The characterization and testing of banked cell substrates is a critical component of the control of biotechnological and biological products. Characterization of the MCB allows the manufacturer to assess this source with regard to presence of cells from other lines, adventitious agents, endogenous agents, and molecular contaminants (e.g., toxins or antibiotics from the host organism). The objective of this testing is to confirm the identity, purity, and suitability of the cell substrate for manufacturing use. In some cases, additional testing such as tumorigenicity or karyology may be useful. The testing program chosen for a given cell substrate will vary according to the biological properties of the cells (e.g., growth requirements), its cultivation history (including use of human-derived and animal-derived biological reagents), and available testing procedures. The extent of characterization of a cell substrate may influence the type or level of routine testing needed at later stages of manufacturing. Manufacturers should perform tests for identity and purity once for each MCB, and tests of stability during cell cultivation once for each product to be registered. In addition, tests of purity and limited tests of identity should be performed once on each WCB. Also, applicants should consult the ICH guideline on viral safety. Relevant tests among those described below should be performed and described in the market application, along with the results of the testing.

For cell lines containing exogenously assembled expression constructs, the relevant ICH guideline on rDNA expression constructs should be consulted for guidance on the characterization of nucleotide and amino acid sequences. It may also be useful to examine, by similar methods, the coding sequences in some nonrecombinant DNA-derived cell lines where the gene sequences have been characterized and are well understood. However, it is not considered necessary to carry out investigations of the sequences encoding complex natural products, for example, families of related gene products, microbial vaccine antigens, or monoclonal antibodies from hybridomas.

Manufacturers are also encouraged to employ "state-of-the-art" methods and technological improvements in cell substrate characterization and testing as they become available, as long as the specificity, sensitivity, and precision of the newer methods are at least equivalent to those of existing methods.

The manufacturer may choose to characterize WCB instead of the MCB, if justified.

1. Tests of Identity

Appropriate tests should be performed to determine that the banked cell is what it is represented to be. Either phenotypic or genotypic characteristics may be used in identity testing. It is not considered necessary to do all the possible tests. Tests of identity are generally performed on the MCB. In addition, limited identity testing is generally performed on each WCB.

a. Metazoan Cells

For human or animal cells which grow attached to a substratum, morphological analysis may be a useful tool in conjunction with other tests. In most cases, isoenzyme analysis is sufficient to confirm the species of origin for cell lines derived from human or animal sources; other tests may be appropriate depending on the history of the cell line. Other technologies may be substituted to confirm species of origin, including, for example, banding cytogenetics or use of

species-specific antisera. An alternative strategy would be to demonstrate the presence of unique markers, for example, by using banding cytogenetics to detect a unique marker chromosome, or DNA analysis to detect a genomic polymorphism pattern (e.g., restriction fragment length polymorphism, variable number of tandem repeats, or genomic dinucleotide repeats). Either confirmation of species of origin or presence of known unique cell line markers is considered an adequate test of identity. Expression of the desired product may represent a complementary approach to confirmation of identity.

b. Microbial Cells

For most microbial cells, analysis of growth on selective media is usually adequate to confirm host cell identity at the species level for the host cell bank and the transformed cell bank. For *Escherichia coli*, where a variety of strains may be used, biological characterization methods such as phage typing should be considered as supplementary tests of identity. For plasmid banks, identity assessment can be accomplished as described by the ICH document on analysis of the expression construct. Expression of the desired product is also considered adequate to confirm the identity of the microbial expression system.

2. Tests of Purity

A critical aspect of cell development and banking is the assessment that the MCB and WCB are biologically pure, that is, are free from adventitious microbial agents and adventitious cellular contaminants. The impact of selective agents and antibiotics on the detection of adventitious microbial contaminants should be considered when planning and performing these tests.

a. Metazoan Cells

Tests for the presence of bioburden (bacteria and fungi) should be performed on individual containers (1% of the total number but not less than two containers) of the MCB and WCB. In all other aspects, the current methodologies described in either the European Pharmacopoeia (Ph. Eur.), the Japanese Pharmacopoeia (JP) or the U.S. Pharmacopoeia (USP) for testing microbial limits or microbial sterility may be considered adequate.

Tests for the presence of mycoplasma should be performed on the MCB and WCB. Current procedures considered adequate include both the agar and broth media procedures as well as the indicator cell culture procedure. Current methods for mycoplasma testing are described in Ph. Eur., JP, and "Points to Consider in the Characterisation of Cell Lines Used to Produce Biologicals" (FDA, CBER, 1993). Testing cells derived from a single container is generally considered adequate. For nonmammalian animal cell lines, alternative controls and/or assay conditions may be appropriate; manufacturers should consult with the national/regional regulatory authority for appropriate methodology.

If future efforts to harmonize bioburden and mycoplasma assays are fruitful, then the scientifically appropriate harmonized assay should be used.

Virus testing of cell substrates should be designed to detect a wide spectrum of viruses by using appropriate screening tests and relevant specific tests, based on the cultivation history of the cell line, to detect possible contaminating viruses. Applicants should consult the ICH guideline on viral safety. For product classes not covered by the viral safety guideline, the current WHO documents for use of animal cells may be consulted.

The purity of cell substrates can be compromised through contamination by cell lines of the same or different species of origin. The choice of tests to be performed depends upon whether opportunities have existed for cross-contamination by other cell lines. In some cases, it may be necessary to maintain growing cultures of different cell lines in the same laboratory. During procedures in cell banking where open manipulations are performed, care should be taken to ensure that simultaneous open manipulations of other cell lines are avoided to prevent cross-contamination. Whenever another cell line was present in the cell banking room at the same time that open cell banking procedures were being performed (such as cell expansion, pooling, or aliquoting of the chosen cell line), the cell banks should be tested for the presence of cells from (or products derived from) the second cell line. In general, the methods described in section 2.3.1 to assess cell identity are also considered adequate tests to detect cross-contamination by other cell lines. Additional assurance of lack of cross-contamination can be provided by successful preparation of the intended product from the cell substrate.

b. Microbial Cells

The design and performance of specific tests for adventitious microbial agents and adventitious cellular contaminants in microbial cell banks should take into account the properties of the banked cell, the likely contaminants based upon scientific literature, source, methods and materials used for cultivation, and other organisms present in the banking laboratory. For example, visual examination of the characteristics of well-isolated colonies is suggested, using several microbiological media, of which some do and some do not support growth of the cell substrate. However, it is not intended that manufacturers necessarily characterize resistant mutants of the cell substrate arising from such studies, or other artifacts of such assays. Rather, the purpose of such assays is to detect existing contaminants.

3. Cell Substrate Stability

Another dimension to cell characterization is appropriateness for intended use in production. There are two concerns for cell substrate stability: consistent production of the intended product and retention of production capacity during storage under defined conditions.

For the evaluation of stability during cultivation for production, at least two time points should be examined, one using cells which have received a minimal number of subcultivations, and another using cells at or beyond the limit of in vitro cell age for production use described in the marketing application. The limit of in vitro cell age for production use should be based on data derived from production cells expanded under pilot plant scale or commercial scale conditions to the proposed limit of in vitro cell age for production use or beyond. Generally, the production cells are obtained by expansion of cells from the WCB; cells from the MCB could be used with appropriate justification. This demonstration of cell substrate stability is commonly performed once for each product marketing application.

Evaluation of the cell substrate with respect to the consistent production of the intended product of interest should be the primary subject of concern. The type of testing and test article(s) used for such assessments will depend on the nature of the cell substrate, the cultivation methods, and the product. For cell lines containing recombinant DNA expression constructs, consistency of the coding sequence of the expression construct should be verified in cells cultivated to

the limit of in vitro cell age for production use or beyond by either nucleic acid testing or product analysis, as described in the relevant ICH guideline. For nonrecombinant cell lines in which the coding sequence for the desired product has already been analyzed at the MCB or WCB level, invariability of the protein coding sequence during production should be verified in the production cells cultivated to the proposed limit of in vitro cell age for production use or beyond by either nucleic acid testing or analysis of the purified protein product.

Where the product cannot be analyzed as described above, other specific traits which may include, for example, morphological characteristics, growth characteristics, biochemical markers, immunological markers, productivity of the desired product, or other relevant genotypic or phenotypic markers may be useful for the assessment of cell substrate stability. In some cases, where direct comparison of the characteristics of the MCB with those of the production cells at or beyond the limit of in vitro cell age is difficult or impossible, one may compare the characteristics of cells at the initial stages of cultivation or production to those of cells at or beyond the limit of in vitro cell age for production use in order to assess cell stability during production. Indices such as, for example, oxygen or glucose consumption rates, ammonia or lactate production rates may be useful for such testing. Increases in the defined limit of in vitro cell age for production use should be supported by data from cells which have been expanded to the proposed new limit of in vitro cell age. For diploid cell lines, data should be presented that establish the finite in vitro life span of the cells from the WCB under conditions representative of those employed for manufacturing use.

Evidence for banked cell stability under defined storage conditions will usually be generated during production of clinical trial material from the banked cells. Data from the determination of cell viability when the preserved cells are reconstituted for production of clinical trial supplies will verify that the revived cells have survived the preservation process. Data from the preparation of clinical materials will demonstrate that the revived cells can be used to prepare the desired product. Available data should be clearly documented in the application dossiers, plus a proposal for monitoring of banked cell stability should be provided. The proposed monitoring can be performed at the time that one or more containers of the cryopreserved bank is thawed for production use, when the product or production consistency is monitored in a relevant way, or when one or more containers of the cryopreserved MCB is thawed for preparation of a new WCB (and the new WCB is properly qualified), as appropriate. In the case when production does not take place for a long period of time, viability testing on the cell bank used as a source of the production substrate should be performed at an interval described in the marketing application. If the viability of the cell substrate is not significantly decreased, generally no further testing of the MCB or WCB is considered necessary.

4. Tests for Karyology and Tumorigenicity

Utilization of karyology and tumorigenicity testing for evaluating the safety of a diploid cell line or characterizing a new cell line may be useful depending on the cells, the nature of the product and the manufacturing process. Extensive analysis to determine the relative abundance of aneuploid cells has not been found to be useful. Karyology need not be determined for rodent cell lines or new cell lines known to be nondiploid. However, cytogenetic analysis may be an adequate method to assess cell substrate identity or purity as described in sections 2.3.1 and 2.3.2. Repetition of tumorigenicity testing for cells with already documented evidence of tumorigenicity is not considered necessary.

For products that are highly purified and that contain no cells, karyology and tumorigenicity testing are generally not considered necessary, provided that appropriate limits for residual host cell DNA are shown to be consistently met by either process validation studies or by lot release testing.

In general, products for which the presence of live cells cannot be excluded or which have little downstream purification (e.g., some conventional live virus vaccines) will need such characterization of the cell substrate. The utility of tumorigenicity testing and chromosomal analysis for new cell substrates for unpurified products should be evaluated on a case-by-case basis. Use of cell lines known to be tumorigenic or to possess abnormal karyology should be evaluated in terms of risk–benefit for each product application when the product contains cells or when not highly purified.

Products that are manufactured in genetically unmodified MRC-5 or WI-38 cells do not need characterization of these cell substrates by karyology or tumorigenicity since extensive characterization has already been performed and published for these cell lines. However, for each MRC-5 and WI-38 WCB generated, manufacturers should confirm, once, that the cells grown in the manner to be used in production are diploid and have the expected life span.

For new or previously uncharacterized diploid cell substrates, confirmation of diploid karyology should be presented and tumorigenic potential should be established, using cells from the MCB. Methods for karyological and tumorigenicity analysis may be found in the WHO document "WHO Requirements for Use of Animal Cells as in vitro Substrates for the Production of Biologicals" (WHO Technical Report Series, in press).

GLOSSARY

Cell Bank—A cell bank is a collection of appropriate containers, whose contents are of uniform composition, stored under defined conditions. Each container represents an aliquot of a single pool of cells.

Cell Line—Type of cell population which originates by serial subculture of a primary cell population, which can be banked.

Continuous Cell Line—A cell line having an infinite capacity for growth. Often referred to as "immortal" and previously referred to as "established".

Diploid Cell Line—A cell line having a finite in vitro life span in which the chromosomes are paired (euploid) and are structurally identical to those of the species from which they were derived.

Host Cells—See Parental Cells.

In Vitro Cell Age—Measure of time between thaw of the MCB vial(s) to harvest of the production vessel measured by elapsed chronological time, by population doubling level of the cells, or by passage level of the cells when subcultivated by a defined procedure for dilution of the culture.

Metazoan—Organism of multicellular animal nature.

MCB (Master Cell Bank)—An aliquot of a single pool of cells which generally has been prepared from

the selected cell clone under defined conditions, dispensed into multiple containers, and stored under defined conditions. The MCB is used to derive all working cell banks. The testing performed on a new MCB (from a previous initial cell clone, MCB or WCB) should be the same as for the MCB unless justified.

Parental Cells—Cell to be manipulated to give rise to a cell substrate or an intermediate cell line. For microbial expression systems, it is typical to also describe the parental cells as the host cell. For hybridomas, it is typical to also describe the parental cells as the cells to be fused.

WCB (Working Cell Bank)—The Working Cell Bank is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the MCB under defined culture conditions.

REFERENCE

ICH Harmonized Tripartite Guideline Q5A(R1), US Food and Drug Administration 1998.

Appendix 1: Primary Cell Substrates

Introduction

The principles contained in this document apply in general to biotechnological/biological products prepared from characterized banked cells. However, a number of biological products, in particular certain viral vaccines, are prepared using primary cells.

Because primary cell cultures are used within the first passage after establishment from the tissue of origin, it is not possible to carry out extensive characterization of the cells prior to their use as is done for banked cell substrates. In addition, biological products produced using primary cell substrates often do not undergo extensive processing (e.g., purification). Despite these differences, the approach taken to assure the suitability and safety of primary cell substrates for production of biologicals is analogous, in many respects, to that outlined in this document and in other guidelines.

This Annex outlines cell substrate-related information that should be included in marketing applications for biological products prepared using primary cells. This information falls into three general categories: (1) Information concerning the source tissue (or organ) and other animal-derived raw materials used for the establishment of primary cell substrates, (2) information concerning the preparation of primary cell substrates, and (3) testing performed on primary cell substrates to ensure the safety of the product.

Source Tissue and Other Raw Materials

Information should be provided about the animals used as a source of tissue for the preparation of primary cell substrates. Tissue should be derived from healthy animals subjected to veterinary and laboratory monitoring to certify the absence of pathogenic agents. Whenever possible, donor animals should be obtained from closed, specific pathogen-free (when available) colonies or flocks. Animals used as tissue donors should not have been used previously for experimental studies. Animals should be adequately quarantined for an appropriate period of time prior to use for the preparation of cells. In some countries, animals may need to be quarantined in the country where the primary cells are prepared. Manufacturers should consult with national/regional authorities for specific requirements.

Information on materials and components used for the preparation of primary cell substrates should be provided, including the identity and source of all reagents of human or animal origin. A description of testing performed on components of animal origin to certify the absence of detectable contaminants and adventitious agents should be included.

Preparation of Primary Cell Substrates

Methods used for isolation of cells from tissue, establishment of primary cell cultures, and maintenance of cultures should be described.

Testing of Primary Cell Substrates

Tests performed on primary cell substrates to qualify them for use in production should be described. As noted, the nature of primary cell substrates precludes extensive testing and characterization prior to use. Testing to demonstrate the absence of adventitious agents in these substrates is therefore conducted concurrently and may include Observation of production or uninfected control cultures before, during, and beyond the period of production; inoculation of culture fluids from production and uninfected control cultures into various susceptible indicator cell cultures capable of detecting a wide range of relevant viruses, followed by examination for cytopathic changes and testing for the presence of hemadsorbing viruses; and other tests for specific agents (such as relevant retroviruses) as necessary. Additional information concerning specific viral tests may be found in the relevant national/regional/international guidelines.

Appropriate testing regimens and test methods for cells used in the production of specific products will vary depending on the donor species used as a source of tissue, adventitious agents potentially present, the nature of the product, its intended clinical use, aspects of the manufacturing process, and the extent of testing performed on the final product. Applicants should explain and justify the approach taken with respect to their specific product.

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Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process

I. INTRODUCTION

A. Objectives of the Guideline

The objective of this document is to provide principles for assessing the comparability of biotechnological/biological products before and after changes are made in the manufacturing process for the drug substance or drug product. Therefore, this guideline is intended to assist in the collection of relevant technical information, which serves as evidence that the manufacturing process changes will not have an adverse impact on the quality, safety, and efficacy of the drug product. The document does not prescribe any particular analytical, nonclinical, or clinical strategy. The main emphasis of the document is on quality aspects.

B. Background

Manufacturers[1] of biotechnological/biological products frequently make changes to manufacturing processes[2] of products[3] both during development and after approval. Reasons for such changes include improving the manufacturing process, increasing scale, improving product stability, and complying with changes in regulatory requirements. When changes are made to the manufacturing process, the manufacturer generally evaluates the relevant quality attributes of the product to demonstrate that modifications did not occur that would adversely impact[4] the safety and efficacy of the drug product. Such an evaluation should indicate whether or not confirmatory nonclinical or clinical studies are appropriate.

While ICH documents have not specifically addressed considerations for demonstrating comparability between prechange and postchange product, several ICH documents have provided guidance for technical information and data to be submitted in marketing applications that can also be useful for assessing manufacturing process changes. This document builds upon the previous ICH guidelines and provides additional direction regarding approaches to

- comparing postchange product to prechange product following manufacturing process changes and
- assessing the impact of observed differences in the quality attributes caused by the manufacturing process change for a given product as it relates to safety and efficacy of the product.

C. Scope

The principles adopted and explained in this document[5] apply to the following:

- Proteins and polypeptides, their derivatives, and products of which they are components, for example, conjugates. These proteins and polypeptides are produced from recombinant or nonrecombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures;
- Products where manufacturing process changes are made by a single manufacturer, including those made by a contract manufacturer, who can directly compare results from the analysis of prechange and postchange product; and
- Products where manufacturing process changes are made in development or for which a marketing authorization has been granted.

The principles outlined in this document might also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids. Manufacturers are advised to consult with the appropriate regional Regulatory Authority to determine applicability.

D. General Principles

The goal of the comparability exercise is to ensure the quality, safety, and efficacy of drug product produced by a changed manufacturing process, through collection and evaluation of the relevant data to determine whether there might be any adverse impact on the drug product due to the manufacturing process changes.

The demonstration of comparability does not necessarily mean that the quality attributes of the prechange and postchange product are identical, but that they are highly similar and that the existing knowledge is sufficiently predictive to ensure that any differences in quality attributes have no adverse impact upon safety or efficacy of the drug product.

A determination of comparability can be based on a combination of analytical testing, biological assays, and, in some cases, nonclinical and clinical data. If a manufacturer can provide assurance of comparability through

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[1] For convenience, when the term "manufacturer" is used, it is intended to include any third party having a contractual arrangement to produce the intermediates, drug substance, or drug product on behalf of the marketing authorization holder (or the developer, if prior to market authorization).

[2] For convenience, when the term "manufacturing process(es)" is used, it also includes facilities and equipment that might impact on critical processing parameters and, thereby, on product quality.

[3] For convenience, when the term "product" is used without modifiers, it is intended to refer to the intermediates, drug substance, and drug product.

[4] Improvement of product quality is always desirable and encouraged. If the results of the comparability exercise indicate an improved quality suggesting a significant benefit in efficacy and/or safety, the pre- and postchange product may not be comparable. However, this result could be considered acceptable. The manufacturer is advised to consult the appropriate regional Regulatory Authority.

[5] This document applies to situations in which all three of the bulleted conditions are present.

analytical studies alone, nonclinical or clinical studies with the postchange product are not warranted. However, where the relationship between specific quality attributes and safety and efficacy has not been established, and differences between quality attributes of the pre- and postchange product are observed, it might be appropriate to include a combination of quality, nonclinical, and/or clinical studies in the comparability exercise.

To identify the impact of a manufacturing process change, a careful evaluation of all foreseeable consequences for the product should be performed. In consideration of this evaluation, appropriate criteria to define highly similar postchange product can be established. Generally, quality data on the pre- and postchange product are generated, and a comparison is performed that integrates and evaluates all data collected, for example, routine batch analyses, in-process control, process validation/evaluation data, characterization, and stability, if appropriate. The comparison of the results to the predefined criteria should allow an objective assessment of whether or not the pre- and postchange product are comparable.

Following the evaluation of the quality attributes, the manufacturer could be faced with one of several outcomes, including the list as follows:

- Based on appropriate comparison of relevant quality attributes, pre- and postchange products are highly similar and considered comparable, that is, no adverse impact on safety or efficacy profiles is foreseen;
- Although the pre- and postchange product appears highly similar, the analytical procedures used are not sufficient to discern relevant differences that can impact the safety and efficacy of the product. The manufacturer should consider employing additional testing (e.g., further characterization) or nonclinical and/or clinical studies to reach a definitive conclusion;
- Although the pre- and postchange product appears highly similar, some differences have been observed in the quality attributes of the prechange and postchange product, but it can be justified that no adverse impact on safety or efficacy profiles is expected, based on the manufacturer's accumulated experience, relevant information, and data. In these circumstances, pre- and postchange product can be considered comparable;
- Although the pre- and postchange product appears highly similar, some differences have been identified in the comparison of quality attributes and a possible adverse impact on safety and efficacy profiles cannot be excluded. In such situations, the generation and analysis of additional data on quality attributes are unlikely to assist in determining whether pre- and postchange products are comparable. The manufacturer should consider performing nonclinical and/or clinical studies;
- Differences in the quality attributes are so significant that it is determined that the products are not highly similar and are therefore not comparable. This outcome is not within the scope of this document and is not discussed further.

II. GUIDELINES

A. Considerations for the Comparability Exercise

The goal of the comparability exercise is to ascertain that pre- and postchange drug product is comparable in terms of quality, safety, and efficacy. To meet this goal, the product should be evaluated at the process step most appropriate to detect a change in the quality attributes. This may entail evaluating the product at multiple stages of manufacture. For example, even though all process changes occurred in the manufacture of the drug substance, in cases where the drug product could be impacted by the change, it might be appropriate to collect data on both the drug substance and the drug product to support the determination of comparability. Comparability can often be deduced from quality studies alone (limited or comprehensive analysis, as appropriate), but might sometimes need to be supported by comparability bridging studies. The extent of the studies necessary to demonstrate comparability will depend on the following:

- The production step where the changes are introduced;
- The potential impact of the changes on the purity as well as on the physicochemical and biological properties of the product, particularly considering the complexity and degree of knowledge of the product (e.g., impurities, product-related substances);
- The availability of suitable analytical techniques to detect potential product modifications and the results of these studies; and
- The relationship between quality attributes and safety and efficacy, based on overall nonclinical and clinical experience.

When considering the comparability of products, the manufacturer should evaluate, for example, the following:

- Relevant physicochemical and biological characterization data regarding quality attributes;
- Results from analysis of relevant samples from the appropriate stages of the manufacturing process (e.g., intermediate, drug substance, and drug product);
- The need for stability data, including those generated from accelerated or stress conditions, to provide insight into potential product differences in the degradation pathways of the product and, hence, potential differences in product-related substances and product-related impurities;
- Batches used for demonstration of manufacturing consistency;
- Historical data that provide insight into potential "drift" of quality attributes with respect to safety and efficacy, following either a single or a series of manufacturing process changes. That is, the manufacturer should consider the impact of changes over time to confirm that an unacceptable impact on safety and efficacy profiles has not occurred.

In addition to evaluating the data, manufacturers should also consider the following:

- Critical control points in the manufacturing process that affect product characteristics, for example, the impact of the process change on the quality of in-process materials, as well as the ability of downstream steps to accommodate material from a changed cell culture process;
- Adequacy of the in-process controls including critical control points and in-process testing: In-process controls for the post-change process should be confirmed, modified, or created, as appropriate, to maintain the quality of the product;
- Nonclinical or clinical characteristics of the drug product and its therapeutic indications (see section 2.5).

B. Quality Considerations

1. Analytical Techniques

The battery of tests for the comparability exercise should be carefully selected and optimized to maximize the potential for

detecting relevant differences in the quality attributes of the product that might result from the proposed manufacturing process change. To address the full range of physicochemical properties or biological activities, it might be appropriate to apply more than one analytical procedure to evaluate the same quality attribute (e.g., molecular weight, impurities, secondary/tertiary structures). In such cases, each method should employ different physicochemical or biological principles to collect data for the same parameter to maximize the possibility that differences in the product caused by a change in the manufacturing process might be detected.

It can be difficult to ensure that the chosen set of analytical procedures for the prechange product will be able to detect modifications of the product due to the limitations of the assays (e.g., precision, specificity, and detection limit) and the complexity of some products due to molecular heterogeneity. Consequently, the manufacturer should determine the following:

- Whether or not existing tests remain appropriate for their intended use or should be modified. For example, when the manufacturing process change gives rise to a different impurity profile in the host cell proteins, manufacturers should confirm that the test used to quantitate these impurities is still suitable for its intended purpose. It might be appropriate to modify the existing test to detect the new impurities.
- The need to add new tests as a result of changes in quality attributes that the existing methods are not capable of measuring. That is, when specific changes in quality attributes are expected as a result of a process change (e.g., following addition of a new raw material or modification of a chromatographic purification step), it might be appropriate to develop new analytical procedures, that is, to employ additional analytical techniques above and beyond those used previously for characterization or routine testing.

The measurement of quality attributes in characterization studies does not necessarily entail the use of validated assays but the assays should be scientifically sound and provide results that are reliable. Those methods used to measure quality attributes for batch release should be validated in accordance with ICH guidelines (ICH Q2A, Q2B, Q5C, Q6B), as appropriate.

2. Characterization

Characterization of a biotechnological/biological product by appropriate techniques, as described in ICH Q6B, includes the determination of physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants, and quantity.

When a manufacturing process change has been made that has the potential to have an impact on quality attributes, a complete or limited (but rationalized) repetition of the characterization activity conducted for the market application is generally warranted to directly compare the prechange and postchange product. However, additional characterization might be indicated in some cases. For example, when process changes result in a product characterization profile that differs from that observed in the material used during nonclinical and clinical studies or other appropriate representative materials (e.g., reference materials, marketed batches), the significance of these alterations should be evaluated. Results of comprehensive characterization of the material used in pivotal clinicial trials could provide a useful point of reference for subsequent comparability excercises.

Each of the following criteria should be considered as a key point in the conduct of the comparability exercise:

***Physicochemical Properties*:** The manufacturer should consider the concept of the desired product (and its variants) as defined in ICH Q6B when designing and conducting a comparability exercise. The complexity of the molecular entity with respect to the degree of molecular heterogeneity should also be considered. Following a manufacturing process change, manufacturers should attempt to determine that higher order structure (secondary, tertiary, and quaternary structure) is maintained in the product. If the appropriate higher order structural information cannot be obtained, a relevant biological activity assay (see biological activity below) could indicate a correct conformational structure.

***Biological Activity*:** Biological assay results can serve multiple purposes in the confirmation of product quality attributes that are useful for characterization and batch analysis, and, in some cases, could serve as a link to clinical activity. The manufacturer should consider the limitations of biological assays, such as high variability, that might prevent detection of differences that occur as a result of a manufacturing process change.

In cases where the biological assay also serves as a complement to physicochemical analysis, for example, as a surrogate assay for higher order structure, the use of a relevant biological assay with appropriate precision and accuracy might provide a suitable approach to confirm that change in specific higher order structure has not occurred following manufacturing process changes. Where physicochemical or biological assays are not considered adequate to confirm that the higher order structure is maintained, it might be appropriate to conduct a nonclinical or clinical study.

When changes are made to a product with multiple biological activities, manufacturers should consider performing a set of relevant functional assays designed to evaluate the range of activities. For example, certain proteins possess multiple functional domains that express enzymatic and receptor-mediated activities. In such situations, manufacturers should consider evaluating all relevant functional activities.

Where one or more of the multiple activities are not sufficiently correlated with clinical safety or efficacy or if the mechanism of action is not understood, the manufacturer should justify that nonclinical or clinical activity is not compromised in the postchange product.

Immunochemical Properties: When immunochemical properties are part of the characterization (e.g., for antibodies or antibody-based products), the manufacturer should confirm that postchange product is comparable in terms of the specific properties.

Purity, Impurities, and Contaminants: The combination of analytical procedures selected should provide data to evaluate whether a change in purity profile has occurred in terms of the desired product.

If differences are observed in the purity and impurity profiles of the postchange product relative to the prechange product, the differences should be evaluated to assess their potential impact on safety and efficacy. Where the change results in the appearance of new impurities, the new impurities should be identified and characterized when possible. Depending on the impurity type and amount, it might be appropriate to conduct nonclinical or clinical studies to confirm that there is no adverse impact on safety or efficacy of the drug product.

Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits for drug substance or drug product. New contaminants should be evaluated to assess their potential impact on the quality, safety, and efficacy of the product.

3. Specifications

The tests and analytical procedures chosen to define drug substance or drug product specifications alone are generally not considered adequate to assess the impact of manufacturing process changes since they are chosen to confirm the routine quality of the product rather than to fully characterize it. The manufacturer should confirm that the specifications after the process change are appropriate to ensure product quality. Results within the established acceptance criteria, but outside historical manufacturing control trends, might suggest product differences that warrant additional study or analysis. Modification, elimination, or addition of a test (i.e., in the specification) might be indicated where data suggest that the previous test is no longer relevant for routine batch analysis of the postchange product. For example, the elimination of bovine serum from the cell culture process would remove the need for related analyses. However, a widening of the acceptance criteria is generally not considered appropriate unless justified. In some cases, additional tests and acceptance criteria on the relative amount of specific new impurities might be appropriate if the impurity profile is different following the manufacturing process changes. When evaluating both the test methods and acceptance criteria for the postchange product, it is important to consider the general principles for setting specifications as defined in Q6B, that is, the impact of the changes on the validated manufacturing process, characterization studies, batch analysis data, stability data, and nonclinical and clinical experience.

4. Stability

For certain manufacturing process changes, even slight modifications of the production procedures might cause changes in the stability of the postchange product. Any change with the potential to alter protein structure or purity and impurity profiles should be evaluated for its impact on stability, since proteins are frequently sensitive to changes, such as those made to buffer composition, processing and holding conditions, and the use of organic solvents. Furthermore, stability studies might be able to detect subtle differences that are not readily detectable by the characterization studies. For example, the presence of trace amounts of a protease might only be detected by product degradation that occurs over an extended time period; or, in some cases, divalent ions leached from the container closure system might change the stability profile because of the activation of trace proteases not detected in stability studies of the prechange product. Therefore, real-time/real temperature stability studies on the product potentially affected by the change should be initiated, as appropriate.

Accelerated and stress stability studies are often useful tools to establish degradation profiles and provide a further direct comparison of prechange and postchange product. The results thus obtained might show product differences that warrant additional evaluation, and also identify conditions indicating that additional controls should be employed in the manufacturing process and during storage to eliminate these unexpected differences. Appropriate studies should be considered to confirm that suitable storage conditions and controls are selected.

ICH Q5C and Q1A(R) should be consulted to determine the conditions for stability studies that provide relevant data to be compared before and after a change.

C. Manufacturing Process Considerations

A well-defined manufacturing process with its associated process controls assures that acceptable product is produced on a consistent basis. Approaches to determining the impact of any process change will vary with respect to the specific process, the product, the extent of the manufacturer's knowledge of and experience with the process, and development data generated. The manufacturer should confirm that the process controls in the modified process provide at least similar or more effective control of the product quality, compared to those of the original process.

A careful consideration of potential effects of the planned change on steps downstream and quality parameters related to these steps is extremely important (e.g., for acceptance criteria, in-process specification, in-process tests, in-process hold times, operating limits, and validation/evaluation, if appropriate). This analysis will help identify which tests should be performed during the comparability exercise, which in-process or batch release acceptance criteria or analytical procedures should be reevaluated and which steps should not be impacted by the proposed change. For example, analysis of intermediates might suggest potential differences that should be evaluated to determine the suitability of existing tests to detect these differences in the product. The rationale for excluding parts of the process from this consideration should be justified.

While the process will change and the associated controls might be redefined, the manufacturer should confirm that prechange and postchange products are comparable. To support the comparison, it is often useful to demonstrate, for example, that specific intermediates are comparable or that the modified process has the capability to provide appropriate levels of removal for process- and product-related impurities, including those newly introduced by the process change. To support process changes for approved products, data from commercial-scale batches are generally indicated.

The process assessment should consider such factors as the criticality of the process step and proposed change, the location of the change and potential for effects on other process steps, and the type and extent of change. Information that can aid this assessment is generally available from several sources. The sources can include knowledge from process development studies, small-scale evaluation/validation studies, experience with earlier process changes, experience with equipment in similar operations, changes in similar manufacturing processes with similar products, and literature. Although information from external sources is useful to some extent, it is within the context of the specific manufacturing process and specific product that the change should be assessed.

When changes are made to a process, the manufacturer should demonstrate that the associated process controls, including any new ones, provide assurance that the modified process will also be capable of providing comparable product. The modified process steps should be reevaluated and/or revalidated, as appropriate. The in-process controls, including critical control points and in-process testing, should ensure that the postchange process is well controlled and maintains the quality of the product. Typically, reevaluation/revalidation activities for a simple change might be limited to the affected process step, if there is no evidence to indicate that there is impact on the performance of

subsequent (downstream) process steps, or on the quality of the intermediates resulting from the subsequent steps. When the change considered affects more than a single step, more extensive analysis of the change and resultant validation might be appropriate.

Demonstration of state of control with the modified/changed manufacturing process might include, but is not limited to, such items as

- establishment of modified specifications for raw, source and starting materials, and reagents;
- appropriate bioburden and/or viral safety testing of the postchange cell banks and cells at the limit of in vitro cell age for production;
- adventitious agent clearance;
- removal of product- or process-related impurities, such as residual host cell DNA and proteins; and
- maintenance of the purity level.

For approved products, an appropriate number of postchange batches should be analyzed to demonstrate consistent performance of the process.

To support the analysis of the changes and the control strategy, the manufacturer should prepare a description of the change that summarizes the prechange and the postchange manufacturing process and that clearly highlights modifications of the process and changes in controls in a side-by-side format.

D. Demonstration of Comparability during Development

During product development, it is expected that multiple changes in the manufacturing process will occur that could impact drug product quality, safety, and efficacy. Comparability exercises are generally performed to demonstrate that nonclinical and clinical data generated with prechange product are applicable to postchange product in order to facilitate further development and, ultimately, to support the marketing authorization. Comparability studies conducted for products in development are influenced by factors such as the stage of product development, the availability of validated analytical procedures, and the extent of product and process knowledge, which are limited at times due to the available experience that the manufacturer has with the process.

Where changes are introduced in development before nonclinical studies, the issue of assessing comparability is not generally raised because the manufacturer subsequently conducts nonclinical and clinical studies using the postchange product as part of the development process. During early phases of nonclinical and clinical studies, comparability testing is generally not as extensive as for an approved product. As knowledge and information accumulate, and the analytical tools develop, the comparability exercise should use available information and will generally become more comprehensive. Where process changes are introduced in late stages of development and no additional clinical studies are planned to support the marketing authorization, the comparability exercise should be as comprehensive and thorough as one conducted for an approved product. Some outcomes of the comparability studies on quality attributes can lead to additional nonclinical or clinical studies.

In order for a comparability exercise to occur during development, appropriate assessment tools should be used. Analytical procedures used during development might not be validated, but should always be scientifically sound and provide results that are reliable and reproducible. Because of the limitations of the analytical tools in early clinical development, physicochemical and biological tests alone might be considered inadequate to determine comparability, and therefore, bridging nonclinical and/or clinical studies, as appropriate, might be needed.

E. Nonclinical and Clinical Considerations

1. Factors to be Considered in Planning Nonclinical and Clinical Studies

Determinations of product comparability can be based solely on quality considerations (see section 2.2) if the manufacturer can provide assurance of comparability through analytical studies as suggested in this document. Additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish comparability. The extent and nature of nonclinical and clinical studies will be determined on a case-by-case basis in consideration of various factors, which include among others the following:

Quality findings

- Drug product—The type, nature, and extent of differences between the postchange product and the prechange product with respect to quality attributes including product-related substances, the impurity profile, stability and excipients. For example, new impurities could warrant toxicological studies for qualification.
- Results of the evaluation/validation studies on the new process including the results of relevant in-process tests.
- Availability, capability, and limitation of tests used for any comparability studies.

The nature and the level of knowledge of the product

- Product complexity, including heterogeneity and higher order structure—Physicochemical and in vitro biological assays might not be able to detect all differences in structure and/or function.
- Structure-activity relationship and strength of the association of quality attributes with safety and efficacy.
- Relationship between the therapeutic protein and endogenous proteins and the consequences for immunogenicity.
- Mode(s) of action (unknown vs. known, single vs. multiple active sites).

Existing nonclinical and clinical data relevant to the product, aspects of product use, and product class

- Therapeutic indications/target patient groups—The impact of possible differences can vary between patient groups, for example, risk for unintended immunogenicity. It may be appropriate to consider the consequences separately for each indication.
- Posology, for example, dosing regimen, route of administration—The risk of certain possible consequences of a difference, such as immunogenicity, could be higher with chronic administration as compared to short-term administration; subcutaneous administration might induce immunogenicity more often than intravenous administration.
- The therapeutic window/dose-response curve—The impact of a certain change could be different for products that have a wide therapeutic window as compared to those with a more narrow window. The safety or efficacy of products with a steep or a bell-shaped dose-response curve can be affected by minor changes in pharmacokinetics or receptor binding.

- Previous experience, for example, immunogenicity, safety—The experience with the original product or with other products in the same class can be relevant, especially with regard to rare adverse effects, for example, knowledge about the consequences of immunogenicity.
- PK/PD relation, distribution, and clearance.

2. Type of Studies

The nonclinical and clinical studies referred to in this document might include, depending on the situation, PK studies, PD studies, PK/PD studies, clinical efficacy studies, specific safety studies, immunogenicity studies, and pharmacovigilance studies. The purpose of these studies is to enable comparison of pre- and postchange product. Where appropriate, these studies should be direct comparative studies.

GLOSSARY

Comparability Bridging Study—A study performed to provide nonclinical or clinical data that allows extrapolation of the existing data from the drug product produced by the current process to the drug product from the changed process.

Comparable—A conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion.

Comparability Exercise—The activities, including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable.

Quality Attribute—A molecular or product characteristic that is selected for its ability to help indicate the quality of the product. Collectively, the quality attributes define identity, purity, potency and stability of the product, and safety with respect to adventitious agents. Specifications measure a selected subset of the quality attributes.

REFERENCES

Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin (ICH Guideline Q5A).

Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (ICH Guideline Q5B).

Stability Testing of Biotechnological/Biological Products (ICH Guideline Q5C).

Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (ICH Guideline Q5D).

Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (ICH Guideline Q6B).

Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (ICH Guideline Q7A).

Validation of Analytical Procedures (ICH Guideline Q2A).

Validation of Analytical Procedures: Methodology (ICH Guideline Q2B).

Common Technical Document (ICH Guideline M4Q).

Stability Testing of New Drug Substances and Products (ICH Guideline Q1A) (Second Revision).

Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH Guideline S6).

Statistical Principles for Clinical Trials (ICH Guideline E9).

Choice of Control Group and Related Issues in Clinical Trials (ICH Guideline E10).

11

Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

I. INTRODUCTION

A. Objective

This guidance document provides general principles on the setting and justification, to the extent possible, of a uniform set of international specifications for biotechnological and biological products to support new marketing applications.

B. Background

A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product, or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. "Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

Specifications are one part of a total control strategy designed to ensure product quality and consistency. Other parts of this strategy include thorough product characterization during development, upon which many of the specifications are based, adherence to Good Manufacturing Practices, a validated manufacturing process, raw materials testing, in-process testing, stability testing, and so on.

Specifications are chosen to confirm the quality of the drug substance and drug product rather than to establish full characterization and should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

C. Scope

The principles adopted and explained in this document apply to proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or nonrecombinant cell-culture expression systems and can be highly purified and characterized using an appropriate set of analytical procedures.

The principles outlined in this document may also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids. To determine applicability, manufacturers should consult with the appropriate regulatory authorities.

This document does not cover antibiotics, synthetic peptides and polypeptides, heparins, vitamins, cell metabolites, DNA products, allergenic extracts, conventional vaccines, cells, whole blood, and cellular blood components. A separate ICH Guideline, "Specifications: Test Procedures and Acceptance Criteria for New Drugs Substances and New Drug Products: Chemical Substances" addresses specifications, and other criteria for chemical substances.

This document does not recommend specific test procedures or specific acceptance criteria nor does it apply to the regulation of preclinical and/or clinical research material.

II. PRINCIPLES FOR CONSIDERATION IN SETTING SPECIFICATIONS

A. Characterization

Characterization of a biotechnological or biological product (which includes the determination of physicochemical properties, biological activity, immunochemical properties, purity, and impurities) by appropriate techniques is necessary to allow relevant specifications to be established. Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency and data from stability studies, and relevant development data.

Extensive characterization is performed in the development phase and, where necessary, following significant process changes. At the time of submission, the product should have been compared with an appropriate reference standard, if available. When feasible and relevant, it should be compared with its natural counterpart. Also, at the time of submission, the manufacturer should have established appropriately characterized in-house reference materials, which will serve for biological and physicochemical testing of production lots. New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate.

1. Physicochemical Properties

A physicochemical characterization program will generally include a determination of the composition, physical properties, and primary structure of the desired product. In some cases, information regarding higher-order structure of the desired product (the fidelity of which is generally inferred by its biological activity) may be obtained by appropriate physicochemical methodologies.

An inherent degree of structural heterogeneity occurs in proteins due to the biosynthetic processes used by living organisms to produce them; therefore, the desired product can be a mixture of anticipated posttranslationally modified forms (e.g., glycoforms). These forms may be active and their presence may have no deleterious effect on the safety and efficacy of the product (section 2.1.4). The manufacturer should define the pattern of heterogeneity of the desired product and demonstrate consistency with that of the lots used in preclinical and clinical studies. If a consistent pattern of product heterogeneity is demonstrated, an evaluation of the activity,

efficacy, and safety (including immunogenicity) of individual forms may not be necessary.

Heterogeneity can also be produced during manufacture and/or storage of the drug substance or drug product. Since the heterogeneity of these products defines their quality, the degree and profile of this heterogeneity should be characterized, to assure lot-to-lot consistency. When these variants of the desired product have properties comparable to those of the desired product with respect to activity, efficacy, and safety, they are considered product-related substances. When process changes and degradation products result in heterogeneity patterns, which differ from those observed in the material used during preclinical and clinical development, the significance of these alterations should be evaluated.

Analytical methods to elucidate physicochemical properties are listed in Appendix 6.1. New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate.

For the purpose of lot release (section 4), an appropriate subset of these methods should be selected and justified.

2. Biological Activity

Assessment of the biological properties constitutes an equally essential step in establishing a complete characterization profile. An important property is the biological activity that describes the specific ability or capacity of a product to achieve a defined biological effect.

A valid biological assay to measure the biological activity should be provided by the manufacturer. Examples of procedures used to measure biological activity include

- animal-based biological assays, which measure an organism's biological response to the product;
- cell culture-based biological assays, which measure biochemical or physiological response at the cellular level; and
- biochemical assays, which measure biological activities such as enzymatic reaction rates or biological responses induced by immunologic interactions.

Other procedures such as ligand and receptor binding assays, may be acceptable.

Potency (expressed in units) is the quantitative measure of biological activity based on the attribute of the product, which is linked to the relevant biological properties, whereas, quantity (expressed in mass) is a physicochemical measure of protein content. Mimicking the biological activity in the clinical situation is not always necessary. A correlation between the expected clinical response and the activity in the biological assay should be established in pharmacodynamic or clinical studies.

The results of biological assays should be expressed in units of activity calibrated against an international or national reference standard, when available and appropriate for the assay utilized. Where no such reference standard exists, a characterized in-house reference material should be established and assay results of production lots reported as in-house units.

Often, for complex molecules, the physicochemical information may be extensive but unable to confirm the higher-order structure which, however, can be inferred from the biological activity. In such cases, a biological assay, with wider confidence limits, may be acceptable when combined with a specific quantitative measure. Importantly, a biological assay to measure the biological activity of the product may be replaced by physicochemical tests only in those instances where

- sufficient physicochemical information about the drug, including higher-order structure, can be thoroughly established by such physicochemical methods, and relevant correlation to biologic activity demonstrated; and
- there exists a well-established manufacturing history.

Where physicochemical tests alone are used to quantitate the biological activity (based on appropriate correlation), results should be expressed in mass.

For the purpose of lot release (section 4), the choice of relevant quantitative assay (biological and/or physicochemical) should be justified by the manufacturer.

3. Immunochemical Properties

When an antibody is the desired product, its immunologic properties should be fully characterized. Binding assays of the antibody to purified antigens and defined regions of antigens should be performed, as feasible, to determine affinity, avidity, and immunoreactivity (including cross-reactivity). In addition, the target molecule bearing the relevant epitope should be biochemically defined and the epitope itself defined, when feasible.

For some drug substances or drug products, the protein molecule may need to be examined using immunochemical procedures (e.g., ELISA and Western-blot) utilizing antibodies which recognize different epitopes of the protein molecule. Immunochemical properties of a protein may serve to establish its identity, homogeneity or purity, or serve to quantify it.

If immunochemical properties constitute lot release criteria, all relevant information pertaining to the antibody should be made available.

4. Purity, Impurities, and Contaminants

- **Purity**

  The determination of absolute, as well as relative purity, presents considerable analytical challenges, and the results are highly method-dependent. Historically, the relative purity of a biological product has been expressed in terms of specific activity (units of biological activity per mg of product), which is also highly method-dependent. Consequently, the purity of the drug substance and drug product is assessed by a combination of analytical procedures.

  Because of the unique biosynthetic production process and molecular characteristics of biotechnological and biological products, the drug substance can include several molecular entities or variants. When these molecular entities are derived from anticipated posttranslational modification, they are part of the desired product. When variants of the desired product are formed during the manufacturing process and/or storage and have properties comparable to the desired product, they are considered product-related substances and not impurities (section 2.1.1).

  Individual and/or collective acceptance criteria for product-related substances should be set, as appropriate.

  For the purpose of lot release, (section 4), an appropriate subset of methods should be selected and justified for determination of purity.
- **Impurities**

  In addition to evaluating the purity of the drug substance and drug product, which may be composed of the desired product and multiple product-related substances, the manufacturer should also assess impurities, which may be present. Impurities may be either process or product related. They can be of known structure, partially characterized, or unidentified. When adequate quantities of

impurities can be generated, these materials should be characterized to the extent possible and, where possible, their biological activities should be evaluated.

Process-related impurities encompass those that are derived from the manufacturing process, that is, cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (see "Appendix", section 6.2.1). Product-related impurities (e.g., precursors, certain degradation products) are molecular variants arising during manufacture and/or storage, which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.

Further, the acceptance criteria for impurities should be based on data obtained from lots used in preclinical and clinical studies and manufacturing consistency lots.

Individual and/or collective acceptance criteria for impurities (product-related and process-related) should be set, as appropriate. Under certain circumstances, acceptance criteria for selected impurities may not be necessary (section 2.3).

Examples of analytical procedures, which may be employed to test for the presence of impurities, are listed in Appendix 6.2. New analytical technology and modifications to existing technology are continually being developed and should be utilized when appropriate.

For the purpose of lot release (section 4), an appropriate subset of these methods should be selected and justified.

- **Contaminants**

  Contaminants in a product include all adventitiously introduced materials not intended to be part of the manufacturing process, such as chemical and biochemical materials (e.g., microbial proteases), and/or microbial species. Contaminants should be strictly avoided and/or suitably controlled with appropriate in-process acceptance criteria or action limits for drug substance or drug product specifications (section 2.3). For the special case of adventitious viral or mycoplasma contamination, the concept of action limits is not applicable, and the strategies proposed in ICH Harmonized Tripartite Guidelines "Quality of Biotechnological/Biological Products: Viral Safety Evaluation of Biotechnology Derived Products Derived from Cell Lines of Human or Animal Origin" and "Quality of Biotechnological/Biological Products: Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products" should be considered.

5. Quantity

Quantity, usually measured as protein content, is critical for a biotechnological and biological product and should be determined using an appropriate assay, usually physicochemical in nature. In some cases, it may be demonstrated that the quantity values obtained may be directly related to those found using the biological assay. When this correlation exists, it may be appropriate to use measurement of quantity rather than the measurement of biological activity in manufacturing processes, such as filling.

B. Analytical Considerations

1. Reference Standards and Reference Materials

For drug applications for new molecular entities, it is unlikely that an international or national standard will be available. At the time of submission, the manufacturer should have established an appropriately characterized in-house primary reference material, prepared from lot(s) representative of production and clinical materials. In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material. Where an international or national standard is available and appropriate, reference materials should be calibrated against it. While it is desirable to use the same reference material for both biological assays and physicochemical testing, in some cases, a separate reference material may be necessary. Also, distinct reference materials for product-related substances, product-related impurities, and process-related impurities, may need to be established. When appropriate, a description of the manufacture and/or purification of reference materials should be included in the application. Documentation of the characterization, storage conditions, and formulation supportive of reference material(s) stability should also be provided.

2. Validation of Analytical Procedures

At the time the application is submitted to the regulatory authorities, applicants should have validated the analytical procedures used in the specifications in accordance with the ICH Harmonized Tripartite Guidelines "Validation of Analytical Procedures: Definitions and Terminology" and "Validation of Analytical Procedures: Methodology," except where there are specific issues for unique tests used for analyzing biotechnological and biological products.

C. Process Controls

1. Process-Related Considerations

Adequate design of a process and knowledge of its capability are part of the strategy used to develop a manufacturing process, which is controlled and reproducible, yielding a drug substance or drug product that meets specifications. In this respect, limits are justified based on critical information gained from the entire process spanning the period from early development through commercial scale production.

For certain impurities, testing of either the drug substance or the drug product may not be necessary and may not need to be included in the specifications if efficient control or removal to acceptable levels is demonstrated by suitable studies. This testing can include verification at commercial scale in accordance with regional regulations. It is recognized that only limited data may be available at the time of submission of an application. This concept may, therefore, sometimes be implemented after marketing authorization, in accordance with regional regulations.

2. In-Process Acceptance Criteria and Action Limits

In-process tests are performed at critical decision making steps and at other steps where data serve to confirm consistency of the process during the production of either the drug substance or the drug product. The results of in-process testing may be recorded as action limits or reported as acceptance criteria. Performing such testing may eliminate the need for testing of the drug substance or drug product (section 2.3.1). In-process testing for adventitious agents at the end of cell culture is an example of testing for which acceptance criteria should be established.

The use of internal action limits by the manufacturer to assess the consistency of the process at less critical steps is also important. Data obtained during development and validation runs should provide the basis for provisional action limits to be set for the manufacturing process. These limits, which are the responsibility of the manufacturer, may be used to initiate investigation or further action. They should be further

refined as additional manufacturing experience and data are obtained after product approval.

3. Raw Materials and Excipient Specifications

The quality of the raw materials used in the production of the drug substance (or drug product) should meet standards, appropriate for their intended use. Biological raw materials or reagents may require careful evaluation to establish the presence or absence of deleterious endogenous or adventitious agents. Procedures which make use of affinity chromatography (e.g., employing monoclonal antibodies), should be accompanied by appropriate measures to ensure that such process-related impurities or potential contaminants arising from their production and use do not compromise the quality and safety of the drug substance or drug product. Appropriate information pertaining to the antibody should be made available.

The quality of the excipients used in the drug product formulation (and in some cases, in the drug substance), as well as the container/closure systems, should meet pharmacopoeial standards, where available and appropriate. Otherwise, suitable acceptance criteria should be established for the nonpharmacopoeial excipients.

D. Pharmacopoeial Specifications

Pharmacopoeias contain important requirements pertaining to certain analytical procedures and acceptance criteria, which, where relevant, are part of the evaluation of either the drug substance or drug product. Such monographs, applicable to biotechnological and biological products, generally include, but are not limited to tests for sterility, endotoxins, microbial limits, volume in container, uniformity of dosage units, and particulate matter. With respect to the use of pharmacopoeial methods and acceptance criteria, the value of this guidance is linked to the extent of harmonization of the analytical procedures of the pharmacopoeias. The pharmacopoeias are committed to developing identical or methodologically equivalent test procedures and acceptance criteria.

E. Release Limits vs. Shelf life Limits

The concept of release limits versus shelf life limits may be applied where justified. This concept pertains to the establishment of limits, which are tighter for the release than for the shelf life of the drug substance or drug product. Examples where this may be applicable include potency and degradation products. In some regions, the concept of release limits may only be applicable to in-house limits and not to the regulatory shelf life limits.

F. Statistical Concepts

Appropriate statistical analysis should be applied, when necessary, to quantitative data reported. The methods of analysis, including justification and rationale, should be described fully. These descriptions should be sufficiently clear to permit independent calculation of the results presented.

III. JUSTIFICATION OF THE SPECIFICATION

The setting of specifications for drug substance and drug product is part of an overall control strategy which includes control of raw materials and excipients, in-process testing, process evaluation or validation, adherence to Good Manufacturing Practices, stability testing, and testing for consistency of lots. When combined in total, these elements provide assurance that the appropriate quality of the product will be maintained. Since specifications are chosen to confirm the quality rather than to characterize the product, the manufacturer should provide the rationale and justification for including and/or excluding testing for specific quality attributes. The following points should be taken into consideration when establishing scientifically justifiable specifications.

- *Specifications are linked to a manufacturing process.*
  Specifications should be based on data obtained from lots used to demonstrate manufacturing consistency. Linking specifications to a manufacturing process is important, especially for product-related substances, product-related impurities, and process-related impurities. Process changes and degradation products produced during storage may result in heterogeneity patterns, which differ from those observed in the material used during preclinical and clinical development. The significance of these alterations should be evaluated.
- *Specifications should account for the stability of drug substance and drug product.*
  Degradation of drug substance and drug product, which may occur during storage, should be considered when establishing specifications. Because of the inherent complexity of these products, there is no single stability-indicating assay or parameter that profiles the stability characteristics. Consequently, the manufacturer should propose a stability-indicating profile. The result of this stability-indicating profile will then provide assurance that changes in the quality of the product will be detected. The determination of which tests should be included will be product-specific. The manufacturer is referred to the ICH Harmonized Tripartite Guideline: "Stability Testing of Biotechnological/Biological Products."
- *Specifications are linked to preclinical and clinical studies.*
  Specifications should be based on data obtained for lots used in preclinical and clinical studies. The quality of the material made at commercial scale should be representative of the lots used in preclinical and clinical studies.
- *Specifications are linked to analytical procedures.*
  Critical quality attributes may include items such as potency, the nature and quantity of product-related substances, product-related impurities, and process-related impurities. Such attributes can be assessed by multiple analytical procedures, each yielding different results. In the course of product development, it is not unusual for the analytical technology to evolve in parallel with the product. Therefore, it is important to confirm that data generated during development correlate with those generated at the time the marketing application is filed.

IV. SPECIFICATIONS

Selection of tests to be included in the specifications is product specific. The rationale used to establish the acceptable range of acceptance criteria should be described. Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency, and data from stability studies, and relevant development data.

In some cases, testing at production stages rather than at the drug substance or drug product stages may be appropriate and acceptable. In such circumstances, test results should be considered as in-process acceptance criteria and

included in the specification of drug substance or drug product in accordance with the requirements of the regional regulatory authorities.

A. Drug Substance Specification

Generally, the following tests and acceptance criteria are considered applicable to all drug substances (for analytical procedures see section 2.2.2). Pharmacopoeial tests (e.g., endotoxin detection) should be performed on the drug substance, where appropriate. Additional drug substance specific acceptance criteria may also be necessary.

1. Appearance and Description

A qualitative statement describing the physical state (e.g., solid, liquid) and color of a drug substance should be provided.

2. Identity

The identity test(s) should be highly specific for the drug substance and should be based on unique aspects of its molecular structure and/or other specific properties. More than one test (physicochemical, biological, and/or immunochemical) may be necessary to establish identity. The identity test(s) can be qualitative in nature. Some of the methods typically used for characterization of the product as described in section 2.1 and in Appendix 6.1 may be employed and/or modified as appropriate for the purpose of establishing identity.

3. Purity and Impurities

The absolute purity of biotechnological and biological products is difficult to determine and the results are method-dependent (section 2.1.4.). Consequently, the purity of the drug substance is usually estimated by a combination of methods. The choice and optimization of analytical procedures should focus on the separation of the desired product from product-related substances and from impurities.

The impurities observed in these products are classified as process-related and product-related impurities:

- Process-related impurities (section 2.1.4) in the drug substance may include cell culture media, host cell proteins, DNA, monoclonal antibodies, or chromatographic media used in purification, solvents, and buffer components. These impurities should be minimized by the use of appropriate well-controlled manufacturing processes.
- Product-related impurities (section 2.1.4) in the drug substance are molecular variants with properties different from those of the desired product formed during manufacture and/or storage.

For the impurities, the choice and optimization of analytical procedures should focus on the separation of the desired product and product-related substances from impurities. Individual and/or collective acceptance criteria for impurities should be set, as appropriate. Under certain circumstances, acceptance criteria for selected impurities may not be required (section 2.3).

4. Potency

A relevant, validated potency assay (section 2.1.2) should be part of the specifications for a biotechnological or biological drug substance and/or drug product. When an appropriate potency assay is used for the drug product (section 4.2.4), an alternative method (physicochemical and/or biological) may suffice for quantitative assessment at the drug substance stage. In some cases, the measurement of specific activity may provide additional useful information.

5. Quantity

The quantity of the drug substance, usually based on protein content (mass), should be determined using an appropriate assay. The quantity determination may be independent of a reference standard or material. In cases where product manufacture is based upon potency, there may be no need for an alternate determination of quantity.

B. Drug Product Specification

Generally, the following tests and acceptance criteria are considered applicable to all drug products. Each section (4.2.1–4.2.5) is cross-referenced to respective sections (4.1.1–4.1.5) under Drug Substance. Pharmacopoeial requirements apply to the relevant dosage forms. Typical tests found in the pharmacopoeia include, but are not limited to sterility, endotoxin, microbial limits, volume in container, particulate matter, uniformity of dosage units, and moisture content for lyophilized drug products. If appropriate, testing for uniformity of dosage units may be performed as in-process controls and corresponding acceptance criteria set.

1. Appearance and Description

A qualitative statement describing the physical state (e.g., solid, liquid), color, and clarity of the drug product should be provided.

2. Identity

The identity test(s) should be highly specific for the drug product and should be based on unique aspects of its molecular structure and for other specific properties. The identity test(s) can be qualitative in nature. While it is recognized that in most cases, a single test is adequate, more than one test (physicochemical, biological, and/or immunochemical) may be necessary to establish identity for some products. Some of the methods typically used for characterization of the product as described in section 2.1 and in Appendix 6.1 may be employed and/or modified as appropriate for the purpose of establishing identity.

3. Purity and Impurities

Impurities may be generated or increased during manufacture and/or storage of the drug product. These may be either the same as those occurring in the drug substance itself, process-related, or degradation products which form specifically in the drug product during formulation or during storage. If impurities are qualitatively and quantitatively (i.e., relative amounts and/or concentrations) the same as in the drug substance, testing is not necessary. If impurities are known to be introduced or formed during the production and/or storage of the drug product, the levels of these impurities should be determined and acceptance criteria established.

Acceptance criteria and analytical procedures should be developed and justified, based upon previous experience with the drug product, to measure changes in the drug substance during the manufacture and/or storage of the drug product.

The choice and optimization of analytical procedures should focus on the separation of the desired product and product-related substances from impurities including degradation products, and from excipients.

4. Potency

A relevant, validated potency assay (section 2.1.2) should be part of the specifications for a biotechnological and biological drug substance and/or drug product. When an appropriate potency assay is used for the drug substance, an alternative

method (physicochemical and/or biological) may suffice for quantitative assessment of the drug product. However, the rationale for such a choice should be provided.

5. Quantity

The quantity of the drug substance in the drug product, usually based on protein content (mass), should be determined using an appropriate assay. In cases where product manufacture is based upon potency, there may be no need for an alternate determination of quantity.

6. General Tests

Physical description and the measurement of other quality attributes is often important for the evaluation of the drug product functions. Examples of such tests include pH and osmolarity.

7. Additional Testing for Unique Dosage Forms

It should be recognized that certain unique dosage forms may need additional tests other than those mentioned above.

GLOSSARY

Acceptance Criteria—Numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures which the drug substance or drug product or materials at other stages of their manufacture should meet.

Action Limit—An internal (in-house) value used to assess the consistency of the process at less critical steps.

Biological Activity—The specific ability or capacity of the product to achieve a defined biological effect. Potency is the quantitative measure of the biological activity.

Contaminants—Any adventitiously introduced materials (e.g., chemical, biochemical, or microbial species) not intended to be part of the manufacturing process of the drug substance or drug product.

Degradation Products—Molecular variants resulting from changes in the desired product or product-related substances brought about overtime and/or by the action of, for example, light, temperature, pH, water, or by reaction with an excipient and/or the immediate container/closure system. Such changes may occur as a result of manufacture and/or storage (e.g., deamidation, oxidation, aggregation, proteolysis). Degradation products may be either product-related substances, or product-related impurities.

Desired Product—(1) The protein which has the expected structure, or (2) the protein which is expected from the DNA sequence and anticipated posttranslational modification (including glycoforms), and from the intended downstream modification to produce an active biological molecule.

Drug Product (Dosage Form; Finished Product)—A pharmaceutical product type that contains a drug substance, generally, in association with excipients.

Drug Substance (Bulk Material)—The material which is subsequently formulated with excipients to produce the drug product. It can be composed of the desired product, product-related substances, and product- and process-related impurities. It may also contain excipients including other components such as buffers.

Excipient—An ingredient added intentionally to the drug substance which should not have pharmacological properties in the quantity used.

Impurity—Any component present in the drug substance or drug product, which is not the desired product, a product-related substance, or excipient including buffer components. It may be either process or product related.

In-house Primary Reference Material—An appropriately characterized material prepared by the manufacturer from a representative lot(s) for the purpose of biological assay and physicochemical testing of subsequent lots, and against which in-house working reference material is calibrated.

In-house Working Reference Material—A material prepared similarly to the primary reference material that is established solely to assess and control subsequent lots for the individual attribute in question. It is always calibrated against the in-house primary reference material.

Potency—The measure of the biological activity using a suitably quantitative biological assay (also called potency assay or bioassay), based on the attribute of the product which is linked to the relevant biological properties.

Process-Related Impurities—Impurities that are derived from the manufacturing process. They may be derived from cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g., inducers, antibiotics, or media components), or downstream processing (e.g., processing reagents or column leachables).

Product-Related Impurities—Molecular variants of the desired product (e.g., precursors, certain degradation products arising during manufacture, and/or storage) which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.

Product-Related Substances—Molecular variants of the desired product formed during manufacture and/or storage, which are active and have no deleterious effect on the safety and efficacy of the drug product. These variants possess properties comparable to the desired product and are not considered impurities.

Reference Standards—Refer to international or national standards.

Specification—A specification is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use. "Conformance to specification" means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

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APPENDICES

6.1 Appendix for Physicochemical Characterization

This appendix provides examples of technical approaches which might be considered for structural characterization and confirmation, and evaluation of physicochemical properties of the desired product, drug substance, and/or drug product. The specific technical approach employed will vary from product to product and alternative approaches, other than those included in this Appendix, will be appropriate in many cases. New analytical technology and modifications to existing technology are continuously being developed and should be utilized when appropriate.

6.1.1. Structural Characterization and Confirmation

(a) Amino acid sequence
The amino acid sequence of the desired product should be determined to the extent possible using approaches such as those described in items (b) through (e) and then compared with the sequence of the amino acids deduced from the gene sequence of the desired product.

(b) Amino acid composition
The overall amino acid composition is determined using various hydrolytic and analytical procedures, and compared with the amino acid composition deduced from the gene sequence for the desired product, or the natural counterpart, if considered necessary. In many cases, amino acid composition analysis provides some useful structural information for peptides and small proteins, but such data are generally less definitive for large proteins. Quantitative amino acid analysis data can also be used to determine protein content in many cases.

(c) Terminal amino acid sequence
Terminal amino acid analysis is performed to identify the nature and homogeneity of the amino- and carboxy-terminal amino acids. If the desired product is found to be heterogeneous with respect to the terminal amino acids, the relative amounts of the variant forms should be determined using an appropriate analytical procedure. The sequence of these terminal amino acids should be compared with the terminal amino acid sequence deduced from the gene sequence of the desired product.

(d) Peptide map
Selective fragmentation of the product into discrete peptides is performed using suitable enzymes or chemicals and the resulting peptide fragments are analyzed by HPLC or other appropriate analytical procedure. The peptide fragments should be identified to the extent possible using techniques such as amino acid compositional analysis, N-terminal sequencing, or mass spectrometry. Peptide mapping of the drug substance or drug product using an appropriately validated procedure is a method that is frequently used to confirm desired product structure for lot release purposes.

(e) Sulfhydryl group(s) and disulfide bridges
If, based on the gene sequence for the desired product, cysteine residues are expected, the number and positions of any free sulfhydryl groups and/or disulfide bridges should be determined, to the extent possible. Peptide mapping (under reducing and nonreducing conditions), mass spectrometry, or other appropriate techniques may be useful for this evaluation.

(f) Carbohydrate structure
For glycoproteins, the carbohydrate content (neutral sugars, amino sugars, and sialic acids) is determined. In addition, the structure of the carbohydrate chains, the oligosaccharide pattern (antennary profile), and the glycosylation site(s) of the polypeptide chain is analyzed, to the extent possible.

6.1.2. Physicochemical Properties

(a) Molecular weight or size
Molecular weight (or size) is determined using size exclusion chromatography, SDS-polyacrylamide gel electrophoresis (under reducing and/or nonreducing conditions), mass spectrometry, and other appropriate techniques.

(b) Isoform pattern
This is determined by isoelectric focusing or other appropriate techniques.

(c) Extinction coefficient (or molar absorptivity)
In many cases, it will be desirable to determine the extinction coefficient (or molar absorptivity) for the desired product at a particular UV/visible wavelength (e.g., 280 nm). The extinction coefficient is determined using UV/visible spectrophotometry on a solution of the product having a known protein content as determined by techniques such as amino acid compositional analysis, or nitrogen determination, and so on. If UV absorption is used to measure protein content, the extinction coefficient for the particular product should be used.

(d) Electrophoretic patterns
Electrophoretic patterns and data on identity, homogeneity, and purity can be obtained by polyacrylamide gel electrophoresis, isoelectric focusing, SDS-polyacrylamide gel electrophoresis, Western-blot, capillary electrophoresis, or other suitable procedures.

(e) Liquid chromatographic patterns
Chromatographic patterns and data on the identity, homogeneity, and purity can be obtained by size exclusion chromatography, reverse-phase liquid chromatography, ion-exchange liquid chromatography, affinity chromatography, or other suitable procedures.

(f) Spectroscopic profiles
The ultraviolet and visible absorption spectra are determined as appropriate. The higher-order structure of the product is examined using procedures such as circular dichroism, nuclear magnetic resonance (NMR), or other suitable techniques, as appropriate.

6.2 Appendix for Impurities

This appendix lists potential impurities, their sources, and examples of relevant analytical approaches for detection. Specific impurities and technical approaches employed, as in the case of physicochemical characterization, will vary from product to product and alternative approaches, other than those listed in this appendix will be appropriate in many

cases. New analytical technology and modifications to existing technology are continuously being developed, and should be applied when appropriate.

6.2.1. Process-Related Impurities and Contaminants

These are derived from the manufacturing process (section 2.1.4) and are classified into three major categories: cell substrate-derived, cell culture-derived, and downstream-derived.

(a) Cell substrate-derived impurities include, but are not limited to, proteins derived from the host organism and nucleic acid (host cell genomic, vector, or total DNA). For host cell proteins, a sensitive assay for example, immunoassay, capable of detecting a wide range of protein impurities is generally utilized. In the case of an immunoassay, a polyclonal antibody used in the test is generated by immunization with a preparation of a production cell minus the product-coding gene, fusion partners, or other appropriate cell lines. The level of DNA from the host cells can be detected by direct analysis on the product (such as hybridization techniques). Clearance studies, which could include spiking experiments at the laboratory scale, to demonstrate the removal of cell substrate-derived impurities such as nucleic acids and host cell proteins may sometimes be used to eliminate the need for establishing acceptance criteria for these impurities.
(b) Cell culture-derived impurities include, but are not limited to, inducers antibiotics, serum, and other media components.
(c) Downstream-derived impurities include, but are not limited to, enzymes, chemical and biochemical processing reagents (e.g., cyanogen bromide, guanidine, oxidizing and reducing agents), inorganic salts (e.g., heavy metals, arsenic, nonmetallic ion), solvents, carriers, ligands (e.g., monoclonal antibodies), and other leachables.

For intentionally introduced, endogenous and adventitious viruses, the ability of the manufacturing process to remove and/or inactivate viruses should be demonstrated as described in ICH Harmonized Tripartite Guideline "Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin."

6.2.2. Product-Related Impurities Including Degradation Products

The following represents the most frequently encountered molecular variants of the desired product and lists relevant technology for their assessment. Such variants may need considerable effort in isolation and characterization in order to identify the type of modification(s). Degradation products arising during manufacture and/or storage in significant amounts should be tested for and monitored against appropriately established acceptance criteria.

(a) Truncated forms: Hydrolytic enzymes or chemicals may catalyze the cleavage of peptide bonds. These may be detected by HPLC or SDS-PAGE. Peptide mapping may be useful, depending on the property of the variant.
(b) Other modified forms: Deamidated, isomerized, mismatched S-S linked, oxidized, or altered conjugated forms (e.g., glycosylation, phosphorylation) may be detected and characterized by chromatographic, electrophoretic, and/or other relevant analytical methods (e.g., HPLC, capillary electrophoresis, mass spectroscopy, circular dichroism).
(c) Aggregates: The category of aggregates includes dimers and higher multiples of the desired product. These are generally resolved from the desired product and product-related substances, and quantitated by appropriate analytical procedures (e.g., size exclusion chromatography, capillary electrophoresis).

12

Essential Clean-Room Design Elements

One of the most important components of pharmaceutical manufacturing is the environment under which the production is carried out. The design and layout of a manufacturing facility is critical to preventing cross-contamination, exposure to workers, and generally making a safe product for human or animal consumption. These considerations are more important in the processing of sterile products where contamination of any type can render the product unsuitable. These products are thus processed in clean rooms. A clean room is defined by ISO 14644-1 as "a room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room and in which other relevant parameters, e.g. temperature, humidity, and pressure, are controlled as necessary." The design of clean room HVAC systems is a specialty area requiring the unique understanding of cleanliness guidelines, airflow, room pressurization, code requirements, specialty equipment, precise control, and many more details.

In this chapter, details regarding the design components of various types of clean-room environments found in a sterile manufacturing area are discussed. Smart designing requires that the facility be put together in a most cost-effective manner, have the lowest possible maintenance cost, and be readily validated. Generally, clean rooms are highly energy intensive to operate as these rooms systems include process equipment, HVAC systems, lighting, etc. HVAC systems in clean rooms are dramatically different from their counterparts in commercial buildings in terms of reliability, safety requirements, and scale. Benchmarking energy use in clean rooms is particularly important in that there is little industry data available to compare energy use. The lack of energy data and standard metrics makes comparison difficult or impossible. It is also difficult to set appropriate design goals, compare performance over time, and compare performance against other similar clean rooms. Clean-room energy benchmarking can provide baseline information to better understand clean-room energy performance and can provide information to identify energy-saving opportunities.

The conventional unit of measurement for fine particles is the μm or micrometer. A micrometer or μm is a millionth of a meter, or approximately 0.000040 of an inch. A human hair varies from 30 to 200 μ in diameter, with the average human hair being approximately 100 μm. Airborne particles range in size from 0.001 to 1000 μm, the latter having a very short "life." Atmospheric rain is a good example of a 1000-μm particle. Particles of 0.001 μm are bordering on molecular size. Earlier designs of clean rooms were concerned with controlling particles in the 0.5 μm and larger size range. In the 1980s, the limit was lowered to the 0.3 μm and larger size range and a decade later the range was 0.1 μm; today, we control particles sizes of 0.05 μm and larger.

Pharmaceutical clean rooms offer a different challenge from those encountered in electronics industry or medical procedure rooms because the general requirement and the level of contaminants are predictable and constant. Since the smallest particle human body sheds is approximately 7 μm (based on the finest capillary diameter in humans), which is also the approximate size of a bacteria, restricting particles to a smaller size than this would substantially reduce pyrogenic materials. As a result, the particles of 5 micron size are generally excluded from clean room environment. Naturally occurring contaminants include microorganisms, sand, organic matter, excrements of animals, and pollen; man-produced contaminants include tobacco smoke, unburned hydrocarbons, fly ash, farm dusts, construction dusts, engine exhausts, and unfiltered industrial exhausts. Manufacturing operation-generated contaminants come from garments, packaging materials, and mechanical operations. Humans constitute on the largest source of contamination. On an average, a person sheds approximately 1.5 lb of skin per year, scale by scale; add this to dandruff, makeup, hair, and clothing fibers and we have an active particle-generating machine. Contaminants are divided as organic or inorganic with varied structural complexity, ability to coalesce, and disperse in air, making it very difficult to profile the contamination profile of a room or a process. Even though attempts have been made to quantify the contamination potential using various permutations and combinations of activities, garments, and other room conditions, these remain of limited value in designing the clean rooms based on contamination potential. The basic rules of fewest operators (machines are less contaminating), fewer abrupt motions, appropriate garments, and strict adherence to entry and exit SOPs remain the strongest measure of containing contaminants.

Clean rooms are categorized by their cleanliness levels and the type of airborne material that is controlled; the latter definition is more pertinent to design of aseptic areas where the goal is to reduce the quantity of living organisms or their by-products, these are called bio–clean rooms. A "white room" is an area where visible particles larger than 25 μm are controlled; the designation comes from the white painted rooms of the past to show their cleanliness; this is designated as 500K areas. Other classifications include 100K, 10K, 0.1K, 0.01K, 0.001K clean rooms, aseptic areas, and bio–clean rooms. The basic principle in controlling particles in the air involves recirculation of the room air through filter that removes these particles; in a more conventional system where the air moves in the room in a turbulent matter, even settled particles are picked up; this puts strain on the system compared to a laminar flow system where the air flows in a designated vertical or horizontal path. Thus, the quality or room air is highly dependent on the air-handling system where the effectiveness is determined by the type and number of air filters, the number of room air changes per hour, and the air distribution patterns within the room. The air patterns are determined by where the diffuser is located; if there is one diffuser in the room providing a spread of air, this will have a sweeping action throughout the room and is likely to leave many "dead" air pockets in the room and even increasing the air changes per hour will not help much since

Table 1 The ISO 14644-1 Clean Room Standards

	Maximum Particles/m^3						
Class	≥0.1μ	≥0.2μ	≥0.3μ	≥0.5μ	≥1μ	≥5μ	209E Equiv.
ISO 1	10	2					
ISO 2	100	24	10	4			
ISO 3	1000	237	102	35	8		Class 1
ISO 4	10,000	2370	1020	352	83		Class 10
ISO 5	100,000	23,700	10,200	3520	832	29	Class 100
ISO 6	1,000,000	237,000	102,000	35,200	8320	293	Class 1000
ISO 7				352,000	83,200	2930	Class 10,000
ISO 8				3,520,000	832,000	29,300	Class 100,000
ISO 9				35,200,000	8,320,000	293,000	Room air

higher velocity might kick more dust in the air. The most efficient systems would have low air velocity and covering a larger surface area of the ceiling to produce a steady or constant down flow of clean air, which would gently sweep the air in the room. This type of design is called a "vertical laminar flow clean room," the most expensive type of facility to construct but justified for contamination sensitive products; a good example is the laboratory-scale laminar flow hood that can be used to protect the samples from humans and also humans from samples depending on the flow pattern and direction. When applied into a room, good vertical laminar flow can be achieved with air changes of approximately 600 or more per hour only with the entire ceiling acting as diffuser and the floor serving the return flow. Obviously, this would be a very high-cost facility; cost reductions are possible by using multiple diffusers appropriately placed and using low-level wall returns and keeping them as close as possible to areas where most particles are generated.

Clean facilities are rated in terms of the amount of airborne contaminants present; the first document recognizing this was the United States Air Force Technical Order 00-25-203, which was followed by the U.S. Federal Standard 209 that provided a more universal industry standard; this was officially abandoned in 2001 and replaced by ISO 14644-1 but continues to be widely quoted. In 209E, there were no particles larger than 5 μm which are allowed in Class 10,000 or better mainly to eliminate pyrogenic materials. The ISO 14644-1 also recognized particles 5 U or larger and none are allowed in Class 10,000 or ISO 4 environment (Table 1).

The designers and operators of clean rooms are directed to a series of documents published by the ISO organization that pertain to design and operations of these rooms; these are listed below in the chronologic order of their issuance (http:/www.iso.org):

ISO 14644-1:1999: Cleanrooms and associated controlled environments-–Part 1: Classification of air cleanliness. Edition: 1 | Stage: 90.92 | TC 209. ICS: 13.040.35. Document available as of: 1999-05-06.

ISO 14644-2:2000: Cleanrooms and associated controlled environments-–Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1. Edition: 1 | Stage: 90.92 | TC 209. ICS: 13.040.35. Document available as of: 2000-09-07.

ISO 14644-4:2001: Cleanrooms and associated controlled environments-–Part 4: Design, construction and start-up. Edition: 1 | Stage: 90.93 | TC 209. ICS: 13.040.35. Document available as of: 2001-04-12.

ISO 14698-1:2003: Cleanrooms and associated controlled environments-–Biocontamination control-–Part 1: General principles and methods. Edition: 1 | Stage: 90.20 | TC 209. ICS: 13.040.35. Document available as of: 2003-09-17.

ISO 14698-2:2003: Cleanrooms and associated controlled environments-–Biocontamination control-–Part 2: Evaluation and interpretation of biocontamination data. Edition: 1 | Stage: 90.20 | TC 209. ICS: 13.040.35. Document available as of: 2003-10-10.

ISO 14644-5:2004: Cleanrooms and associated controlled environments-–Part 5: Operations. Edition: 1 | Stage: 90.93 | TC 209. ICS: 13.040.35. Document available as of: 2004-08-13.

ISO 14644-7:2004: Cleanrooms and associated controlled environments-–Part 7: Separative devices (clean air hoods, gloveboxes, isolators and mini-environments). Edition: 1 | Stage: 90.60 | TC 209. ICS: 13.040.35. Document available as of: 2004-10-07.

ISO 14644-3:2005: Cleanrooms and associated controlled environments—Part 3: Test methods. Edition: 1 | Stage: 90.20 | TC 209. ICS: 13.040.35. Document available as of: 2005-12-06.

ISO 14644-8:2006: Cleanrooms and associated controlled environments—Part 8: Classification of airborne molecular contamination. Edition: 1 | Stage: 60.60 | TC 209. ICS: 13.040.35. Document available as of: 2006-08-10.

ISO 21501-4:2007: Determination of particle size distribution—Single particle light interaction methods—Part 4: Light scattering airborne particle counter for clean spaces. Edition: 1 | Stage: 60.60 | TC 24/SC 4. ICS: 19.120. Document available as of: 2007-05-07.

ISO 14644-6:2007: Cleanrooms and associated controlled environments—Part 6: Vocabulary. Edition: 1 | Stage: 60.60 | TC 209. ICS: 13.040.35. Document available as of: 2007-07-04.

Room design starts with identifying the contaminants to assure that the design is not an overkill—as it happens more often, adding to the cost of the product. The most expensive clean rooms are the vertical laminar flow type and the least expensive are horizontal flow turbulent rooms. In most instances, a facility would have several different types of air-quality rooms to focus air type contact based on need. The following flowchart describes the decreasing order of cost of clean rooms:

> Vertical laminar flow and perforated floor and return through floor → Vertical flow and solid floor and sidewall returns and laminar flow benches → Vertical and solid floor and sidewall returns → Controlled areas with laminar flow benches dispersed throughout the floor plan → Uncontrolled area with vertical laminar flow benches clustered together.

In a vertical flow laminar room with air returning through the floor, a laminar flow is maintained throughout the room preventing cross-contamination within the room; when the floor is solid and the air returns through low-level returns, the air takes a sweeping action, often turbulent action and cross-contamination from items within the room is less stringent; in this case, the cleanliness of the room is maintained through a scrubbing action through repeated exchanges of air through HEPA filters. The most significant cost-reduction measure is the use of spot air where the contamination is to be avoided. It is best achieved by providing laminar downdraft clean air over the specific process or product instead of the entire room, which can be maintained at a lesser quality conserving substantial cost (e.g., a Class 100 downdraft laminar flow air over vial filling machines in a Class 10,000 room). Spot laminar draft is also very useful where different temperature needs to be maintained such as in the case of downstream processing of biological drug purification. Ideally, the chromatography process is conducted under a laminar flow with low temperature of 5°C to 8°C. Keeping the entire room cold increases the cost of operation and makes it difficult for the operators to work, making them less efficient. In such cases, the ideal design would be a belt of laminar flow downdraft at a colder temperature. Obviously, this approach is not recommended if the operations are spread out through the entire room and cannot be integrated and restricted to a particular area of the room.

Whereas the standard of clean rooms is rising in many industries including the electronics industry, such is not the case for the pharmaceutical industry since here the main source of contamination remains the operator—humans. Given the smallest capillary in humans is approximately 5 μm, the size of the smallest particle shed by humans is fixed. With more automation and use of robotic systems, it is possible to reduce the cleanliness requirements making the product less expensive to manufacture. It is for this reason that the planning for designing clean rooms requires complete understanding of the process, measures to optimize and automate the process, and reduce as much as possible human traffic in clean rooms, whether for the process needs or maintenance needs. An optimal design would require a time-motion analysis, slack removal, and optimal placement of equipment. An important consideration rather unique to pharmaceutical clean rooms is the avoidance of pyrogenic materials in sterile product manufacturing; this may require extraordinary measures to keep the room cleaner and validated.

I. OPTIMIZED DESIGNS

Since clean rooms have complex mechanical systems and high construction, operating, and energy costs, it is important to perform the clean-room design in a methodical way. Given below is a listing of major considerations in optimizing the cost of installation and operation of clean rooms:

1. Layout, material, and personnel flow: It is important to evaluate the people and material flow within the clean-room suite. People are the largest contamination source and all critical processes should be isolated from personnel access doors and pathways. The most critical spaces should have a single access to prevent the space from being a pathway to other less critical spaces. Some pharmaceutical and biopharmaceutical processes are susceptible to cross-contamination from other pharmaceutical and biopharmaceutical processes. Process cross-contamination needs to be carefully evaluated for raw material inflow routes and containment, material process isolation, and finished product outflow routes and containment.
2. Degree of space cleanliness and classification: To be able to select a clean-room classification, it is important to know the primary clean-room classification standard and what the particulate performance requirements are for each cleanliness classification. The Institute of Environmental Science and Technology (IEST) Standard 14644-1 provide the different cleanliness classifications (1, 10, 100, 1000, 10,000, and 100,000) and the allowable number of particles at different particle sizes. For example, a Class 100 clean room is allowed a maximum of 3500 particles/cu ft at 0.1 μm and larger, 750 particles/cu ft at 0.2 μm and larger, 300 particles/cu ft at 0.3 μm and larger, 100 particles/cu ft at 0.5 μm and larger, and 24 particles/cu ft at 1.0 μm and larger. Space cleanliness classification has a substantial impact on a clean-room cost, and maintenance. It is important to carefully evaluate reject/contamination rates at different cleanliness classifications and regulatory agency requirements, such as the FDA. Typically, the more sensitive the process, the more stringent cleanliness classification should be used. There should be no more than two orders of magnitude difference in cleanliness classification between connecting spaces. For example, it is not acceptable for a Class 100,000 clean room to open into a Class 100 clean room, but it is acceptable for a Class 100,000 clean room to open into a Class 1000 clean room.
3. Space pressurization: Maintaining a positive space air pressure, in relation to adjoining dirtier cleanliness classification spaces, is essential in preventing contaminants from infiltrating into a clean room. It is very difficult to consistently maintain the cleanliness classification when it has neutral or negative space pressurization. As a rule of thumb, a pressure differential of 0.03 to 0.05 in w.g. is effective in reducing contaminant infiltration. Space pressure differentials above 0.05 in. w.g. do not provide substantially better contaminant infiltration control than 0.05 in. w.g. Since higher space pressure differential means higher energy cost and difficulty in complying, minimal pressure differences that work should be used. Also, a higher-pressure differential requires more force in opening and closing doors and may lead to these being held open for longer time. The recommended maximum pressure differential across a door is 0.1 in. w.g. At 0.1 in. w.g., a 3-by-7-ft door requires 11 lb of force to open and close. A clean-room suite may need to be reconfigured to keep the static pressure differential across doors within acceptable limits. The same cleanliness classification. Air infiltration should not go from a dirtier cleanliness classification space to a cleaner cleanliness classification space.
4. Space supply airflow: The numbers of air changes determine the cleanliness classification. For example, a Class 100,000 clean room has a 15 to 30 ach (air changes per hour) range. The rate of air change should take the anticipated activity within the clean room into account. A Class 100,000 (ISO 8) clean room having a low occupancy rate, low particle-generating process, and positive space pressurization in relation to adjacent dirtier cleanliness spaces might use 15 ach, while the same clean room having high occupancy, frequent in/out traffic, high particle-generating process, or neutral space pressurization will

probably need 30 ach. The designer needs to evaluate the specific application and determine the air change rate to be used. Other variables affecting space supply airflow are process exhaust airflows, air infiltrating in through doors/openings, and air leakage out through doors/openings. IEST has published recommended air change rates in Standard 14644-4. "Gown/Degown" has the most in/out travel but is not a process critical space, resulting in 20 ach. Sterile air lock adjacent to critical production spaces may be used as a buffer with 40 ach. A Class 1000 (ISO 6) clean room may require a 150-ach rate.

5. Space air leak: The majority of clean rooms are under positive pressure, resulting in planned air leakage into adjoining spaces having lower static pressure and unpredictable air leakage through electrical outlets, light fixtures, window frames, door frames, wall/floor interface, wall/ceiling interface, and access doors. It is important to understand that rooms are not hermetically sealed and do have leakage. A well-sealed clean room will have a 1% to 2% volume leakage rate. When using active supply, return, and exhaust air control devices, there needs to be a minimum of 10% difference between supply and return airflow to statically decouple the supply, return, and exhaust air valves from each other. If the valves are not statically separated, their controls can end up fighting each other. The amount of air leakage through doors is dependent upon the door size, the pressure differential across the door, and how well the door is sealed (gaskets, door drops, and closure). As an example, the air leakage through the 3-by-7-ft door is approximately 190 cfm with a differential static pressure of 0.03 in. w.g. and 270 cfm with a differential static pressure of 0.05 in. w.g.
6. Space and air balance: Space air balance consists of adding all the airflow into the space (supply and infiltration) and all the airflow leaving the space (exhaust, leakage, and return) being equal.
7. Other variables:
   a. Temperature: Clean-room workers wear smocks or full bunny suits over their regular clothes to reduce particulate generation and potential contamination. Because of this extra clothing, it is important to maintain a lower space temperature for worker comfort. A space temperature range between 66 and 70°F will provide comfortable conditions.
   b. Humidity:Because of a high airflow, a large electrostatic charge is developed in clean-room air. When the ceiling and walls have high electrostatic charge and space has low relative humidity, airborne particulate will attach to the surface. When the space relative humidity increases, the electrostatic charge is discharged and all the captured particulate is released in a short time period, causing the clean room to go out of specification. Having high electrostatic charge can also damage electrostatic discharge sensitive materials. It is important to keep the space relative humidity high enough to reduce the electrostatic charge build up. A relative humidity of 45% + 5% is considered the optimal humidity level.
   c. Luminosity: Very critical processes might require laminar flow to reduce the chance of contaminants getting into the air stream between the HEPA filter and the process. IEST Standard #IESTWGCC006 provides airflow luminosity requirements.
   d. Electrostatic discharge: Beyond the space humidification, some processes are very sensitive to electrostatic discharge damage and it is necessary to install grounded conductive flooring.
   e. Noise levels and vibration: Some precision processes are very sensitive to noise and vibration.
8. Mechanical system layout: Unlike normal air-conditioning systems, clean-room systems have substantially more supply air than needed to meet cooling and heating loads. Class 100,000 (ISO 8) and lower ach Class 10,000 (ISO 7) clean rooms can have all the air go through the AHU. The return air and outside air are mixed, filtered, cooled, reheated, and humidified before being supplied to terminal HEPA filters in the ceiling. To prevent contaminant recirculation in the clean room, the return air is picked up by low wall returns. For higher ach Class 10,000 (ISO 7) and cleaner clean rooms, the airflows are too high for all the air to go through the AHU; a small portion of the return air is sent back to the AHU for conditioning and the remaining air is returned to the recirculation fan.
9. Heating and cooling calculations: When performing the clean-room heating/cooling calculations, take the following into consideration:
   a. Use the most conservative climate conditions (99.6% heating design, 0.4% dry-bulb/median wet-bulb cooling design, and 0.4% wet-bulb/median dry-bulb cooling design data)
   b. Include infiltration into calculations
   c. Include humidifier manifold heat into calculations
   d. Include process load into calculations
   e. Include recirculation fan heat into calculations
10. Mechanical room space: Clean rooms are mechanically and electrically intensive. As the cleanliness classification becomes cleaner, more mechanical infrastructure space is needed to provide adequate support to the clean room. Using a 1000-sq-ft clean room as an example, a Class 100,000 (ISO 8) clean room will need 250 to 400 sq ft of support space, a Class 10,000 (ISO 7) clean room will need 250 to 750 sq ft of support space, a Class 1000 (ISO 6) clean room will need 500 to 1000 sq ft of support space, and a Class 100 (ISO 5) clean room will need 750 to 1,500 sq ft of support space. The actual support square footage will vary depending upon AHU airflow and complexity (simple: filter, heating coil, cooling coil, and fan; complex: sound attenuator, return fan, relief air section, outside air intake, filter section, heating section, cooling section, humidifier, supply fan, sound attenuator, and discharge plenum) and number of dedicated clean-room support systems (exhaust, recirculation air units, chilled water, hot water, steam, and DI/RO water). It is important to make provision for the required mechanical equipment space square footage to the project architect early in the design process.
11. Problem avoidance: The following are some of the most frequent problems found in clean-room design. These problems are, of course, of a general nature but are repeated time and again:
   a. Horizontal surface materials are selected, which hide, rather than illuminate and display contaminants to the employees.
   b. Clean benches and tables have sharp edges, which wear garments, and produce large amounts of contaminants directly at the workstation.
   c. Normally, white is chosen as the prime color for any clean room. However, this is not the best color from the industrial consultant's point of view. Colors do not affect the cleanliness of the room.

d. Bench heights found in clean rooms sometimes do not follow industrial engineering recommendations of general industry.
e. There is a lack of testing, checking-out, and certifying clean-room equipment for acceptable use in clean rooms.
f. Automatic material handling equipment is excluded from the clean environment.
g. Equipment is supplied to the clean room in a contaminated state.
h. Use of approved clean-room material is low.

12. Types of Contaminants. While great emphasis is placed on number of particles in the air, the type of particles are often more important for bio–clean rooms where viable airborne particles create special problem situations. These particles come from personnel emission (sneezing, coughing, exhalations, and perspiration), growth of fungi and bacteria in room crevices, and unclean areas. Microorganisms are carried by dust particles and thus reducing particles generally reduce viable counts as well. However, when allowed to grow, single bacteria can grow into a million count within 10 to 12 hours, particularly where liquid products are handled, providing moisture and nutrition for growth. While general cleanliness with reduced particle count will improve all operations requiring clean environment, there must be a cost-advantage analysis made in the design of clean rooms. Not all particles are bad; so we need to define not only the number and size of particles allowed but also the nature of these particles. In the case of parenteral products, contamination in the form of particulate matter is defined as unwanted mobile insoluble matter that may originate from an intrinsic or extrinsic source. Intrinsic contamination is material not removed from the solution and the extrinsic particle comes from air during filling operations.
13. Air changes: The minimum air-handling system for clean rooms is designed to change the room air through HEPA filters eight times per hour. This number of room air changes will provide a Class 100,000 condition per Federal Standard 209E, provided that the room volume is not very large or of any unusual dimension. Turbulent flow–designed rooms, which depend on room air changes to achieve their cleanliness level greater than 24,000 cu ft, present difficulties in airborne contamination control. A room air change rate of 20 per hour will provide a Class 10,000 clean-room condition. A room air change rate of 45 per hour will provide Class 1000 conditions. As the size of clean room increases, difficulties arise in predicting the efficiency of HVAC systems as the airflow patterns become difficult to predict, not only because of the hydrodynamic effects but for the complex interactions with larger number of operators, their entry and exit paths, work movements, and equipment that would be found in larger rooms. Long distances to exits and personnel traffic patterns in large rooms are also significant factors, which contribute to increased airborne particulate levels.
14. Room pressure: Whereas tight-sealing doors are used to isolate room environment, these are seldom very effective since these must be continually opened and closed and always have air leakage. To assure that room air is only allowed to travel in a specified path, clean rooms are pressurized; the function of increased pressure is to force clean air out of any cracks or openings, thus preventing contaminated outside air from forcing its way into the room. The increased pressure also creates an outward flow of air when the entry doors are open, reducing the entry of outside air. Rooms are pressurized by discharging excess room air through a pressure sensing-regulated barometric damper. However, this requires making up the lost air not only through leaks but also to keep the quality of air needed by the operators. A minimum of 200 cu ft of fresh air per hour per employee is usually required. In many areas, local government regulations will mandate the quantity of fresh air that is required. A positive pressure of no more than 0.10 in water gauge between the clean room and uncontrolled areas is adequate for most applications. If more than one room is involved, it may be necessary to raise this value so that the rooms may be staged from the most closely controlled room to the least-controlled room. Where rooms are staged, a 0.05 in water gauge differential pressure is sufficient between rooms. It is important to realize that higher differential of pressure between rooms makes the doors difficult to operate and results in large fluctuations or pressure that may not be desirable.
15. Filters: Filters to remove room particles are rated by the percentage of airborne particles they remove. Generally, HEPA filter should be rated at least 99.97% by the DOP (dioctylphthalate) test. If a filter system allows too many smaller particles to go through, these particles may coalesce in the room and result in larger count, so it is important that a filter not only restrict a specific size of particles but the overall number of particles, albeit small, it allows to go through. More efficient HEPA-ULPA can be are more efficient than HEPA filters and can be used with a maximum resistance differential pressures of 10 in or 25 cm water gauge. The allowable pressure differential in filter resistance is determined by the fan capacity and thus a fan of suitable capacity must be selected to deliver the desired airflow against the total resistance constituted by the ductwork and the dust- or particle-loaded filter. Variable speed fans that are controlled by a feedback mechanism allow constant airflow despite increase in the filter resistance and are highly recommended to avoid frequent adjustments to the HVAC control systems. However, with increased speed of fans, the pressure rises at the filter surface leading to risk of perforation and it is for this reason that all filters are to be replaced periodically.
16. Garments: People and process produce the highest number of contaminant particles; the personnel emissions are further increased when wearing improper garments. Proper clean garment selection, cleaning, maintenance, repairing, and wearing are major concerns of a good clean rooms or bio-clean-rooms operation. These factors are of equal importance to the design of clean rooms. An effective way to upgrade a clean facility is to remove street clothes before dressing with clean garments. Street clothes have billions of particles on their surfaces. Leaving these clothes outside the room reduces contaminant levels in the clean room or bio–clean room. The type of garment used in the clean rooms is of great significance; for example, in light movement, snap smock produces approximately 500,000 particles, standard coverall approximately 50,000, 2-piece coverall 20,000, Tyvek coverall 5,000, and membrane coverall only 50 particles.
17. Construction materials: The construction material used in clean rooms is critical to maintaining the room classification. Whereas there are different tolerances of specification of construction material for different classifications

(to keep the cost low), some general principles are applicable to all clean rooms.

- Free of discontinuities, openings, pits, porosity, crevices, etc. by which contaminating material can be retained or enter.
- Resistant to deterioration abrasion or other damage in the normally expected usage (more particularly the specific contaminants anticipated).
- Able to dissipate dissipation of electrostatic charges (more important in environments where low humidity is inevitable or desired).
- Sound dampening.
- Reflective of ambient light and of desired (appealing and nonfatiguing) color.
- Insulating against temperature and/or moisture.
- Easily workable with similar and other materials (e.g., glass, steel etc.)
- Available in different shapes, sizes, and specification as needed.
- Repairable or replaceable during the life of the facility without breaching cleanliness.
- Will not warp or shrink (to prevent leakages and contaminants collecting) and sustain constraints of structure, minor ground movements (earthquake), and vibrations. If a material of acceptable cost cannot be found that would meet above requirements, materials can be combined that provide different qualities as described above. For example, a low-cost wall material can be gypsum wall with a vinyl laminate on the clean room side and the gypsum board appropriately sealed to prevent particle shedding. Recently, many prefabricated wall systems have become available that are highly suitable for special use rooms like bio–clean rooms.

II. TURBULENT TYPE CLEAN ROOMS

Clean rooms are differentiated based on types of airflow. When the airflow is predictable, these are called laminar flow rooms and the other type is turbulent flow room, which also have similar unidirectional flow (as air is circulated through returns), the difference between two types is significant. Both type of rooms remove particles by the process of dilution and filtration, in one case it is random and in the other the particles generated are immediately removed (laminar) requiring much higher air exchange rates and appropriate placement of diffusers to make sure that there are no dead spaces left in the room.

Clean rooms can be a single freestanding room or a single room with a locker and air-shower entry, or a complex of clean rooms with pressure gradients between rooms. Clean rooms require a support space or area adjacent to the clean facility. It has a cleanliness level between Class 100,000 and 500,000. It is positioned between the clean area and the rest of the factory and allows material to be prepared to enter the clean room as well as product to exit and be prepared for transport and storage. This area is needed in order to handle boxes, etc. for loading and unloading materials. This support space is usually designed as a controlled area. This support space is usually forgotten during the design and then has to be added on after room construction.

Turbulent clean rooms use a variety of wall surfaces that must be of low particle shedding type. Floors can vary from vinyl tiles to epoxy (the preferred type). The floors should have sealed seams. Ceilings for turbulent flow rooms should be rigid enough to support the stress of high air moving diffusers. They can be painted to prevent shedding particles. Cross-contamination in clean rooms is prevented by using pressurized controls, both positive and negative depending on whether the contamination is to be prevented or controlled from spreading out. A comprehensive design would provide both through a sink created in the entry module.

Filters used must be rated and tested frequently. Methods for testing the efficiency of air filters vary widely and these tests are not always comparable, a note of caution in comparing various filter products. The DOP smoke test is used to rate HEPA filters. The word "smoke", as used by the filter testers, means a high particle density of airborne particles. The term does not refer to any type of combustion process or burning of material. The generation of DOP smoke is closely controlled to maintain the particle diameter of the droplets at 0.3 μm, which is usually considered the most difficult size to remove. A light scattering penetration meter or particle counter is used to evaluate the results and establish the filter's efficiency.

III. VERTICAL FLOW CLEAN ROOMS

An efficient vertical laminar clean-room design envisions a comprehensive layout that allows sufficient room for working conditions but not too much more than what is needed. The reason for this minimalist approach is the cost or installation, maintenance, and operation. Larger rooms are more difficult to validate and to keep validated. For example, the aisles need be no wider than 5 ft, unless larger equipment or supply movement is anticipated. In a research clean room, little regard might be given to the height of the equipment, or its position relative to other room equipment. It is important, however, that at least 4 to 6 in of space separate items of equipment, such as a console and workbench. It is of prime importance that the area above the work be open from the ceiling for maintenance. This allows the contaminant-free air to flow from the ceiling down over the workstation and then to the floor.

In this type of facility, contaminant-generating operations may be performed anywhere in the room without the risk of contaminating the product. This is because there is no transfer of contamination by random airflow between workstations. All air flowing over an individual workstation passes directly from the workstation to the floor and then is refiltered. Each workstation can be considered as totally isolated from every other workstation by the essentially laminar airflow pattern of the room.

The major advantages of a laminar vertical flow include the following:

1. Ability to completely isolate every operation by streamlines of laminar airflow.
2. Produce the shortest distance from contaminant generation to contaminant removal from the room.
3. Yields the lowest contamination level of all the room designs.
4. Prevents heat buildup, since the volume of air available to absorb heat is great and distance the air must travel to air return is at the minimum.

The major disadvantages of a laminar flow vertical flow include the following:

1. Installation cost: Some cost savings can be made through creative and cost-cutting measure yet almost always cost of product produced is a significant factor in justifying use of this design.
2. Maintenance cost: this is proportional to the number of filters used and the high-energy input required.

IV. LAMINAR FLOW CLEAN ROOMS

Turbulent flow clean rooms are less efficient because they lack self-cleanup capabilities to offset contamination brought into the room by personnel and equipment. Contaminants generally settle to the floor and attach to other surfaces and may be reintroduced into the air by changes in air currents or by activity in the room. Turbulent airflow is also not uniform and also the particles are not removed uniformly and personnel often contribute more heavily to contaminants in such turbulent flow rooms. These shortcomings are overcome in a laminar flow design where clean environment is created almost independent of the operations or activity since the particles generated are immediately removed from the surrounding without diluting in the room.

How much of a laminar airflow is (horizontal or vertical) designed into clean rooms depends on the target classification. For example, operational of less than Class 1000, horizontal laminar flow clean rooms are appropriate where a full wall of HEPA filters is positioned to take up the entire cross section of the room through which air passes at rates of 100 ft/min. The airflow patterns are balanced to ensure that a unidirectional flow is established so that particles released by personnel are directed toward the exit end of the room. The exit end of the room is the opposite wall to the HEPA filter bank and the air-conditioning is provided to the room upstream of the HEPA filters. Class 100 and better conditions are better provided by vertical laminar flow clean rooms.

The clean bench provides an ultraclean work area without the expense of constructing an entire room. This spot application of clean air in a laminar flow is obtained by using the HEPA filters at the back of the bench through which air is evenly distributed in a unidirectional flow at a velocity of 100 ft/min. The air streamlines are parallel and any particles created in the processing are simply pushed out of the area without contaminating; the design also allows an open area for operators to maneuver freely. The air quality of the clean bench is rated a minimum of a Class 100, per Federal Standard 209E. Because of the very high cost of air circulation, spot Class 100 environment offers the most cost-effective solutions; for example, in a sterile product filling line, the room can be Class 10,000 while the air above the filling line is Class 100 (laminar flow with soft curtains).

V. HORIZONTAL LAMINAR FLOW CLEAN ROOMS

Use of horizontal laminar flow clean rooms allows ready achievement of Classes of 10 to 1000. In the design of horizontal laminar flow clean rooms, a wall of the room is used as a filter bank, which contains HEPA filters. The choice of which wall to be used will determine the downstream operational contamination level.

The air-conditioning system for a horizontal laminar flow clean room delivers the conditioned air into the return air plenum. Usually, this plenum is above the room, although it may also be on the side of the room or below the room. The over-the-ceiling return may consist of a complete plenum, or it may be constructed of ductwork. The side-of-the-room air return may only be the service corridor, while the below-the-floor air return may be a portion of the floor below or a cellar space. The longer the period of time that the conditioned air has to mix with the primary return air, the more even will be the temperature distribution as the air exits from the HEPA filter wall. This means that the air-mixing operation which is required to produce an even temperature distribution can be less sophisticated.

The effect of changes in temperature, because of the temperature differential within this room, is often more significant as personnel approach the inlet wall and it is for this reason that these rooms are overdesigned to assure that the threshold of contamination is not reached normally. To reduce the air-conditioning requirements, equipment that generates large heat is generally vented out directly or placed such that it is in the downstream pattern to prevent heat from dissipating into room.

Construction material requirements for walls, floors, and ceilings are similar to what is required for other types of rooms.

The horizontal laminar flow clean room will achieve cleanliness levels, approximately two orders of magnitude cleaner than conventional or nonlaminar or turbulent flow clean rooms, at approximately the same cost. However, the horizontal flow room will not isolate operations from each other. These can be achieved by vertical laminar flow patterns. Since operations downstream will be in a dirtier atmosphere than those upstream, staggering the operations requiring cleaner air close to filters solves the problem partly.

Vertical laminar flow clean rooms and bio–clean rooms are differentiated by completeness of the HEPA or ULPA filter ceiling, and then secondly, by whether or not air passes through the floor or has a solid floor. For example, a room that using an entire ceiling grid of top-loaded HEPA filters with standard ceiling height of approximately 8 ft, the air velocity is generally set at 100 ft/min, the number of room air changes per hour will be 750, or one room air-change per every 4.8 seconds. If the filters are properly rated, tested, and certified in place, the particle counter is unlikely to detect even one particle per cubic foot of 0.3 μm and larger. If this room meets its design criteria, this room can be classified as cleaner than a Class I condition. If personnel actions are controlled and clean membrane type garments are worn, the room will operate in this condition also.

Vertical laminar flow rooms are designed as high-bay clean rooms with less than a complete ceiling of filters to allow the lighting to be spaced between rows of filters and to space out the filters to reduce cost.

A second way in which these rooms are described is by the type of floor installed. In raised floors, airflow panels are standard 2′ × 2′ lay-in perforated panels supported on pedestals, which can vary in height from 12 to 30 in. These panels can be obtained also with dampers built into them.

A different approach to airflow floors uses a metal grate approach with prefilters located below the grate. The grate spacing in this particular room is less comfortable to stand on. Larger grate flooring with closer spacing is more comfortable to the feet. Grate flooring also presents problems for supporting chairs and tables.

Generally, long narrow rooms seem to optimize some factors since these rooms are likely to have only one aisleway restricting the movement of personnel to one side of the room; the movement can be further curtailed if the entryway is in the center of the room so that personnel need not walk the

entire length of the aisleway. If the processes are built into both of the walls with a service corridor behind them, they have an additional protection. Personnel emissions, which are the heaviest when walking, are in the center aisleway moving toward the floor protecting the processes.

Aseptic filling operations should be done preferably long, narrow rooms keeping the equipment either in the center or to one side of the room. When double filling operations are performed in the same room, the center corridor is used for personnel traffic. The bio–clean room is laid out with the filling equipment along each wall reducing random walking patterns of personnel forcing compliance without the need to continuously train workers. (Lifetime experience in designing and operating clean rooms tells that whatever can be enforced with design should not be left to training and SOP.)

Another advantage of long narrow rooms is that it allows for utilities to be piped in along the wall and servicing the lines without entering the clean rooms. Many arrangements in the shape of letter I or E are possible depending on the limitations in space reorganization.

Wall construction can be of rigid or panel construction. A modular panel wall system offers advantages for maintenance of electronic consoles and for controlling heat load within the clean room. Wall panels can contain either floor to ceiling or window size removable insert covers for consoles. Consoles can be placed into these insert positions while allowing the main body of the console to remain outside the clean room allowing maintenance personnel to remain outside the clean room. It also allows the heat load of the consoles to be dumped into less controlled spaces. Consoles can be moved easily to remote location for repairs.

Providing required lumens in a vertical flow room can be challenging since placement of recessed lights in the ceiling inevitably reduces the number of HEPA filters and their positioning in the ceiling. This requires adjustment of airflow rates to compensate for the loss of ceiling area. At times, $2' \times 4'$ light panels are inserted into the filter grid system. This design requires extra care in conjunction with room layout to assure that the light must not be positioned where it would cause contamination problems below it. A plastic egg-crate can be installed below the filters and lights to give a more aesthetic appearance as well as providing a reflector for the light.

Alternately, thin line tube mounted below the filter bank can be used; this is a good approach since it does not disturb the filter bank and airflow as long as the shape of the tube mount is aerodynamic and does not protrude any sharp edges. Another method is to use exposed bulbs evenly spaced across the filter hank; this also does not interfere with airflow and gives even light distribution. In high-bay clean rooms, the bulbs can have filters that direct the light toward the floor to maximize the illumination of workspace; this is more important for larger engineering projects.

The rest of the discussion in this chapter will pertain to the qualification and design of the three most commonly encountered classes of clean rooms in pharmaceutical manufacturing: 500K for general use, 100K for clean process, and 10K for sensitive process; in all instances, use of spot vertical laminar areas is made to minimize the cost of processing where applicable and possible.

A. Design of Class 500K Rooms

These rooms are the first level of cleanliness offered in a pharmaceutical manufacturing area and since there are SOPs involved in entering and leaving the area, these are called controlled rooms. Many variations are possible to fit the budgetary needs; many rooms can be retrofitted to comply with this requirement. Prefabricated rooms are also a good choice to achieve this level of cleanliness.

Filtered air in the room need not be through an HEPA filter but at least an 85% efficient filter with several room air changes per hour. Good smooth walls and doors are important whereas wall can be of standard construction, good grade enamel paint is used to cover surfaces. Normally, if the facility is a room and it will be constructed on-site of building materials, as opposed to the erection of a prefabricated panel system, it will be constructed of metal studs with gypsum board attached as the wall facing. This plasterboard needs to be coated. A good grade enamel paint, not latex, should be used. Other basic surface treatments can be used if they can be justified such especially where washing or solvent cleaning is required; more elaborate surface treatments are not usually recommended since the benefit is not seen in room airborne contaminant reduction. Thus the use of stainless steel, vinyl coating, fiberglass sheeting, and Formica-type sheeting are not required in this type of area. In addition, coving installed at the wall/floor interface is not required. Measures taken to eliminate contamination from the walls in these types of areas should not be expensive since the amount of contaminants contributed by walls is always overestimated in comparison to other factors. A smooth, durable surface subject to little or no chipping and flaking is acceptable. Gypsum board or a plaster wall with a good quality enamel paint is sufficient in most cases where impact strength is not essential. Hollow concrete masonry or cinder block construction, owing to its fire resistance and low cost, is also acceptable. If this type of construction is used, every effort should be made to get the finished surface as smooth and hard as possible. This requires filler material to be applied to the masonry or cinder blocks to produce a smooth surface. This surface is then sealed. Epoxy paints have proved very satisfactory in sealing these wall surfaces. The use of wood is not recommended because of fire hazard as well as the changes in wall clearance as a result of variations in room humidity. The use of masonry walls, metal studs and bar joists, and/or metal furring is preferred for this reason. If static charges are a problem, antistatic surface treatments can be applied to the wall materials. Grounding of surfaces is also possible.

Lights may or may not be recessed. There is good concentration on housekeeping practices, once the facility is operating. With that in mind, there is usually a very strong emphasis on floor materials during construction. In these basic areas, it is recognized that the floor will be dirty and that it must be maintained if any degree of dust control is going to be provided by the facility design. Since these areas are primarily concerned with visible contaminants, particles which are at least 25 μm and larger in size, these particles settle quickly on the floor and thus the need to have a good floor level return of air is preferred. Ceiling level returns are problematic as it would not be possible to remove large particles easily. The ceiling supply should have diffusers to spread the air around and allow a sweeping motion to the flow pattern. Air-conditioning systems that control comfortable temperature are needed not for comfort but to reduce the shedding of heavy particles from operators.

The filter bank containing at least medium efficiency filters may be located fairly close to the room. Many times the air-conditioning system is a packaged air-conditioning unit and that is an acceptable option; however, the unit should be positioned so that access to the filter bank is not hindered. Since there is a possibility that the facility may later be fitted

with HEPA filters, provisions for this should be allowed in the early design to avoid large expenses later.

Air ducts downstream of filtration should be non-flaking and smooth; aluminum ducting is recommended although large clean flexible ducting is also acceptable. Stainless steel ducting is not necessary in this type of facility. The filter bank of these areas can be as simple as the prefilters supplied to packaged air-conditioning units or higher efficiency prefilters supplied to a filter bank on a large air-conditioning unit. It is recommended that efficiencies of at least 85% by the National Institute of Standards and Technology (NISTA) test be used. These filters will remove visible and larger particles. It is this sized particle which needs to be controlled in these facilities.

Floors are a particular problem in clean rooms as walking on them subjects them to shear force and generation of particles into hundreds of millions in micron size range as the surface wears off. As a result, flooring that is long-lasting and sturdy is a requirement. Smooth seamless floor surfaces prevent buildup and smooth cleaning through low-level returns and to facilitate this, the joints between floor and walls should be smooth, particularly in bio–clean rooms. When floors are subjected to heavy floor loadings or chemical spills, epoxy and polyester toppings are recommended. The use of tiles creates the risk of cracking of tiles regardless of whether these are rubber or vinyl. Rubber tile and sheet rubber flooring and cove bases should not be used where subject to contact with oily materials. Cove would be recommended if wet floor condition would exist. Flooring with higher electrical resistance may be provided by using static dissipative-type flooring often is recommended; however, solvent explosion hazard exists, use of these types of flooring is not recommended.

Light-colored floors are preferred for their reflectivity ability. Colors should become progressively lighter as the eye travels from the work to the immediate work area, to machines and equipment, to nearby walls, and to other walls and the ceiling. The points of contrast are between the work itself and the bench tops, and the bench tops and the surrounding machinery.

The ceiling of controlled areas is of standard building construction. It can be plaster or gypsum board; in high bays the ceiling is of no consequence, since the area is so open. A ceiling of plaster or gypsum board requires painting. Enamel paint is a sufficient coating for these surfaces. More elaborate coatings will not produce lower contamination levels for this type of facility.

The lights in controlled areas are usually standard fluorescent lighting fixtures as ceiling mounted or suspended type, the latter requiring more housekeeping as they collect particles due to interaction of hydrocarbons in the air (oil) that develop electrical charge and get deposited onto the light fixture along with dust particles that attach to these floating grease droplets. This is not a serious problem in better class rooms such as 100K or 10K where HEPA filters remove these floating droplets but is a known concern in 500K rooms where fluorescent light acting as low-grade electrostatic precipitator requiring frequent cleaning of lighting fixtures.

The entry into Class 500K rooms is not special but lockers should be provided outside the area to allow storage of street-level cover. In many entry areas, because of the outdoor local surroundings, personnel are required to use shoe-cleaning equipment. These shoe cleaners should be provided at the entrance to the clean room. Since the purpose is to reduce visible contaminants, personnel should be required to wash hands prior to entering and this can be done by providing a basic washstand; the purpose is to eliminate gross contaminants collected on the exposed skin; a hot-air drier instead of cloth or paper towel is recommended.[1] The entry room can also double as change room where operators don smocks that can of various types but non-shedding-type and since in this area, both shedding and non-shedding-type clothing may be stored, lockers that seal well are recommended.

A location for a walk-off mat should be provided just prior to the entry into the controlled area. These mats can be made of washable material, which is common at entryways to various office complexes. The purpose is to reduce gross contaminants on the bottom of shoes. Such a mat should be of sufficient length to be effective for wiping shoes, as personnel travel over it. Shoe cleaners can be used to further reduce gross contaminants on shoes of personnel entering into these areas.

In general, a good rule is to operate the Class 500K facility as if it were a Class 100K facility in the SOPs for changing and keeping the contaminants out of the area. The change room or area would ideally have the following:

1. Personnel lockers for weather protective clothing. The construction material for lockers should be non-shedding-type (mostly coming from flaky paint on rusted surfaces).
2. A mechanical shoe cleaner. This is more critical when outside weather conditions are adverse such as snow, mud, or dust is common.
3. Washstands. These can be self-contained systems where the discharge is collected and discarded if plumbing is not available.
4. Hot-air driers of sufficient flow to dry hands quickly; not all operators have the patience required for complete drying.
5. An area or location to put on a basic synthetic fabric smock.
6. A storage cabinet for garments that will be reused. The cabinet must seal properly.
7. A basic air shower; whereas the utility of this pass-through has often been questioned, the fact that each entrant goes through a final blow-down reduces the risk inherent in all SOP-based procedures. It is expensive but if the number of workers is large and entry frequent, this investment is recommended. Some of the earliest air showers were air hoses with nozzles; the current systems make extensive of properly designed nozzles that create a blast to clean surface-attached particles quickly.
8. A location for a walk-off mat. Disposable mat sheets are now most common over washable surfaces; however, these sticky mats often do not work well for capturing larger particles. So, if sticky mats are provided, these should come after a general use friction mat.

The Class 500K can be fitted with spot laminar flow hoods that discharge air into larger area or even packaged air-conditioning units with ducts to spot cool or provide cleaner air.

Utilities in Class 500K rooms should not contribute to particles; for example, when using compressed air, it should be filtered to remove both particles and moisture.

B. Design of Class 100K Rooms

Natural currents of open air spaces are able to maintain air quality of less than 100,000 particles per cubic feet, 0.5 μm

[1] *Note*: The importance of hand washing should be embedded into all training programs and repeated as often as possible as most operators easily become careless

and larger. It takes people to make it worse. The Class 100K rooms are of two types depending on the ceiling height. The low-bay or standard ceiling height clean room has the air supply registers located in the ceiling and the air exhaust grills located at several positions in the wall. The ceiling diffusers mix the cooled air with the room air very effectively. They also mix the contaminated room air with the clean incoming air. This mixing process increases recovery time. A contaminated room requires a long period of time to clean up. The particles have a difficult time being purged out of the room due to this mixing circulation. Airflow patterns are not predictable. Particles make many passes over workstations before being removed. As a result, a Class 100K environment can be achieved with 8-room air changes per hour. The high-bay facility also exhibits turbulent flow conditions and removal of airborne particles is primarily by dilution. When applying the 8 room air changes per hour rule for high-bay clean rooms, an air change is considered the area of the room, times 10 ft.

The wall surface in a Class 100K room is very important; the flaking of wall covering materials contributing most significantly requiring use of materials such as stainless steel, vinyl coating, fiberglass sheeting, and Formica-type sheet. In addition, coving is installed in all corners in a further effort to prevent contaminant problems at the wall/floor interface.

Measures taken to eliminate contamination deriving from the walls have been expensive. In addition, the amount of contaminants contributed by walls has been overestimated. Before present knowledge was available, the tendency was to use whatever material would produce the fewest particles, with almost no regard to cost. A smooth, durable surface subject to little or no chipping and flaking should be acceptable. Gypsum board with good quality paint is satisfactory where impact strength is not essential. When the application of a wainscot is required for impact resistance, the use of hardboard, job-painted factory or prefabricated hardboard, metal (prefinished or job-painted) and an epoxy or similar durable paint is recommended. There should be no horizontal-dividing strip installed between the two wall materials. A flush joint is required.

Hollow concrete masonry is desirable because of its fire resistance and lower cost and its use is allowed in clean rooms, provided the surface is finished smoothly and that may require use of filling materials followed by sealing and painting, preferably with an epoxy material. The use of wood in structural elements is not recommended due to its fire hazard and changes in the frame seals due to moisture effects. The use of masonry walls, metal studs and bar joists, and/or metal furring is preferred for this reason. Coved wall corners are not necessary unless they can be justified by the time saved during cleaning of the walls, as is required in bio–clean rooms, or which may be necessary because of a peculiar operation. The sealing of the walls should be adequate to prevent any large losses in pressure.

Window and door frames and the doors themselves should be constructed of metal and set into the clean room so that they come close to being flush with the interior walls. Window frames may be constructed of aluminum, steel, plastic, or other highly durable material.

In designing clean rooms, it is advisable to take out any operation controls and consoles outside of room sine these panels produce a lot of heat and particles; control panel of a lyophilizer would be a good example of this. Similarly, any equipment that can be installed in a wall so that it could be serviced from outside substantially reduced particle load inside the clean room; again, a large lyophilizer or autoclave should be designed in the walls with opening in the clean room. The use of modular wall panels can greatly enhance the operation of the clean room.

Visibility in a clean room is a highly desirable feature not only to reduce claustrophobia of workers but also allow monitoring of the work inside as well as inspections by visitors. Glass has all the surface advantages of porcelain enamel or stainless steel and is comparable in cost.

Floors contribute significantly to particle count as the surface wears off. High resistance floors include vinyl, which is tough and somewhat elastic reducing the sheer force of friction by deflecting it through the surface. Coved corners, where the floor meets the walls, will simplify the cleaning operation. The joints should be tight and sealed if possible. There are two methods of sealing joints in vinyl sheeting. One method uses a solvent to dissolve the adjoining sheets and run them together. This method experiences difficulty in the seam area because of permanent softening, which allows contaminants to collect. If this procedure is used, it is necessary that the seam area be returned to the original flooring hardness if satisfactory results are to be obtained. Generally, this method of sealing vinyl flooring is not recommended because of the difficulties with existing installations. The other method uses heat to seal the vinyl, usually placing a bead of material on the joint and heat-sealing it in a precision routed grove, which joins the vinyl sheet material or large vinyl tiles. When long lengths of coiled floor material, such as vinyl, arc to be used for surfacing the floor of a clean room, it is suggested that the covering be first laid out over the area and allowed to flatten out for several days before being bonded to the floor to allow for shrinking.

Resilient flooring such as vinyl is not recommended in facilities where equipment floor loadings can be high. For these areas, a surface treatment bonding with floor is required. This treatment can be a tough surface coating or a tough surface topping. Two types of surface coatings are epoxy and polyurethane. These coatings are also very chemical resistant. The epoxy coating, which is recommended for clean rooms, must be troweled onto the floor surface. It is a putty or jelly-like two-part system, which combines to form a hard, durable, chemically resistant, and monolithic surface. It has excellent wear resistance properties, which translates into a low contaminant-emitting surface. Some of the disadvantages of this coating including that it reflects sound, it is a hard surface and thus uncomfortable to stand on for longer period of time and is liable to develop cracks if the underlayment moves because epoxy is a hard continuous coating.

Polyurethane is a more efficient material than epoxy for coating concrete floors in chemical process areas. It has greater qualities of expansion and contraction, has approximately five times the abrasion resistance, and its resistance to acids is comparable. It does provide a monolithic floor condition. The stability of the subfloor is of prime importance in all flooring material. Concrete floors must be bone dry during the process of installation.

If floor loading is not a concern, then resilient flooring with its ability to span minor fissures has a great advantage. If there is any movement in a concrete floor, it will, obviously, work to the disadvantage of rigid floors. Their lack of flexibility will cause cracks to develop comparable to the substrate. Resilient flooring, such as a vinyl sheet, will expand with slight floor movement and will prevent cracks in the flooring.

Since ceilings are not subjected to potential impact, they may be surfaced with any material that does not produce or collect contaminants and is easily cleaned. Many clean-room

ceilings are of the suspended type where the panels and lights are set in channels suspended from the existing ceiling. This type of support must be properly constructed. Since the lay-in panels are held in place by the channel edge and gravity, there is ample space for pressure loss and contamination entry unless proper panel sealing is provided.

The area above the clean room is usually highly contaminated resulting in dust accumulation over ceiling panels; thus, if these are moved or cracks develop as a result of negative pressure in the room, this dust can readily enter the clean room. As a result, a very study grid system must be used when using ceiling panels. Also, these ceilings cannot be removed from inside the room requiring their maintenance from the topside of the ceiling and that requires enough work space or a mezzanine above the clean rooms.

Ceiling surfacing materials can be less abrasion proof than walls and floors, but most of the other characteristics, which are required in clean-room materials, are valid here. The electrical engineer for lighting fixtures form a large part of the ceiling, normally specifies lenses. Care should be taken in using any ceiling material in a suspended system to avoid flutter and uncontrolled escape of air pressure. The ceiling should be detailed with some form of clip-down device. Since pressure in the room is designed in most cases to be greater than in the plenum above, the ceiling panels will have a tendency to rise. It is for this reason that the very light corrugated plastic panels frequently used in luminous ceilings should not be used in clean rooms.

The ceiling diffusers are of standard type located in the ceiling of the clean room. The filter bank is located near the air-conditioning unit, and so the primary purpose of the ceiling diffusers is to mix the cool conditioned air with the warmer air of the room as quickly and turbulently as possible. But in mixing the air for temperature distribution, it is also mixing the entrained airborne contaminants continually. This reduces the ability of the room to recover from an induced high particulate emission. It is strongly suggested that if such an air delivery system is used, that an HEPA filter diffuser be used instead, so that duct contaminants, because of poor main filter bank seals and violations, do not enter the room.

The most economical design suggests a base level illumination of 100-ft candles at bench level for the room supplemented by high-intensity light sources at those workstations requiring it. In an effort to reduce contaminant sources in a clean room, many clean rooms have installed flush ceiling lights, which can be serviced from above the ceiling. Servicing recessed lights with flush faceplates from below is a far better solution than servicing lights from above the ceiling. Flush mounted lights should not have framing surfaces with recesses to prevent collection of contaminants. When lights are to be serviced from inside the clean room, they should be changed all at one time on a scheduled basis. Data on optimum lamp replacement time are available from the manufacturer. This maintenance should be performed when the room is shut down. Sufficient time can then be allowed after replacement to permit the room contamination level to return to normal.

Fluorescent and other discharge-type lamps are by nature a potential source of radio (RF) interference. RF interference can adversely affect sensitive electronic equipment, resulting in erroneous or erratic readings or disturbing static. Corning Glass Works #70 Low Brightness Lens Panels, or an equal substitute, should be provided on all fluorescent fixtures with possible RF interference.

When pressurization of clean rooms is used, it is necessary that the pressure be maintained during entry to and exit from the room. This is accomplished by means of an air lock. An air lock is a small chamber with interlocked doors. The size of the air lock depends upon its use. A personnel air lock may be only large enough for one person or it may be large enough for a group of people, depending upon the number of people that must enter the clean room in a given length of time. Pass boxes, used for tools and equipment, should be designed as air locks unless their size is so small that the pressure loss would be insignificant.

Equipment should not be moved into or out of the clean room during normal operation. Replacement or new equipment should be installed when the room is not in operation. Ample time should also be allowed after completion of the task to permit the room to "clean up." If it is anticipated that equipment will have to be moved during room operation, an equipment air lock should be provided.

Sinks in all clean rooms, which are used for the final washing of hands, should have valves, which do not require hand control and instead operated by wrist, forearm, knee, foot, or sensor triggered.

It is important that personnel leave their jewelry, wristbands, and other attachments outside the clean-room area.

Utility placement and method of distribution are to be considered carefully. The distribution of service lines (water, electrical power, vacuum, compressed gas, etc.) presents a problem to the clean-room user who must build flexibility into his clean working area. For rooms with a stable workload, this may not be as much of a problem. Lines must be brought to equipment in various room locations, and these lines should not present a dust-collecting surface or interfere with air or workflow. In some cases, trenching has been provided throughout the room so that a connection is not far from any location. Trenching should not be used in bio–clean rooms as it offers great difficulty in removing trench covers and a loose fit would attract dirt. A narrow metal edge at the trench joint flushed with the flooring on each side helps solve this problem.

Lines arc also brought in through wall connections by means of specially built utility panels in rows of workbenches. Utility penetrations should be sealed to prevent pressure loss, airborne contaminants, and living organisms such as ants, spiders, etc. Airborne contamination entry occurs because of outside wind conditions causing pressure changes within the building. The utility chases are the path of least resistance and can act as a miniature duct system to channel contaminants into a clean area.

If it is necessary to run horizontal exposed lines into the room, they should be covered and coved into the wall surface. Placing the piping against the wall and covering with fiberglass and epoxy compound also works well.

Technical power systems of different frequencies should be run separately. Higher-frequency systems must be shielded to prevent interference with test equipment.

Specific provisions for constant, thorough clean up throughout the construction of a clean facility must be a part of the design. Constant, thorough cleaning and vacuuming of furred wall spaces and other potential sources of dust should be performed until the spaces are closed off. All dust-producing construction activities such as sawing, planning, and sanding should be accomplished if possible outside the clean areas. Construction planners should consider the sequence of operations in order to schedule dirty work such as cutting or plastering, breaking up concrete, and excavating ahead of other operations.

All air-handling ducts intended for use downstream of HEPA filters should be thoroughly cleaned and sealed at the

factory prior to shipment. After erection, the ducts should be vacuum cleaned with an industrial type vacuum cleaner and sealed until used. All openings in the duct system must remain sealed during construction. Air must never be permitted to flow into or out of the ducts unless the HEPA filters are in place.

All equipment, furniture, utilities, and material installed under the construction contract should be thoroughly cleaned by the general contractor prior to his turning the facility over to the user. When equipment is placed in the room prior to acceptance, provisions should be made to clean the equipment. The above precautionary measures should be clearly outlined in the specifications and included in the facility design.

Location of a clean room should be seriously considered before construction begins. Localized ground vibrations, as experienced at most industrial areas, should not be overlooked. Transmitted energies from ground vibrations and/or air-carried vibrations in the range of 0 to 200 cps can disrupt fine precision measurements.

Consideration should be given to isolating the noise and vibration generated by equipment and machinery in support areas from clean rooms where precision work with delicate instruments is being performed. Duct liners should not be used in air ducts for any reason to dampen HVAC noise.

Conventional vibration isolation pads should prove satisfactory for high-frequency vibration. Care should be exercised, however, to ensure that the isolators do not become dust generators or collectors. Low-frequency isolation pads should be specially designed. Above-floor isolating devices for low frequencies should be avoided in order to prevent vibration transmission through ceilings, walls, and floors into the structure.

Since the conventional clean-room operator must control the contamination entering the room, the accepted practice has been to include support rooms adjoining clean areas. Support rooms can include locker rooms, wash and rest rooms, change rooms, and offices. These rooms are generally constructed of the same materials as the clean room. The air-handling system, for the sake of economics, is usually not so elaborate as that in the clean room. Change rooms are provided as an area for employees to change into their clean-room garments. The purpose of a change room is to provide a transition for the employee from a contaminated object to a decontaminated object. The contamination control of personnel depends upon clean garment changing disciplines; however, the design of the change room area can reduce mistakes that take place in this area.

Fire codes normally require several entrances to a large clean room through which personnel can exit in an emergency. These exits are usually designed into the facility and contain a door, which opens by means of a panic bar. Periodically, Fire Department personnel must violate the clean room to check these doors. When these doors are opened, contamination enters into the room. Fire doors, which are not alarmed, can easily become shortcuts for personnel traffic to and from the outside area. Sometimes it is the sales department or upper management, who being pressed for time on a tour of facilities, will violate the clean area by opening up the fire door to let customers see the clean room without having to dress in clean garments.

An alternate fail-safe emergency exit can be constructed using polystyrene foam. Instead of an emergency door covered with vinyl sheet material, fill that door opening with the polystyrene foam. An individual can easily walk through this material in an emergency. This will eliminate room violations at this exit. Personnel cannot use this point to enter the room. It becomes a one way, one time use exit.

Air showers were developed to de-dust personnel prior to their entry into the clean room. Since there is a very delicate balance between the contamination level and the amount of personnel activity in the clean room, it was necessary to clean the contamination clinging to an individual's garments prior to his entry into the clean room. In theory, this was an excellent idea, but in practice it often does not work. One of the difficulties with the air-shower theory is that clean-room operators overestimated the amount of contamination that could be prevented from entering their clean room through the use of air showers. The other primary difficulty was the design of the air showers. Many of them were ineffective. Air velocities on the individual were not high enough to produce efficient contaminant removal. The air-shower exhaust was also inefficient and resulted in subsequent re-entrainment of particulate matter that had been overlooked. All these factors helped to give the air shower a bad reputation.

In facilities containing two or more clean rooms, line-of-sight communication becomes important. This line-of-sight communication is made possible by the installation of a significant amount of windows. Partial or full glass walls are also effective. Line-of-sight communication is the ability of a person to locate or signal another person in a different area without physically moving to that area. By the use of windows and glass walls, production is increased by reducing wasted motions and lost time.

In most production areas, which are not clean rooms or controlled areas, this line-of-sight communication is taken for granted since there are no walls, just large open hay areas. However, in many clean-room complexes, this form of communication is usually not possible because walls without windows were erected and are not easily modified. Large window areas will permit visual communication, in addition to allowing visitors to view the area without actually entering it. This assists production in reducing personnel distractions.

Standard metal doors with glass panels are recommended for this level clean room. If the doors are installed in an air lock or air shower, they may be interlocked. In certain applications, large doors may be necessary because of the size of the product. These doors should be treated to make their interior surface compatible with the clean room. This may require a more durable surface finish such as an epoxy coating.

Building codes and fire codes for clean rooms fall under H6 of the Uniform Building Code in most of the states in the United States. Generally, constructions in the eastern and southern sections of the United States are not covered by it. H6 codes apply to anything where hazardous chemicals are used. These codes apply to new construction as well as modification of existing facilities to which changes are being made.

Clean rooms do not have to be white. Whiteness does not make cleanliness. Usually whiteness fools the eye into believing surfaces are clean. When a color scheme is chosen, it should not cause eye fatigue. Poor color scheme strains eye such as when the areas are not defined or the same color is used for walls, floors, and equipment-containing areas. Making bench tops of different color reduces tension; also when there are dark and light areas in the same room, this produces additional vision fatigue. Any color scheme that make appearance of sunlight helps and in some Scandinavian countries, there is a building code requirement to actually allow sunshine in since they are deprived of it around the year.

Furniture and fixtures for a clean-room use should be selected with care. Materials should be chosen to resist the generation of particles by chipping, flaking, oxidizing, or other deterioration. Latex paint should not be used on surfaces, which are subject to repeated contact with personnel or other objects in the clean room. Should these surfaces require painting, an epoxy, polyester, or similar surface coating should be used. Instructions for the preparation and application of these coatings must be followed exactly in order to obtain desired results. Surfaces must be prepared properly.

Contemplated usage should dictate the choice of materials for clean-room furniture and fixtures. Items, which can expect to be humped, knocked, or scraped by personnel, should possess a tough, resilient, low particle-generating surface. A Formica-type material, or material of equivalent surface qualities, is a good choice for tabletops. Most furniture and fixtures may be of conventional design. Sound engineering economy principles should prevail.

In order to maintain good housekeeping in these facilities, it is recommended that a central vacuum system be installed. The material collected in the room is directed out of the room environment through the vacuum tubes. A wet/dry vacuum system will enhance room clean up.

If a central vacuum is not installed, standard vacuums are not recommended. This is because of the large amount of visible dust, which passes through the low-efficiency filtration installed on these vacuums. There is an exception to this statement. Those portable vacuums, which collect and hold dust materials by passing them through water baths or water filters, are acceptable. These water filter vacuums have much higher collection efficiency and do not discharge visible contaminants back into the room environment. Of course, a clean-room vacuum can be used, which has a HEPA filter on its exhaust.

C. Design of Class 10,000 Clean Rooms

Conventionally designed clean rooms of Class 10,000 cleanliness level are turbulent flow facilities. Cleanliness in the room is accomplished by massive amounts of clean air, when compared to normal air-conditioning standards needed to cool a production space. Clean air dilution and air mixing achieve cleanliness. A Class 10,000 environment can be achieved with 20 room air changes per hour. Standard air-conditioning practice might only require 10% to 20% of this air for cooling requirements.

This type of facility, without the aid of additional air-cleaning benefits of laminar flow clean benches, is about the lowest room operational cleanliness that can be economically and consistently achieved by turbulent airflow techniques. The reason for this is that room personnel are continually emitting airborne contaminants, which in turn are being continually mixed by turbulent airflow diffusers. The room is continually mixing and diluting airborne particles.

There are three primary air patterns used in a conventionally designed clean room. The first air pattern is where air enters into the room through ceiling diffusers, which mix and dilute the room air turbulently. A diffuser is installed typically to cover approximately every 150 ft^2. The second type of air pattern is turbulent but more confined to individual vertical planes. Air enters the room through a single linear slot. The third type of air pattern is similar to the second; however, a large perforated plenum, which runs the length of the room, is used to deliver the air to the room. An improvement to this air delivery system is to use an entire ceiling as a perforated plenum to reduce air turbulence. An improvement on this last air delivery system would be to use terminal diffusers, which can be substituted, in all of the above diffuser patterns. Diffusers should not be located in less than every eight ceiling panels in order to give sufficient contaminant removal.

Terminal Diffuser Filters are ducted, hooded minipleat, bead-separator style filter units. They are lightweight, low in profile and are available in HEPA and ULPA efficiencies. These filter units are designed to offer minimum air resistance at any given level of efficiency.

Each filter shall be tested and certified to have an efficiency of not less than a given percentage on micrometer particles. Each filter shall be scan tested at the factory and certified that it has no pinhole leaks in accordance with IES-RP-CC-001. The clean filter static pressure drop shall be no greater than water gauge when operated at an airflow rate of a given cubic feet per minute. Filter medium shall be pleated glass with adhesive bead separators. The media pack shall be sealed on all sides with a solid resin sealant to form a leak proof seal. The filter frame shall be constructed of anodized extruded aluminum per AAC22A31, providing a structurally rigid frame with dimensions of "height × width" depth. Overall dimensions shall be correct to within −1/8" to 0". The back plate/collar assembly shall be one piece 24 ga.-galvanized steel in 10" or 12" diameter. The center divider shall have one access port for leak testing and airflow balancing. Circular diffusion disc shall be 0.050" perforated aluminum, screwdriver adjustable to 90 fpm (± 20%). The grille screen shall be 24 ga. white epoxy-coated carbon steel. This eliminates the possibility of leaks at welded collars.

Clean rooms of the Class 10,000 cleanliness level come in all sizes and ceiling heights. The rooms can be differentiated into low-bay and high-bay rooms, or clean rooms of a standard ceiling height of 8 to 10 ft. Clean rooms can also be of much greater height, some of which exceed 100 ft in height, for satellite and space-related operations.

Generally speaking, these rooms maintain Class 10,000 operational levels by the air-handling system, providing a range of 20 room air changes per hour. If these same amounts of room air changes are provided by a combination of air-handling system and room air recirculation clean benches, such as horizontal laminar flow units, Class 10,000 clean-room environments will be maintained.

As a general observation, standard ceiling height clean rooms have been designed with rectangular floor plans. This has allowed additional wall areas to accept modular panels containing operational equipment, such as electronic consoles or process equipment.

Small rooms of less than 500 ft^2 generally have a square floor plan, while rooms larger than this size have rectangular floor plans. By numerical count, there are many more rooms of greater than 500 ft^2. This is usually because of the overall total investment in equipment, such as air showers, change rooms, and air-handling equipment. The cost of the physical construction of the room is a smaller expense compared to the total cost of building the room. Thus to add additional floor area for future expansion at the time of construction is not a major percentage increase. The initial square room is expanded on one wall even before construction is complete and the resulting floor plan is rectangular.

Sometimes the floor plan of a clean room is "U" shaped or "E" shaped, to increase wall area and facilitate wall penetration from the service area. The service areas are the open ends of the letter plans. The reason for doing this is to restrict dirty items of equipment from the clean room. By providing these floor plans, sufficient wall space is available to make necessary wall penetrations. The second reason is that the

heat load of this equipment does not have to be processed through the clean room air-handling system. The heat load is placed in the service area.

Clean-room complexes have no general floor plans that are similar. The floor plans of these facilities are generated based on product operations. Individual rooms are designated for operations and a product flow is established. The rooms are then situated to allow that flow of product to pass smoothly through the facility. Sometimes entry into these facilities is at one end of the complex. Other times, the entry corridor brings personnel in a garment change area that is located in the center of the complex.

Measures taken to eliminate contamination deriving from the walls have been expensive. In addition, the amount of contaminants contributed by the walls has been overestimated. Before present knowledge was available, the tendency was to use whatever material would produce the fewest particles, with almost no regard to cost.

A smooth, durable surface subject to little or no chipping and flaking will be a satisfactory wall material. In some designs, gypsum board with good quality paint is satisfactory where impact strength is not essential. When the application of a wainscot is required for impact resistance, metal is recommended. It is also recommended that no horizontal dividing strip be installed between two wall materials. A flush joint is preferred.

In an effort to reduce construction costs, reduce the time of construction, and produce an excellent clean-room environment, various companies have developed clean-room wall and ceiling systems. Modular systems consist of wall panels attached to each other through a single draw rod attachment method. The panels are constructed of aluminum-clad hardboard over a corrugated core material. Wood stiles and rails are used for other edges. The panels are painted with a no shedding lacquer. Panels meet a Class A Flame Spread Rating, National Code No. 101. Wall panels are easily removed providing a clear opening for equipment installation or removal.

Doors are generally having a 2-in-thick aluminum frame. Clear or colored Plexiglas panels form the center sections. Push and pull-type hardware is standard with locking hardware optional. Doors are factory hung and shipped with standard panel hardware for quick installation.

Window panels are ideally floor-to-ceiling 8-ft panels either 2-ft or 4-ft wide, with painted steel frames. The center section is clear of colored Plexiglas. The window area is either 19-1/2-in or 43-1/2-in wide by 91-1/2-in high. A 4-ft wide guardrail is supplied for the exterior of the panel in most applications. Window panels are mounted in the same manner as wall panels.

A heavy duty white enameled, 1-1/2-in deep T-bar interlocking steel grid, white enameled, with a resealable gasket material for all lay-in components, is recommended. The grid structure is attached to an overhead structural member, which is part of the clean-room facility. No host building attachments are required for ceiling support in standard ceiling widths. Ceiling structures are self-supporting, wall to wall, for spans up to 20′. Wider spans will require either overhead attachment to host the building or serve as a column support. Ceiling tiles are Class 100 compatible 2′ × 4′ lay-in type.

All internal room wiring and control circuits are appropriately located for servicing. Duplex outlets are provided as required. Sealed 2′ × 4′ lay-in light fixtures are supplied in sufficient quantity to provide 100-ft candles at desktop level. A pluggable buss duct system for power distribution is used where necessary to simplify power hookup of the facility to one drop per buss run. Buss runs can be as long as required for power distribution. Each 10′ section of buss will provide 12 pluggable outlets for service distribution, of which approximately 40% will be available for process equipment hookup.

Plate glass has been the product of choice for many years in clean rooms. One of its drawbacks is its static charge buildup. If a room has much glass area, it can have significant glass surface static charges. A product, which eliminates this static problem, is a static dissipative window. The key to effective static charge removal is the proper installation of the material.

There are many materials which can be used to provide a sufficient floor covering for a Class 10,000 clean room. The economic selection depends on the production use of the clean room. A vinyl square on the floor is sufficient for the clean room under these conditions: if an area is going to be used for light assembly of small components, if there will not be a spillage of fluids on the floor, if there is no biological constraints on the room, if there is no heavy floor loading due to wheeled traffic, if there is not much personnel traffic or movement in the room, and if there will be little need for much liquid chemical cleaning on the floor.

If, however, any of the above conditions change, (such as there will be a fluid spillage on the floor, or there is a biological concern, or there is much personnel traffic in the room, or there will be much fluid chemical cleaning), then a monolithic sheet material is indicated. This material should be seamless to prevent cracks from forming wherein fluids or bacteria can settle. This sheet material should be vinyl if there are no incompatibilities involved.

When sheet vinyl is used on floors, as indicated above, coving of this material to the wall is recommended. Coving is brought up to the wall. If there are chemical incompatibilities, then the sheet floor material that might be selected could be rubber-based material. An alternate solution to the chemical problem, as well as to the heavy floor-loading problem, is to use an epoxy coating over the base concrete floor. A urethane coating could also be used to gain both chemical resistance and a high-wear surface.

The ceilings in Class 10,000 clean rooms can be of plaster or of a suspended type. When using a plaster or plasterboard material, the ceiling should be coated. The minimum coating should be enamel paint. Wall/ceiling interfaces should be filled with a head of material, so that contaminants do not lodge in a sharp corner during cleaning. Ceiling surfaces do attract particles electrostatically, and they will have to be cleaned. Suspended ceilings use "T" bar grid systems with lay-in panels. The "T" bar grid should be of a high quality material and be able to support the ceiling tiles without distortion. The "T" bar system will need to support lay-in light fixtures, as well as terminal HEPA filters, or at the very least, air supply diffusers. The ceiling tiles should have a smooth vinyl surface, or similar smooth reformed surface coating. Ceiling tiles are usually 2′ × 4′ panels, some of, which can also provide acoustical treatment. A smooth ceiling is desirable, which will provide ease of cleaning and offer fewer surfaces to collect fine particles. Fixtures, which attach to the ceiling and are a sealed assembly, may also be used. However, they offer more surface area to collect particles and require more time for cleaning. Further, some fixtures will act as electrostatic attractors and collect more than their share of contaminants—requiring more frequent cleaning.

When a suspended ceiling is used, it must contain a method of clipping down the ceiling panels. This is necessary since most rooms operate at a positive pressure. The ceiling panels must be rigid enough so that when they are clipped

down, they do not flex or bend, because of the positive air pressure, which can cause an arching or upward bowing to the panel. The reverse condition of downward bowing would happen if the rooms were under negative pressure.

Light levels at working surfaces should be 125-ft candles of shadowless illumination. This lighting level is a comfortable intensity for employee work functions, which require visual acuity. The eye compensates for light intensities above this value when the eye pupil restricts light entry. Increasing the light intensity usually is a waste of money because lighting fixtures are bought, which are not required, and power is expended, which is not needed. Further, additional air-conditioning and power will be needed to cool the lights that are not needed. Recessed light fixtures are recommended in facilities of this type. Light patterns can vary from clean room to clean room. Another approach to give shadowless illumination is to install a "T" bar grid system with translucent panels; these "T" bar systems may have air slots in it to allow a more even air distribution pattern.

The use of various vinyl materials to construct an inexpensive clean room is a proven method of design. These units are provided with HEPA-filtered air at the ceiling of the unit. Lighting is through the transparent ceiling. The key to the cleanliness level in these facilities is the amount of clean air delivered to the enclosure. In order to maintain a Class 10,000 condition, the total volume of the enclosure must be changed every 3 minutes with HEPA-filtered air. In the case of the small units above, one 2-by-4-ft HEPA filter ceiling module provides 800 cu ft of air per minute, which will provide more than one air change per minute. This is more than the 20 air changes per hour, which is needed to maintain Class 10,000 conditions in a clean room.

Because it is so difficult to maintain Class 10,000 environments by turbulent flow techniques, these facilities are provided with good air showers and garment change areas in which personnel can fully prepare for clean-room entry.

There are many variations on the proper order and technique of dressing prior to entering into a bio–clean room. The location for entry contains secure type clothing storage lockers for personnel weather protective clothing, jewelry, and other items of value normally carried or worn by personnel. These lockers should be designed to allow the hanging of coats, store overshoes, and have holding bins for jewelry, watches, bracelets, rings, wallets, keys, purses, etc. The locker is provided with a means of attaching a combination lock. The area selected should be large enough to handle the entire shift at one time. These lockers are usually located in a wide aisleway, leading to the change room entrance. Also provided is a shoe cleaner with rotating brushes. It may contain one or more shoe cleaners, depending on the number of persons entering in a short period of time. A central vacuum system location point should be placed in this shoe. A walk-off mat is positioned after shoe cleaning and at the entrance to the first air shower. This air shower is meant to clean heavy- and medium-sized particle off the surface of personnel street clothes. If the entrants to the clean room will be required to remove their street clothes before donning clean garments, then this air shower can be eliminated.

When personnel exit the first air-shower location, they should enter into a washbasin area where they operate it remotely. Washstands of conventional types may be used. Personnel should be required to wash hands and face to remove cosmetics and after-shave talc from their faces. Linen towels can be provided here since it is very difficult to dry the face with a hot-air drier. If personnel are to enter into a bio–clean room, this washstand should be constructed of stainless steel. It can be equipped with a foot-, knee-, or hand position sensor-operated water control valves. The next location contains a hot air, HEPA-filtered hand dryer. This dryer can be sensor operated or foot operated. A large "ON" button switch is not desirable, because people forget and will hit the switch with their clean hands rather than with their elbow. The next station contains a dispenser for under gloves if they are to be used. This dispenser should contain the various size gloves in compartments that are easily opened. If they are disposable gloves and there is packaging associated with the glove, a trash receptacle should be located nearby. The next station provides alcohol or other hand-sanitizing dispenser for personnel entering a bio–clean room. The next station is where personnel dress with headwear, face mask, and then the outer garment cover. Then a spray bottle containing sodium hypochlorite (standard liquid household bleach) and disposable wipes are located in a holding shelf for personnel entering into a bio–clean room. Each individual will use this material prior to putting on shoes or shoe covers. Finally, a bench divides the room and is designed to allow continual use of disinfectant on its surface. Just prior to the next station, a full-length mirror should be located near this area at the exit point of the area. A space should be provided alongside that mirror to display a full-sized photo poster of one of the clean-room employees properly garmented. As persons finally exit from the area, they should step onto a tacky mat and then enter into the second air shower if the garments are not synthetic material, are not processed through a clean-room laundry, or the garment will be used for more than one entry into the clean room. If clean laundered garments are provided with a Class A or B rating, and the garments are only going to be worn once and then recycled to be cleaned, then the second air shower is not needed. However, if garments are of a dirtier class cleanliness level, per ASTM-51-73 method, or garments are going to be reused, then a second air shower is indicated. If in this air shower air velocities are greater than 60 miles per hour of localized impact on the garment surface to be used, then safety goggles should be required in the air shower. This is to prevent airborne particles from being blown in the eyes.

The storage of garments is under HEPA-filtered air in storage cabinet to store garments in a clean condition until the garments are worn again. A clean air storage cabinet, or storage location under the HEPA filters, should be provided so that garments, that will be reused, can be stored without being contaminated by the air of the change area.

The distribution of utilities in Class 10,000 clean rooms depends on the product to be manufactured within the room. A light assembly operation in a large area may function acceptably with standard electrical outlets in walls and in floor penetrations. Since floor penetration is not allowed in pharmaceutical manufacturing, ceiling drops are needed except for the wall receptacles.

Wherever utility penetrations are made, they must be sealed into the penetrated surface. This is to prevent atmosphere changes associated with violent weather conditions from forcing contaminants through these openings into the room. This situation can occur during electrical storms when weather fronts put a wind load on one side of a building, where the utility chases are located, and when an exhaust vent from the clean room to the roof is at a negative pressure and there is a power failure. Because of the exhaust vent and lack of air-conditioning, the clean room changes to a negative pressure. The utility chases are at a positive pressure. The result is that contaminants are driven into the clean room. Sealed utility chases prevent this from occurring.

Control panels, which are user friendly, should be installed in clean rooms. They should be readily accessible. Displays on control panels should be arranged so that only critical information value is prominently presented. This will allow rapid reaction to undesirable events.

One solution to air handling in panel constructed facilities is to use individual blower modules to draw the air from the air return grill at the floor level and move it back over the ceiling to the "T" bar mounted air supply diffuser.

Support rooms and areas should be provided between the clean room and factory or warehouse areas. These areas generally are designed as Class 500,000 areas. They provide a relatively clean location for entry of materials into the clean room and a location for final package of products destined for storage or shipping. These areas contain pass-through boxes to allow material entry and exit. Support space is a function of the process and the volume of product to be handled. Here, pass-through boxes allow materials to enter and exit the clean rooms in a clean state. This support area uses a sheet vinyl floor, which is bounded on one side by the clean room, and on the other three sides by standard wall construction and enamel paint. Air supplied by the diffusers is filtered through 95% efficient filters.

Pass-through boxes are subjected to a large amount of wear and should be constructed of a material that will resist abrasion and rough use. Stainless steel is best. However, a laminate material will be satisfactory for light loads. The box edges should be reinforced. A double door design with an interlock to permit only one door to be opened at a time, will prevent direct contact of personnel between the clean room and the outside areas through the opening. Another method provides a turntable arrangement with one opening, which must be turned to one side for access. Pass-through box framing should be metal to ensure rigid support. Since pass-through boxes are designed to prevent a direct opening between rooms, a means of communication should be provided alongside the box. This can be an intercommunication system, a voice diaphragm, or a speaking tube. An air vent may also be provided in the box to help purge it of contaminants.

VI. THE USP <797> GUIDELINES

Since July 2004, USP Chapter <797> had been undergoing scrutiny and the updated version of the chapter was posted on http://www.usp.org on December 3, 2007, and it has become official on June 1, 2008. The revised chapter is based on thousands of comments received during 30 months of open review and is the result of countless hours of work on the part of the USP Sterile Compounding Expert Committee (2005–2010). This is a broad presentation to facilitate compliance with USP <797> provisions regarding architectural, environmental, and physical standards required for compounding sterile drug preparations.

A. Issues

USP issued its revised version of Chapter 797 (<797>) with a number of changes clarifying issues related to physical infrastructure such as mechanical, electrical, and architectural items for both sterile compounding and hazardous sterile compounding of drug products. The USP <797> is a valuable set of guidelines based on contemporary consensus-based safe practices that describe a best practice for establishing safe processes in compounding sterile medications. USP <797> is considered to be an official minimum standard for compounding sterile medications and it is therefore enforceable by the FDA, state boards of pharmacy, and other regulatory agencies. As such, USP <797> is an enforceable requirement that mandates procedures and processes for sterile drug compounding (mixing) of pharmaceuticals in a clean-room environment. USP <797> establishes ISO requirements for acceptable clean-room airborne particulate concentrations and assessment procedures.

B. Definitions

1. Clean room (also known as the buffer room) is a space in which the concentration of the airborne particles is controlled to meet a specified cleanliness class. For hazardous and nonhazardous clean rooms, mentioned below in Paragraph E with the recommended Option 2, the required level of cleanliness is ISO Class 7. Class 7 clean room limits the maximum concentration of particles to 10,000 particles per cubic feet (352,000 per cubic meter of 0.5 μm or larger).
2. Anteroom is a space leading into and out of the hazardous or nonhazardous clean rooms. This is a transitional space in which activities such as, hand hygiene, garbing procedures, staging of components, and other activities are performed. While the ISO classification of the anteroom serving the hazardous clean room shall be same as the clean room, that is, ISO 7, the ISO classification of the anteroom serving the nonhazardous clean room shall be ISO 8 (or ISO 7, if the architectural design in place incorporates a common anteroom for both hazardous and nonhazardous clean rooms). Anterooms are transition spaces, which ensure direction of airflow and help maintain the required pressure relationships. Nonhazardous clean rooms should be maintained at 0.02-in to 0.03-in positive pressure with respect to their anterooms, which, in turn, should be maintained at 0.02-in positive air pressure with respect to the adjoining circulation spaces. Hazardous clean rooms should be maintained at 0.02-inch negative pressure with respect to their anterooms, which, in turn, should be maintained at 0.02-inch positive air pressure with respect to the adjoining circulation spaces. Use of the anterooms prevents large swings in temperature. Each anteroom shall be equipped an automatic hand washing basin. Anteroom serving hazardous clean room should also be equipped with an eyewash station. For the hazardous clean rooms, anterooms can be used for storing the hazardous drugs so that the use of a dedicated storage room can be avoided.
3. Primary engineering control (PEC): This is an ISO Class 5 space or a device in which compounded sterile preparations (CSPs) take place. While the choice of the ISO 5 device is left to the discretion of the pharmacists using the facilities, the following four devices are recommended:
   a. Biological safety cabinets (BSC): Use of these cabinets is recommended for the hazardous clean rooms. These are vented cabinets meant of the protection of personnel, products, and environment. Air drawn by the BSC should be exhausted outdoors after passing through HEPA filters, integral or duct-mounted external, by a dedicated exhaust fan.
   b. Laminar airflow workstation (LAFW): Use of these devices is recommended for the nonhazardous clean rooms. These devises can be 100% recirculatory type.
   c. CAI (Compounding Aseptic Isolator): This is a form of isolator designed for maintaining aseptic environment within itself. Air exchange into and out of the isolator shall be done through HEPA filters.

   d. CACI (Compounding Aseptic Containment Isolator): This is a form of CAI, designed to provide worker protection from exposure to unacceptable levels to drug exposure. Hundred percent exhaust of the air is required while dealing with hazardous substances. Air exchange into and out of the isolator shall be done through HEPA filters.
4. Air lock: A small room or space ("pass-through" chamber or window) between two rooms of different air pressure, with interlocked doors (one tightly closed at all times) to prevent loss of pressure in the higher-pressure room.

The USP <797> describes three risk levels defined by the complexity of the pharmaceutical compounding process, namely, low-, medium-, and high-risk level compounding, all of which require that work involving the sterile pharmaceutical compounding shall take place under ISO Class 5 conditions within a buffer area that should be ISO Class 7 with appropriate air-conditioning and humidity controls in place in the buffer area environment. These standards are to be exemplified in every category. Class 5 environments require hundreds of air changes of HEPA-filtered air, stringent gowning and masking requirements, anteroom, etc. The Class 5 environment is achievable in four ways:

Option 1: Provide a Class 5 clean room.
Option 2: Provide a Class 5 environment in a PEC defined above. Locate this device in ISO Class 7 buffer room and protect the integrity of the clean-room requirement by providing an ISO Class 7 anteroom for the hazardous clean room, and an ISO Class 8 anteroom for the nonhazardous clean room.
Option 3: Perform all sterile pharmaceutical compounding within a CACI for low-risk levels.
Option 4: Consider use of a portable clean room.

C. Recommendations

1. Determine the risk level of compounding typically performed within the pharmacy (low, medium, or high) and the volume of work to be accomplished at peak periods. The medical centers can perform this essential task with guidance from the USP 797 Workgroup and Chief of Pharmacy. Consider Options 1 to 4 for their impact on ventilation and architectural issues:
   a. Option 1: ISO Class 5 clean rooms will be a very difficult option to follow, primarily because of the severe operational difficulties associated with gowning, masking, scrubbing, very high rate of air changes, and the high cost of the HVAC and architectural features. More importantly, if the air-handling system fails, it will not be possible to continue to use the space for sterile compounding until the system is back up again.
   b. Option 2: Class 7 clean rooms would be easier to construct and maintain than option 1 from an HVAC standpoint requiring on the order of minimum 30 air changes per hour which may include 15 air changes per hour from an ISO Class 5 air-recirculating device, and not hundreds. To simplify the HVAC system design, VA has opted to supply all 30 air changes per hour from the environmental air-handling unit and not use a secondary, dedicated air-circulating unit as stipulated in USP <797> pages 27–28. See the attached room data sheets for HVAC design parameters. The room, however, must be able to maintain the defined particle count during peak operations. Architectural features, however, will still apply such as monolithic, cleanable surfaces, with anteroom and gowning, masking scrubbing, etc. Also, if the air-handling system fails, it would still be possible to continue use the space to maintain ISO Class 5 environment within the operating PEC device.
   c. Option 3: The least impacted option could be the use of CACIs, where a surrounding clean-room environment and air lock and anteroom are not required. However, it may not be possible to perform all procedures in these enclosures.
   d. Option 4: A portable clean room would cost in the range of $40,000 to $80,000, but would be less than a total physical renovation or new addition of a space.
2. For the hazardous clean room, the ISO Class 5 PEC device should be BSC NSF Class II (laminar flow), type B2, with 100% exhaust to outside.
3. A DX (Direct Expansion) system for cooling should not be used. Use of chilled water is more effective in providing accurate environmental control. While it is preferable to provide emergency power for the heating, ventilating and air-conditioning system including all exhaust fans serving the clean rooms and support area, at least the dedicated exhaust fan serving the BSC cabinet, should be on emergency power.
4. Air locks and anterooms: The use of air locks and anterooms should be carefully planned. The medical center staff may consider provision of an air lock in addition to an anteroom where they expect a high volume of compounding in the clean room, otherwise use of an anteroom should be sufficient to maintain pressure in the clean room.
5. Pass-through chamber: Depending on the size and space availability in the clean room and volume of compounding done, the medical center may consider provision of a pass-through window to facilitate passing out of compounded drugs without having pharmacy personnel frequently go in and out of the clean room through an anteroom. The pass-through window should be big enough to facilitate the passage of compounded sterile products or materials and have a tight seal between the clean room and the pharmacy area and should have two access doors. To prevent direct exposure from the clean room to the pharmacy area, both doors should not open at the same time. Provide door interlocks limiting doors to being open.
6. HEPA with prefilters should be accessible for service from outside the clean room.
7. Location of outside air intake is critical. The intake should not be located near plumbing vents, animal room exhausts, generator exhausts, loading docks, automobile entrances, driveways, passenger drop offs, cooling towers, incinerator and boiler stacks, and any other item that may degrade the quality of air. There should be separation of at least 30 ft between the air intakes and exhaust air outlets. Perform a dispersion analysis based on the actual configuration of the pharmacy area, surrounding facilities, and prevailing wind directions, etc. to establish, if a separation of more than 30 ft is required.
8. Monitor room temperature, relative humidity, and pressure via monitoring devices in the clean rooms on a continuing basis.
9. Provide monolithic and cleanable walls, floors, and ceilings.
10. Do not provide floor drains and sinks in the clean room.
11. Operate the dedicated BSC exhaust system around the clock.

12. The external lens of any lighting fixture must be smooth and cleanable.
13. The doorway into the buffer zone or clean room must be of sufficient size to move LAFWs in and out of the buffer zone when required.
14. Seal all wall openings, slots, piping and electrical conduits, and other penetrations to minimize air leakage from the clean room.
15. Provide hand hygiene facilities in the anteroom and touch-less controls to the extent possible to avoid recontamination of hands. Consider items such as automatic controls for entrance door between the anteroom and the clean room. The controls should be on emergency power. Provide electronic devices or photo sensors with time delays for light switches and towel dispensers with electronic sensors. The electronic sensors should be in front of the faucets facing the user to allow water to be run long enough to come to temperature before immersing hands.
16. Provide clothing hooks in the anteroom on the way to the clean room.

Appendix: Air-Handling Unit

AHU Data Sheet

Air-handling unit type	• Variable air volume (VAV) • Note 1
Inside design conditions	Room data sheets
Minimum outside air	Minimum 20%
Minimum supply air changes per hour	Room data sheets
Return air	Room data sheets
Economizer cycle	ASHRAE 90.11—2007
Air balance	Room data sheets
Filtration	• Prefilters, MERV 8 rating • After filters, MERV 14 rating • Final filters, MERV 17 rating • Note 2
Cooling source	• Use chilled water from the central chiller plant • Note 3
Heating source	• Use high-pressure steam from the central boiler plant as the primary source for generating heating hot water and producing "clean steam" for winter humidification • Use medium-pressure steam from the central boiler plant for unit mounted preheat coils
General exhaust system(s)	Required
Special exhaust system(s)	Room data sheets
Heat recovery system	ASHRAE 90.1—2007
Additional energy conservation measures	To meet the mandated goal of 30% additional energy conservation above ASHRAE 90.1—2004, evaluate the use of desiccant dehumidification system to reduce the dew point temperature of the incoming outside air
Emergency power	Required

Nonhazardous Clean Room—Room Data Sheet

Description: The following introductory information is provided for the nonhazardous clean rooms. The room comprises three segments:

1. PEC is a device or a space that provides ISO Class 5 environment for compounding of drugs. Generally, a LAFW is used as the PEC device. The room air need not be exhausted outdoors. Note that USP <797> General Chapter allows the use of a CAI or CACI for low-risk level CSPs even without the use of Class 7 clean room, provided "nonhazardous and radiopharmaceutical CSPs pursuant to a physician's order for a specific patient may be prepared, and administration of such CSPs shall commence within 12 hours of preparation or as recommended by in the manufacturer's package insert whichever is less. See USP <797> for the low-risk conditions.
2. Buffer area is the space in which the PEC is physically located. This is the clean room where activities such as preparation and staging of components used for drug preparation take place. Buffer area is maintained at ISO Class 7 by supplying HEPA-filtered air in a unidirectional manner from the suspended ceiling.
3. Anteroom is an ISO Class 8 or better area, which serves as a transient place to maintain the integrity of buffer area. This space also handles personnel hygiene and garbing of the personnel. Physical separation between the anteroom and buffer area is a wall with doors. Only one set of doors will be able to open at any given time to avoid disruption of the air pressure gradient.

PEC and Buffer Room (Nonhazardous Clean Room)—Room Data Sheet

Inside design conditions	• Cooling mode: 68°F (20°C) dry-bulb temperature (maximum), 55% relative humidity • Heating mode: 68°F (20°C) dry-bulb temperature (minimum), 40% relative humidity (Room level humidity control is not required.)

(*Continued*)

Appendix: Air-Handling Unit (*Continued*)

Minimum supply air changes per hour	30—CV required (Air changes listed above must be able to limit the concentration of the airborne particles. Provide more air changer per hour, if required, to maintain ISO Class 7 particulate count.)
Return air	Permitted
Exhaust air	Not required with 100% recirculatory ISO Class 5. Specific configurations of the BSC cabinets may require exhaust from the room air to outdoors. Coordinate exhaust air volume and system configuration per manufacturer's recommendations.
Individual room temperature control	Required
Room air balance	Positive (+) with respect to the anteroom. (Provide outside air as required to maintain the specified pressure differential)
Room noise level	NC 40
Anteroom (Nonhazardous Clean Room)—Room Data Sheet	
Inside design conditions	• Cooling mode: 68°F (20°C) dry-bulb temperature (maximum), 55% relative humidity • Heating mode: 68°F (20°C)] dry-bulb temperature (minimum), 40% relative humidity. (Room level humidity control is not required.)
Minimum supply air changes per hour	20—CV required (Air changes listed above must be able to limit the concentration of the airborne particles. Provide more air changer per hour, if required, to maintain ISO Class 8 particulate count.)
Return air	Permitted
Exhaust air	Not required
Individual room temperature control	Required
Room air balance	• Positive (+) with respect to circulation space • Negative (−) with respect to buffer room
Room noise level	NC 40

Hazardous Clean Room—Room Data Sheet

Description: The following introductory information is provided for the hazardous clean rooms. The room comprises of three segments:

1. PEC is a device or a space that provides ISO Class 5 environment for compounding of drugs. Generally, a BSC Class II B2 is used as the PEC device through which the air is exhausted outdoors after passing over the duct-mounted HEPA filter. The HEPA is an integral to the BSC unit, and additional in duct HEPA is not needed.
2. Buffer area is the space in which the PEC is physically located. This is the clean room where activities such as preparation and staging of components used for drug preparation take place. Buffer area is maintained at ISO Class 7 by supplying HEPA-filtered air and establishing unidirectional flow.
3. This room can also be used to store hazardous drugs provided adequate storage space is available. Otherwise a separate room is required to store hazardous drugs. This room should be ventilated at minimum 12 air changes per hour with negative pressure. Exhaust from this room should be connected to the special exhaust system serving the buffer room and anteroom.
4. Anteroom is an ISO Class 7 or better area, which serves as a transient place to maintain the integrity of buffer area. This space also handles personnel hygiene and garbing of the personnel. Physical separation between the anteroom and buffer area is a wall with doors. Only one set of doors will be able to open at any given time to avoid disruption of the air pressure gradient.
5. See USP <797> for additional requirement for lighting and ceiling surfaces, caulking, etc.

PEC and Buffer Room (Hazardous Clean Room)—Room Data Sheet	
Inside design conditions	• Cooling mode: 68°F (20°C) dry-bulb temperature (maximum), 55% relative humidity • Heating mode: 68°F (20°C) dry-bulb temperature (minimum), 40% relative humidity. Room level humidity control is not required.
Minimum supply air changes per hour	30—CV Required
Return air	Not permitted
Exhaust air	100% (All air supplied to the buffer room shall be exhausted outdoors without in duct HEPA filters in a manner to avoid facility entrainment and building wake effect. BSC or equivalent ISO Class 5 device shall be served by a special exhaust system without additional in duct HEPA filters in accordance with the manufacturer's recommendations. Buffer area and anteroom below shall be exhausted outdoors through another special exhaust system but without HEPA filters.)
Individual room temperature control	Required
Room air pressure	Negative (−) with respect to the anteroom
Room noise level	NC 40

(*Continued*)

Appendix: Air-Handling Unit (*Continued*)

Anteroom (Hazardous Clean Room)—Room Data Sheet

Inside design conditions	• Cooling mode: 68°F (20°C) dry-bulb temperature (maximum), 55% Relative Humidity • Heating mode: 68°F (20°C) dry-bulb temperature (minimum), 40% relative humidity. (Room level humidity control is not required.)
Minimum supply air changes per hour	30—CV required
Return air	Not permitted
Exhaust air	100%, see buffer room above
Individual room temperature control	Required
Room air balance	Positive (+) with respect to hazardous clean room Positive (+) with respect to Circulation Space whose room pressure is assumed as neutral (0)
Room noise level	NC 40

Controlled Substance Vault and Secured Dispensing Receiving Area--Room Data Sheet

Inside Design Conditions	• Cooling mode: 70°F (21°C) dry-bulb temperature (maximum), 50% relative humidity • Heating Mode: 75°F (24°C) dry-bulb temperature (minimum), 35% Relative Humidity • 5°F (2.8°C) dead-band (Room level humidity control is not required. Room Humidity shall be 40% if this room is served by the same AHU serving the clean rooms above.)
Minimum supply air changes per hour	6—VAV permitted
Return air	Permitted
Exhaust air	Not required
Individual room temperature control	Required
Room air balance	Neutral (0)
Room noise level	NC 40

Dispensing, Prepacking and EXTEMP—Room Data Sheet

Inside design conditions	• Cooling mode: 70°F (21°C) dry-bulb temperature (maximum), 50% relative humidity • Heating mode: 75°F (24°C) dry-bulb temperature (minimum), 40% relative humidity • 5°F (2.8°C) dead-band (Room level humidity control is not required. Room Humidity shall be 40% if this room is served by the same AHU serving the clean rooms above.)
Minimum supply air changes per hour	6—VAV permitted
Return air	Permitted
Exhaust air	Not required
Individual room temperature control	Required
Room air balance	Neutral (0)
Room noise level	NC 40

Note 1: The HVAC system design criteria are based on the latest (December 2007) publication of the USP (The United States Pharmacopeial Convention) Revised Bulletin <797> Pharmaceutical Sterile Preparations. A dedicated air-handling unit is not required to serve the hazardous and/or nonhazardous clean rooms so long as any air-handling unit serving these spaces can meet all requirements outlined in the AHU data sheet and the room data sheets.
Note 2: Locate the final filters (third bed) on the downstream side of the individual air terminal units serving each hazardous and nonhazardous clean room. Oversize the final filters to minimize the pressure drop. For remaining rooms, terminal HEPA filters are not required.
Note 3: Dedicated chiller is required if chilled water is not available year-round.

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Approved Excipients in Sterile Dosage Forms

Ingredient	Dosage Form	Qty	Unit
1,2-dimyristoyl-*sn*-glycero-3-[phospho-s-(1-glycerol)]	IV(infusion); suspension, injection	0.15	%
1,2-dioleoyl-*sn*-glycero-3-phosphocholine	Epidural; injection, suspension, liposomal	0.42	%
1,2-dipalmitoyl-*sn*-glycero-3-[phospho-rac-(1-glycerol)]	Epidural; injection, suspension, liposomal	0.09	%
1,2-distearoyl-*sn*-glycero-3-[phospho-rac-(1-glycerol)]	Intravenous; injection, powder, lyophilized, for liposomal suspsension	8.4	%
1,2-distearoyl-*sn*-glycero-3-phosphocholine	Intravenous; solution, liposome, injection	2.804	%
1-methyl-2-pyrrolidinone	Subcutaneous; injection	25.85	%
Acesulfame potassium	Dental; solution	0.12	%
Acetic acid	Intravenous; injectable	0.01	%
Acetic acid	Intramuscular; injection	0.02	%
Acetic acid	Ophthalmic; solution	0.043	%
Acetic acid	IV(infusion); injection	1	%
Acetic acid	Intravenous; injection	12.75	%
Acetic acid, glacial	Subcutaneous; liquid	0.0107	%
Acetic acid, glacial	Subcutaneous; powder, for injection solution, lyophilized	0.041	%
Acetic acid, glacial	Intravenous; injectable	0.046	%
Acetic acid, glacial	Intravenous; solution, injection	0.051	%
Acetic acid, glacial	Ophthalmic; solution, drops	0.09	%
Acetic acid, glacial	Subcutaneous; solution, injection	0.11	%
Acetic acid, glacial	IM–SC; injection	0.2	%
Acetic acid, glacial	IV–SC; injection	0.2	%
Acetic acid, glacial	IV–SC; liquid	0.2	%
Acetic acid, glacial	Ophthalmic; solution	0.2	%
Acetic acid, glacial	IM–IV; injection	0.25	%
Acetic acid, glacial	Intramuscular; injection	0.25	%
Acetic acid, glacial	IV(infusion); powder, for injection solution, lyophilized	0.27	%
Acetic acid, glacial	IM–IV–SC; injection	0.352	%
Acetic acid, glacial	Intravenous; injection	0.36	%
Acetic acid, glacial	IV(infusion); injection	0.44	%
Acetic acid, glacial	IV(infusion); solution, injection	0.715	%
Acetic acid, glacial	Auricular (otic); suspension, liquid	2.55	%
Acetone sodium bisulfite	Inhalation; solution	0.5003	%
Acetylcysteine	Inhalation; solution	0.5	%
Acetyltryptophan	Intravenous; injection	0.02	%
Adipic acid	Intramuscular; injection	1	%
Alanine	IV(infusion); solution, injection	21	%
Alanine	IV(infusion); injection	77	%

Ingredient	Dosage Form	Qty	Unit
Albumin aggregated	Intravenous; injection	0.15	%
Albumin colloidal	Intravenous; powder, for injection solution	0.1	%
Albumin human	Subcutaneous; injectable	0.1	%
Albumin human	Intravenous; injection	1	%
Albumin human	Intravenous; powder, for injection solution	1	%
Albumin human	IV(infusion); injection	1	%
Albumin human	IV(infusion); powder, for injection solution, lyophilized	80	%
Albumin microshere human serum	Intravenous; injection	0.5	%
Alcohol	Respiratory (inhalation); solution, for inhalation	0.081	%
Alcohol	Ophthalmic; solution	0.5	%
Alcohol	IV–SC; injection	0.945	%
Alcohol	Ophthalmic; solution, drops	1.4	%
Alcohol	IM–IV–SC; injection	6.1	%
Alcohol	IM–IV; solution, injection	10	%
Alcohol	Intramuscular; solution, injection	10	%
Alcohol	IM–IV; injection	11	%
Alcohol	Intramuscular; injection	12	%
Alcohol	Dental; solution	12.8	%
Alcohol	Inhalation; solution	25	%
Alcohol	IV(infusion); solution, injection	30	%
Alcohol	Inhalation; aerosol, spray	33	%
Alcohol	IV(infusion); injection	34.3	%
Alcohol	Intravenous; solution, injection	40	%
Alcohol	Intravenous; injection	49	%
Alcohol	Inhalation; aerosol, metered	95.89	%
Alcohol, dehydrated	IV(infusion); powder, for injection solution, lyophilized	0.0365	%
Alcohol, dehydrated	Ophthalmic; solution	0.5	%
Alcohol, dehydrated	Ophthalmic; solution, drops	0.5	%
Alcohol, dehydrated	Nasal; aerosol, metered	0.7	%
Alcohol, dehydrated	Nasal; aerosol	2	%
Alcohol, dehydrated	IM–IV–SC; injection	4.93	%
Alcohol, dehydrated	Extracorporeal; solution	5	%
Alcohol, dehydrated	Photopheresis; solution	5	%
Alcohol, dehydrated	IM–IV; injectable	10	%
Alcohol, dehydrated	IM–IV; solution, injection	10	%
Alcohol, dehydrated	Intramuscular; injection	10	%
Alcohol, dehydrated	Intramuscular; solution, injection	10	%
Alcohol, dehydrated	Respiratory (inhalation); aerosol, metered	10	%
Alcohol, dehydrated	Dental; solution	11.34	%
Alcohol, dehydrated	IM–IV; injection	20	%
Alcohol, dehydrated	Inhalation; aerosol, metered	34.548	%
Alcohol, dehydrated	Intravenous; solution, concentrate	39.46	%
Alcohol, dehydrated	Intravenous; injection	40	%

Ingredient	Dosage Form	Qty	Unit
Alcohol, dehydrated	IV(infusion); solution, injection	49.7	%
Alcohol, dehydrated	Intravesical; solution	50	%
Alcohol, dehydrated	IV(infusion); injection	80	%
Alcohol, denatured	Dental; gel	1.8	%
Alcohol, diluted	IM–IV; injection	10	%
Alfadex	Intracavitary; powder, for injection solution, lyophilized	0.129	%
Alginic acid	Ophthalmic; suppository, insert, controlled release	1	mg
Alpha-tocopherol	Intravenous; injection, powder, lyophilized, for liposomal suspension	0.064	%
DL-Alpha-tocopherol	Intravenous; solution, concentrate	0.075	%
Aluminum acetate	Auricular (otic); solution	0.79	%
Aluminum sulfate	Auricular (otic); solution	0.79	%
Amerchol-cab	Ophthalmic; ointment	0.002	%
Ammonium acetate	Intramuscular; injection	0.4	%
Ammonium acetate	Intravenous; injection	0.4	%
Ammonium acetate	IV(infusion); injection	0.4	%
Ammonium hydroxide	Intravenous; injection	0.219	%
Ammonium sulfate	Intravenous; injection, suspension, liposomal	0.2	%
Antipyrine	Ophthalmic; solution	0.1	%
Arginine	IV(infusion); solution, injection	29	%
Arginine	Intravenous; powder, for injection solution	78	%
Arginine	IV(infusion); injection	88	%
Ascorbic acid	Intravenous; powder, for injection solution, lyophilized	0.088	%
Ascorbic acid	Inhalation; aerosol, spray	0.1	%
Ascorbic acid	IM–IV; injection	0.2	%
Ascorbic acid	Intravenous; powder, for injection solution	0.2	%
Ascorbic acid	Intravenous; solution, injection	0.2	%
Ascorbic acid	Nerve block; injection	0.2	%
Ascorbic acid	IV(infusion); powder, for injection solution, lyophilized	0.5	%
Ascorbic acid	Intramuscular; injection	1	%
Ascorbic acid	Subcutaneous; injection	1	%
Ascorbic acid	Inhalation; solution	1.02	%
Ascorbic acid	IV(infusion); injection	50.4	%
Ascorbic acid	Intravenous; injection	62.5	%
Ascorbic acid	Inhalation; aerosol, metered	95.95	%
Aspartic acid	IV(infusion); injection	0.68	%
Barium sulfate	Intrauterine; suppository, insert, controlled release	10	mg
Benzalkonium chloride	Intraocular; solution	0.0052	%
Benzalkonium chloride	Ophthalmic; gel	0.008	%
Benzalkonium chloride	Auricular (otic); solution, drops	0.02	%
Benzalkonium chloride	Auricular (otic); suspension	0.02	%
Benzalkonium chloride	Ophthalmic; ointment	0.025	%
Benzalkonium chloride	Ophthalmic; suspension	0.025	%
Benzalkonium chloride	Ophthalmic; suspension, drops	0.025	%

Ingredient	Dosage Form	Qty	Unit
Benzalkonium chloride	Auricular (otic); solution	0.0275	%
Benzalkonium chloride	Nasal; spray, metered	0.1176	%
Benzalkonium chloride	Nasal; spray	0.119	%
Benzalkonium chloride	Ophthalmic; solution, drops	0.512	%
Benzalkonium chloride	Nasal; solution	1	%
Benzalkonium chloride	Ophthalmic; solution	8.8	%
Benzalkonium chloride	Inhalation; solution	20	%
Benzethonium chloride	IM–IV; injection	0.01	%
Benzethonium chloride	IV(infusion); injection	0.012	%
Benzethonium chloride	Auricular (otic); solution, drops	0.02	%
Benzethonium chloride	Nasal; spray, metered	0.02	%
Benzethonium chloride	Intravenous; powder, for injection solution	0.05	%
Benzethonium chloride	Auricular (otic); solution	0.1	%
Benzododecinium bromide	Ophthalmic; solution	0.012	%
Benzododecinium bromide	Ophthalmic; solution, gel forming, extended release	0.012	%
Benzoic acid	Irrigation; solution	0.024	%
Benzoic acid	Intramuscular; solution, injection	0.2	%
Benzoic acid	IM–IV; injection	5	%
Benzyl alcohol	Nasal; spray, metered	0.0366	%
Benzyl alcohol	Intravenous; emulsion, injection	0.1	%
Benzyl alcohol	Subcutaneous; liquid	0.225	%
Benzyl alcohol	Intrathecal; injection	0.45	%
Benzyl alcohol	Nasal; solution	0.5	%
Benzyl alcohol	Intracavitary; powder, for injection solution, lyophilized	0.84	%
Benzyl alcohol	Subcutaneous; solution, injection	0.885	%
Benzyl alcohol	Intra-arterial; injection	0.9	%
Benzyl alcohol	Intradermal; injection	0.9	%
Benzyl alcohol	Intratumor; injection	0.9	%
Benzyl alcohol	Intravenous; solution	0.9	%
Benzyl alcohol	N/A; liquid	0.9	%
Benzyl alcohol	Intralesional; suspension, injection	0.916	%
Benzyl alcohol	Intramuscular; suspension, injection	0.916	%
Benzyl alcohol	Intrasynovial; suspension, injection	0.916	%
Benzyl alcohol	Soft tissue; suspension, injection	0.916	%
Benzyl alcohol	Subconjunctival; injection	0.945	%
Benzyl alcohol	Epidural; injection	1	%
Benzyl alcohol	Extracorporeal; injection	1	%
Benzyl alcohol	IM–IV; injectable	1	%
Benzyl alcohol	Intrabursal; injection	1	%
Benzyl alcohol	Intralesional; injection	1	%
Benzyl alcohol	Intramuscular; injection, sustained action	1	%
Benzyl alcohol	Intrasynovial; injection	1	%
Benzyl alcohol	Soft tissue; injection	1	%

Ingredient	Dosage Form	Qty	Unit
Benzyl alcohol	IM–SC; injection, sustained action	1.2	%
Benzyl alcohol	Intra-articular; Injection	1.5	%
Benzyl alcohol	IV–SC; injection	1.5	%
Benzyl alcohol	Subcutaneous; injection	1.5	%
Benzyl alcohol	IM–IV–SC; injection	1.575	%
Benzyl alcohol	Intravenous; powder, for injection solution	1.8	%
Benzyl alcohol	IM–IV; solution, injection	2	%
Benzyl alcohol	IM–SC; injection	2	%
Benzyl alcohol	Intravenous; injectable	2.02	%
Benzyl alcohol	Intravenous; solution, injection	2.02	%
Benzyl alcohol	IV(infusion); solution, injection	2.02	%
Benzyl alcohol	IV(infusion); injection	3	%
Benzyl alcohol	Intramuscular; injectable	4	%
Benzyl alcohol	IM–IV; injection	5.21	%
Benzyl alcohol	IM–IV; powder, for injection solution	6.69	%
Benzyl alcohol	IV(infusion); powder, for injection solution	6.69	%
Benzyl alcohol	Auricular (otic); suspension, liquid	9	%
Benzyl alcohol	Intramuscular; solution, injection	10	%
Benzyl alcohol	Intravenous; injection	10.4	%
Benzyl alcohol	Intramuscular; injection	10.962	%
Benzyl alcohol	Dental; paste	25	mg
Benzyl benzoate	Intramuscular; solution, injection	15	%
Benzyl benzoate	Intramuscular; injectable	20	%
Benzyl benzoate	Intramuscular; injection	46	%
Benzyl chloride	Intravenous; injection	0.001	%
Bibapcitide	Intravenous; injection	0.01	%
Boric acid	Auricular (otic); solution	0.049	%
Boric acid	Ophthalmic; powder, for solution	0.06	%
Boric acid	Ophthalmic; solution, gel forming, extended release	0.3	%
Boric acid	Intravenous; solution, injection	0.319	%
Boric acid	Ophthalmic; suspension, drops	0.6	%
Boric acid	Ophthalmic; suspension	1	%
Boric acid	Ophthalmic; solution, drops	1.9	%
Boric acid	Ophthalmic; solution	37.2	%
Butylated hydroxyanisole	Nasal; spray, metered	0.0002	%
Butylated hydroxyanisole	IV(infusion); injection	0.0003	%
Butylated hydroxyanisole	Intramuscular; injection	0.03	%
Butylated hydroxyanisole	Nasal; solution	2	%
Butylated hydroxytoluene	IV(infusion); injection	0.001	%
Butylated hydroxytoluene	Intravenous; powder, for injection solution, lyophilized	0.0015	%
Butylated hydroxytoluene	Nasal; spray, metered	0.01	%
Butylated hydroxytoluene	Intramuscular; injection	0.03	%
Caffeine	Ophthalmic; solution	2	%

Ingredient	Dosage Form	Qty	Unit
Calcium	Intramuscular; injection	0.0012	%
Calcium carbonate	Auricular (otic); solution	0.382	%
Calcium carbonate	Respiratory (inhalation); solution, injection	4.024	%
Calcium chloride	Ophthalmic; solution, drops	0.006	%
Calcium chloride	Intravascular; injection	0.0074	%
Calcium chloride	Intravenous; solution, liposome, injection	0.028	%
Calcium chloride	AN, infiltration; injection	0.033	%
Calcium chloride	Caudal block; injection	0.033	%
Calcium chloride	Epidural; injection	0.033	%
Calcium chloride	Nerve block; injection	0.033	%
Calcium chloride	Subcutaneous; injectable	0.04	%
Calcium chloride	Intraocular; solution	0.048	%
Calcium chloride	Ophthalmic; powder, for solution	0.048	%
Calcium chloride	Subcutaneous; injection	0.053	%
Calcium chloride	Intravenous; injection	0.074	%
Calcium chloride	Intraperitoneal; solution	2.57	%
Calcium chloride	IM–IV; injection	4	%
Calcium chloride	Intramuscular; injection	4	%
Calcium gluceptate	Intravenous; injection	5	%
Calcium hydroxide	Intravenous; injection	0.37	%
Calteridol calcium	Intravenous; injection	0.023	%
Carbomer 1342	Ophthalmic; emulsion	0.05	%
Carbomer 934P	Ophthalmic; suspension, drops	0.45	%
Carbomer 940	Ophthalmic; gel	4	%
Carbomer 974P	Ophthalmic; suspension, drops	0.45	%
Carbomer 974P	Ophthalmic; suspension	0.5	%
Carbon dioxide	Inhalation; gas	95	%
Carboxymethylcellulose	Intra-articular; injection	0.2	%
Carboxymethylcellulose	Intramuscular; injection	0.9	%
Carboxymethylcellulose sodium	Intrasynovial; injection	0.1	%
Carboxymethylcellulose sodium	Nasal; spray, metered	0.15	%
Carboxymethylcellulose sodium	Dental; gel	0.4	%
Carboxymethylcellulose sodium	Intra-articular; injection	0.5	%
Carboxymethylcellulose sodium	Ophthalmic; solution, drops	0.5	%
Carboxymethylcellulose sodium	Soft tissue; injection	0.5	%
Carboxymethylcellulose sodium	Intramuscular; injection, microspheres	1	%
Carboxymethylcellulose sodium	Intramuscular; injection	3	%
Carboxymethylcellulose sodium	Intramuscular; powder, for injection solution, lyophilized	3	%
Carboxymethylcellulose sodium	Subcutaneous; implant	16	mg
Carboxymethylcellulose sodium	Dental; paste	174	mg
Castor oil	Ophthalmic; emulsion	1.25	%
Cellulose microcrystalline/carboxymethylcellulose sodium	Nasal; spray, metered	1.5	%
Cellulose microcrystalline/carboxymethylcellulose sodium	Nasal; spray	2	%

Ingredient	Dosage Form	Qty	Unit
Cellulose, microcrystalline	Intra-articular; injection	0.05	%
Cellulose, microcrystalline	Intramuscular; injection	0.05	%
Cellulose, microcrystalline	Nasal; spray, metered	0.15	%
Cellulose, microcrystalline	Intravitreal; implant	1.66	mg
Cellulose, microcrystalline	Intravenous; injection	14.9	%
Cetyl alcohol	Ophthalmic; suspension	0.5	%
Cetyl alcohol	Auricular (otic); suspension	1	%
Charcoal, activated	Intramuscular; injectable	0.3	%
Charcoal, activated	Intravenous; injectable	0.3	%
Chlorobutanol	Nasal; solution	0.05	%
Chlorobutanol	Ophthalmic; solution, drops	0.2	%
Chlorobutanol	Subcutaneous; injection	0.25	%
Chlorobutanol	AN, infiltration; injection	0.4	%
Chlorobutanol	IM–IV–SC; injection	0.5	%
Chlorobutanol	IM–IV; injection	0.5	%
Chlorobutanol	IM–SC; injection	0.5	%
Chlorobutanol	Inhalation; solution	0.5	%
Chlorobutanol	Nasal; spray	0.5	%
Chlorobutanol	Nasal; spray, metered	0.5	%
Chlorobutanol	Nerve block; injection	0.5	%
Chlorobutanol	Ophthalmic; solution	0.5	%
Chlorobutanol	Intramuscular; injectable	0.525	%
Chlorobutanol	Ophthalmic; powder, for solution	0.55	%
Chlorobutanol	IV(infusion); injection	0.6	%
Chlorobutanol	Ophthalmic; ointment	0.65	%
Chlorobutanol	Intramuscular; injection	5	%
Chlorobutanol hemihydrate	Intramuscular; injection	0.525	%
Chlorobutanol hemihydrate	Intravenous; solution, injection	0.525	%
Chlorobutanol, anhydrous	Intravenous; injection	0.5	%
Chlorobutanol, anhydrous	Ophthalmic; solution	0.5	%
Chlorobutanol, anhydrous	Intramuscular; injection	0.525	%
Chloroxylenol	Auricular (otic); solution	0.1	%
Cholesterol	Intravenous; injection, suspension, liposomal	0.319	%
Cholesterol	Epidural; injection, suspension, liposomal	0.33	%
Cholesterol	Intravenous; solution, liposome, injection	0.684	%
Cholesterol	Intravenous; injection, powder, lyophilized, for liposomal suspension	5.2	%
Citrate	Intravenous; injectable	0.72	%
Citric acid	Inhalation; aerosol, metered	0.0002	%
Citric acid	Intravenous; solution, concentrate	0.0025	%
Citric acid	AN, infiltration; injection	0.02	%
Citric acid	Epidural; injection	0.02	%
Citric acid	Nerve block; injection	0.0202	%
Citric acid	Intramuscular; powder, for injection solution	0.03	%

Ingredient	Dosage Form	Qty	Unit
Citric acid	Intrapleural; powder, for injection solution	0.03	%
Citric acid	Intrathecal; powder, for injection solution	0.03	%
Citric acid	Auricular (otic); solution, drops	0.04	%
Citric acid	IM–IV; injectable	0.05	%
Citric acid	Ophthalmic; solution, drops	0.05	%
Citric acid	Intravenous; solution, injection	0.075	%
Citric acid	IM–IV; solution, injection	0.08	%
Citric acid	Intracardiac; injection	0.2	%
Citric acid	IV(infusion); solution, injection	0.2	%
Citric acid	Ophthalmic; solution	0.2	%
Citric acid	IM–SC; injection	0.219	%
Citric acid	Nasal; spray	0.26	%
Citric acid	IM–IV; injection	0.33	%
Citric acid	Inhalation; solution	0.4404	%
Citric acid	Intravenous; solution	0.5017	%
Citric acid	Auricular (otic); solution	1	%
Citric acid	IM–IV–SC; injection	1.262	%
Citric acid	Intramuscular; injection	2	%
Citric acid	Nasal; spray, metered	3.5	%
Citric acid	IV(infusion); injection	5.1	%
Citric acid	IV(infusion); powder, for injection solution	6.92	%
Citric acid	Intravenous; powder, for injection solution, lyophilized	7.692	%
Citric acid	Intravenous; injection	20	%
Citric acid	Nasal; solution	20	%
Citric acid	Intravenous; injectable	41.36	%
Citric acid	Intravenous; powder, for injection solution	50	%
Citric acid monohydrate	IM–IV; injectable	0.05	%
Citric acid monohydrate	IM–IV; solution	0.05	%
Citric acid monohydrate	Intraocular; solution	0.05	%
Citric acid monohydrate	Ophthalmic; solution	0.05	%
Citric acid monohydrate	Ophthalmic; solution, drops	0.05	%
Citric acid monohydrate	Intravenous; injectable	0.052	%
Citric acid monohydrate	Intravenous; solution, injection	0.082	%
Citric acid monohydrate	IM–IV; solution, injection	0.0875	%
Citric acid monohydrate	IV(infusion); solution, injection	0.14	%
Citric acid monohydrate	Intravenous; solution	0.156	%
Citric acid monohydrate	AN, infiltration; injection	0.1613	%
Citric acid monohydrate	Nerve block; injection	0.1613	%
Citric acid monohydrate	Nasal; spray, metered	0.17	%
Citric acid monohydrate	IM–IV; injection	0.361	%
Citric acid monohydrate	Nasal; solution	0.42	%
Citric acid monohydrate	Intramuscular; injectable	0.5	%
Citric acid monohydrate	Intracardiac; injection	1.05	%

Ingredient	Dosage Form	Qty	Unit
Citric acid monohydrate	IV(infusion); injection	1.05	%
Citric acid monohydrate	IM–IV–SC; injection	1.26	%
Citric acid monohydrate	Intravenous; powder, for injection solution	21.9	%
Citric acid monohydrate	Intravenous; powder, for injection solution, lyophilized	41.36	%
Citric acid monohydrate	Intravenous; injection	52.5	%
Citric acid, hydrous	IV(infusion); injection	0.0032	%
Citric acid, hydrous	IM–IV–SC; injection	1.26	%
Citric acid, hydrous	Intravenous; injection	10.5	%
Cottonseed oil	Intramuscular; injection	87.46	%
Creatinine	Ophthalmic; solution, drops	0.2	%
Creatinine	Auricular (otic); solution	0.5	%
Creatinine	Intramuscular; injection	0.5	%
Creatinine	Ophthalmic; solution	0.5	%
Creatinine	IM–IV; injection	0.8	%
Creatinine	Intra-articular; injection	0.8	%
Creatinine	Intralesional; injection	0.8	%
Creatinine	Intrasynovial; injection	0.8	%
Creatinine	Soft Tissue; injection	0.8	%
M-Cresol	IM–IV–SC; injection	0.1	%
M-Cresol	IV(infusion); injection	0.1	%
M-Cresol	Intradermal; injection	0.16	%
M-Cresol	Subcutaneous; suspension, injection	0.172	%
M-Cresol	Subcutaneous; solution, injection	0.22	%
M-Cresol	IM–SC; injection	0.25	%
M-Cresol	Intramuscular; powder, for injection solution, lyophilized	0.3	%
M-Cresol	Subcutaneous; powder, for injection solution, lyophilized	0.3	%
M-Cresol	Subcutaneous; injectable	0.315	%
M-Cresol	Subcutaneous; injection	0.45	%
Croscarmellose sodium	Intramuscular; injection	1	%
Crospovidone	Intra-articular; injection	0.02	%
Crospovidone	Intramuscular; injection	0.02	%
Crospovidone	Implantation; pellet	2	mg
Cysteine	IM–SC; injection, sustained action	0.1	%
Cysteine	IV(infusion); solution, injection	2	%
Cysteine	Intravenous; powder, for injection solution, lyophilized	2.6	%
Cysteine hydrochloride	Intravenous; powder, for injection solution	0.1	%
Cysteine hydrochloride	IV(infusion); powder, for injection solution, lyophilized	1.5	%
Cysteine hydrochloride	IV(infusion); injection	2	%
D&C Red No. 33	Dental; solution	0.0007	%
D&C Yellow No. 10	Dental; gel	0.003	%
Dextran 40	Intravenous; powder, for injection solution, lyophilized	30	%
Dextrose	Intramuscular; injection	4.4	%
Dextrose	IM–IV; injection	5	%

Ingredient	Dosage Form	Qty	Unit
Dextrose	IM–IV; powder, for injection solution	5	%
Dextrose	Intraspinal; injection	5	%
Dextrose	Intravenous; injectable	5	%
Dextrose	Intravenous; powder, for injection solution	5	%
Dextrose	Intravenous; solution, injection	5	%
Dextrose	IV(infusion); powder, for injection solution	5	%
Dextrose	Nasal; spray	5	%
Dextrose	Nasal; spray, metered	5	%
Dextrose	IV(infusion); solution, injection	5.17	%
Dextrose	IV(infusion); injection	5.6	%
Dextrose	Spinal; injection	7.5	%
Dextrose	Intravenous; injection	30	%
Dextrose solution	IV(infusion); powder, for injection solution	5	%
Dextrose, anhydrous	Nasal; spray	0.275	%
Dextrose, anhydrous	Nasal; spray, metered	0.5	%
Dextrose, anhydrous	Intravenous; kit	1.11	gm
Dextrose, anhydrous	IM–SC; injection	3.75	%
Dextrose, anhydrous	Intravenous; injection	4.7	%
Dextrose, anhydrous	IV(infusion); solution, injection	4.7	%
Dextrose, anhydrous	IM–IV; injectable	5	%
Dextrose, anhydrous	Intramuscular; injection	5	%
Dextrose, anhydrous	Intravenous; solution, injection	5	%
Dextrose, anhydrous	IV(infusion); injection	5.43	%
Dextrose, anhydrous	Spinal; injection	8.25	%
Diatrizoic acid	Intramuscular; injection	59.7	%
Diatrizoic acid	Intravenous; injection	59.7	%
Dichlorodifluoromethane	Nasal; aerosol, metered	1.72	%
Dichlorodifluoromethane	Inhalation; aerosol, metered	74.029	%
Dichlorotetrafluoroethane	Nasal; aerosol, metered	0.86	%
Dichlorotetrafluoroethane	Inhalation; aerosol, metered	51.12	%
Diethanolamine	IV(infusion); injection	1.5	%
Dimethyl sulfoxide	Subcutaneous; implant	104	mg
Dimethylsiloxane/methylvinylsiloxane copolymer	Implantation; pellet, implant	142	mg
Dimethylsiloxane/methylvinylsiloxane copolymer	Implantation; rod	142	mg
Dimyristoyl lecithin	IV(infusion); suspension, injection	0.34	%
Dimyristoyl lecithin	Intravenous; powder, for injection solution, lyophilized	7.05	%
Dioctylphthalate	Ophthalmic; suppository, insert, controlled release	2	mg
Disodium sulfosalicylate	IV(infusion); powder, for injection solution, lyophilized	0.032	%
Disofenin	IV(infusion); injection	2	%
Divinylbenzene styrene copolymer	Ophthalmic; suspension, drops	0.75	%
Docusate sodium	Intramuscular; injection	0.015	%
Edamine	Intravenous; injection	0.3755	%
Edamine	IV(infusion); injection	0.392	%

Ingredient	Dosage Form	Qty	Unit
Edetate calcium disodium	Intramuscular; powder, for injection solution	0.005	%
Edetate calcium disodium	Intraperitoneal; powder, for injection solution	0.005	%
Edetate calcium disodium	IV(infusion); injection	0.005	%
Edetate calcium disodium	IV(infusion); powder, for injection solution	0.005	%
Edetate calcium disodium	Nerve block; injection	0.01	%
Edetate calcium disodium	Intra-arterial; injection	0.048	%
Edetate calcium disodium	Intramuscular; injection	0.048	%
Edetate calcium disodium	Subcutaneous; injection	0.17	%
Edetate calcium disodium	Intrathecal; injection	0.216	%
Edetate calcium disodium	Intravenous; injection	0.48	%
Edetate calcium disodium	Intravascular; injection	10	%
Edetate disodium	Intravenous; emulsion, injection	0.005	%
Edetate disodium	Intrabursal; injection	0.01	%
Edetate disodium	Intravenous; infusion	0.01	%
Edetate disodium	Intravenous; injectable	0.01	%
Edetate disodium	Ophthalmic; gel	0.01	%
Edetate disodium	AN, infiltration; injection	0.0111	%
Edetate disodium	Epidural; injection	0.0111	%
Edetate disodium	Nerve block; injection	0.0111	%
Edetate disodium	Respiratory (inhalation); solution, for inhalation	0.03	%
Edetate disodium	Intravascular; injection	0.04	%
Edetate disodium	IV(infusion); solution, injection	0.04	%
Edetate disodium	IM–IV; injectable	0.05	%
Edetate disodium	Intra-articular; injection	0.05	%
Edetate disodium	Intralesional; injection	0.05	%
Edetate disodium	Intravenous; solution	0.05	%
Edetate disodium	Soft tissue; injection	0.05	%
Edetate disodium	IV(infusion); powder, for injection suspension, lyophilized	0.0801	%
Edetate disodium	Auricular (otic); solution	0.1	%
Edetate disodium	Auricular (otic); solution, drops	0.1	%
Edetate disodium	Intramuscular; solution, injection	0.1	%
Edetate disodium	Nasal; spray	0.1	%
Edetate disodium	Ophthalmic; suspension, drops	0.1	%
Edetate disodium	Subcutaneous; injectable	0.1	%
Edetate disodium	Intravenous; solution, injection	0.11	%
Edetate disodium	Ophthalmic; suspension	0.13	%
Edetate disodium	Intravenous; powder, for injection solution, lyophilized	0.15	%
Edetate disodium	IM–IV–SC; injection	0.2	%
Edetate disodium	IM–SC; injection	0.2	%
Edetate disodium	Subcutaneous; injection	0.2	%
Edetate disodium	Ophthalmic; solution, drops	0.3	%
Edetate disodium	Nasal; spray, metered	0.5	%
Edetate disodium	IV(infusion); injection	1	%

Ingredient	Dosage Form	Qty	Unit
Edetate disodium	Inhalation; solution	5	%
Edetate disodium	Nasal; solution	5	%
Edetate disodium	IM–IV; injection	10	%
Edetate disodium	Intramuscular; injection	10	%
Edetate disodium	Intravenous; injection	10	%
Edetate disodium	Ophthalmic; solution	10	%
Edetate disodium, anhydrous	Intramuscular; injection	0.01	%
Edetate disodium, anhydrous	Intravenous; injectable	0.01	%
Edetate disodium, anhydrous	IV(infusion); injection	0.01	%
Edetate disodium, anhydrous	Intravenous; injection	0.025	%
Edetate disodium, anhydrous	Ophthalmic; solution, drops	0.1	%
Edetate sodium	Intramuscular; injection	0.01	%
Edetate sodium	Inhalation; solution	0.02	%
Edetate sodium	Ophthalmic; suspension	0.02	%
Edetate sodium	IV(infusion); solution, injection	0.04	%
Edetate sodium	Ophthalmic; solution	0.1	%
Edetate sodium	IM–IV–SC; injection	0.2	%
Edetic acid	Auricular (otic); suspension	0.001	%
Egg yolk phosphatides	Intravenous; emulsion, injection	1.2	%
Egg yolk phosphatides	Intravenous; injection	1.2	%
Egg yolk phosphatides	IV(infusion); injection	1.8	%
Ethanolamine hydrochloride	Intravenous; injection	0.15	%
Ethylene vinyl acetate copolymer	Ophthalmic; suppository, insert, controlled release	14	mg
Ethylene vinyl acetate copolymer	Periodontal; film, controlled release	51	mg
Ethylene vinyl acetate copolymer	Implantation; rod	61	mg
Ethylene vinyl acetate copolymer	Subcutaneous; rod	61	mg
Ethylene vinyl acetate copolymer	Intrauterine; suppository, insert, controlled release	160	mg
FD&C Blue No. 1	Dental; solution	0.01	%
FD&C Green No. 3	Dental; gel	0.0033	%
FD&C Red No. 40	Dental; solution	0.0006	%
Ferric chloride	Intravenous; injection	6.05	%
Flavor 89-186	Dental; solution	0.08	%
Flavor DF-1530	Dental; gel	0.77	%
Flavor NNS DZ-03226	Nasal; spray, metered	1	%
Flavor peppermint stick FMC 16170	Dental; solution	4.5	%
Fructose	IV(infusion); powder, for injection solution, lyophilized	5	%
Fused sodium ash	Ophthalmic; solution, drops	0.005	%
Gamma-cyclodextrin	Intravenous; injection	5	%
Gelatin	Intramuscular; injection, microspheres	0.13	%
Gelatin	Intramuscular; injection	0.26	%
Gelatin	IM–IV–SC; powder, for injection solution	1.4	%
Gelatin	IV(infusion); injection	2	%
Gelatin	Intravenous; solution	3.48	%

Ingredient	Dosage Form	Qty	Unit
Gelatin	IM–SC; injection	16	%
Gelatin	IM–SC; injection, sustained action	16	%
Gelatin	Dental; paste	180	mg
Gellan gum	Ophthalmic; solution	0.6	%
Gentisic acid	Intravenous; injection	0.056	%
Gentisic acid ethanolamide	IV(infusion); injection	2	%
Gluceptate sodium	Intravenous; injection	7.5	%
Gluceptate sodium	Intravenous; powder, for injection solution	20	%
Gluceptate sodium dihydrate	Intravenous; injection	7.5	%
Glutathione	Intramuscular; injection, sustained action	0.5	%
Glycerin	Auricular (otic); suspension	0.05	%
Glycerin	Nasal; spray, metered	0.223	%
Glycerin	IM–IV–SC; powder, for injection solution	1.2	%
Glycerin	IV–SC; injection	1.2	%
Glycerin	IM–SC; injection	1.6	%
Glycerin	Intradermal; injection	1.6	%
Glycerin	Subcutaneous; suspension, injection	1.6	%
Glycerin	Intramuscular; injectable	1.7814	%
Glycerin	Subcutaneous; injectable	2	%
Glycerin	Ophthalmic; emulsion	2.2	%
Glycerin	Intravenous; emulsion, injection	2.25	%
Glycerin	Intravenous; injectable	2.25	%
Glycerin	IV(infusion); injection	2.5	%
Glycerin	Nasal; solution	2.5	%
Glycerin	Ophthalmic; suspension	2.5	%
Glycerin	Ophthalmic; suspension, drops	2.5	%
Glycerin	Perfusion, biliary; liquid	2.5	%
Glycerin	Ophthalmic; solution, drops	2.6	%
Glycerin	Ophthalmic; solution	3	%
Glycerin	Intramuscular; injection	5.9367	%
Glycerin	Inhalation; solution	7.3	%
Glycerin	Intravenous; injection	12.62	%
Glycerin	Dental; solution	15	%
Glycerin	IM–IV; injection	15	%
Glycerin	IM–IV–SC; injection	15.36	%
Glycerin	IV(infusion); emulsion, injection	22.5	%
Glycerin	Subcutaneous; injection	32.5	%
Glycerin	Auricular (otic); solution	60	%
Glycerin	Auricular (otic); solution, drops	63.6373	%
Glyceryl stearate	Auricular (otic); suspension	0.5	%
Glyceryl stearate	Ophthalmic; suspension	0.5	%
Glyceryl stearate	Dental; paste	64	mg
Glycine	Respiratory (inhalation); powder, for inhalation	0.013	%

Ingredient	Dosage Form	Qty	Unit
Glycine	Subcutaneous; injectable	0.136	%
Glycine	Intravenous; solution, liposome, injection	0.376	%
Glycine	IV(infusion); powder, for injection solution	0.376	%
Glycine	Intramuscular; injection	1.126	%
Glycine	Intramuscular; injectable	2.252	%
Glycine	Subcutaneous; powder, for injection solution	2.4	%
Glycine	Intramuscular; powder, for injection solution, lyophilized	2.76	%
Glycine	Subcutaneous; powder, for injection solution, lyophilized	2.76	%
Glycine	Intramuscular; powder, for injection solution	4	%
Glycine	Intravenous; powder, for injection solution, lyophilized	25	%
Glycine	IV(infusion); solution, injection	42	%
Glycine	IV(infusion); injection	90	%
Glycocholic acid	Intravenous; powder, for injection solution, lyophilized	14	%
Guanidine hydrochloride	Intravenous; injection	0.25	%
Hetastarch	Intravenous; powder, for injection solution	7.36	%
Histidine	Subcutaneous; solution, injection	0.11	%
Histidine	Intravenous; injection, suspension, liposomal	0.155	%
Histidine	IV(infusion); solution, injection	8.5	%
Histidine	IV(infusion); injection	37.2	%
Hydrochloric acid	IM–IV; injectable	0.0249	%
Hydrochloric acid	Auricular (otic); suspension	0.044	%
Hydrochloric acid	Auricular (otic); solution, drops	0.06	%
Hydrochloric acid	Ophthalmic; solution, drops	0.17	%
Hydrochloric acid	Subcutaneous; injection	0.17	%
Hydrochloric acid	Subcutaneous; suspension, injection	0.22	%
Hydrochloric acid	Auricular (otic); solution	0.37	%
Hydrochloric acid	AN, infiltration; injection	0.64	%
Hydrochloric acid	Nerve block; injection	0.64	%
Hydrochloric acid	IV(infusion); powder, for injection suspension, lyophilized	0.834	%
Hydrochloric acid	Ophthalmic; solution	1.06	%
Hydrochloric acid	IV(infusion); injection	1.44	%
Hydrochloric acid	Inhalation; aerosol, metered	1.72	%
Hydrochloric acid	Intravenous; solution	1.825	%
Hydrochloric acid	Inhalation; solution	3.5	%
Hydrochloric acid	Intramuscular; injectable	8	%
Hydrochloric acid	Intravenous; injectable	8	%
Hydrochloric acid	Intravenous; injection	10	%
Hydrochloric acid	IV(infusion); solution, injection	12.7	%
Hydrochloric acid	Intravenous; powder, for injection solution, lyophilized	14.11	%
Hydrochloric acid	Nasal; solution	24.7	%
Hydrochloric acid, diluted	AN, infiltration; injection	1.36	%
Hydrochloric acid, diluted	Nerve block; injection	1.36	%
Hydrocortisone	Auricular (otic); solution	5.5007	%

Ingredient	Dosage Form	Qty	Unit
Hydroxyethyl cellulose	Auricular (otic); solution	0.25	%
Hydroxyethyl cellulose	Ophthalmic; suspension	0.25	%
Hydroxyethyl cellulose	Ophthalmic; solution	0.35	%
Hydroxyethyl cellulose	Ophthalmic; suspension, drops	0.35	%
Hydroxyethyl cellulose	Ophthalmic; solution, drops	0.5	%
Hydroxypropyl methylcellulose 2906	Ophthalmic; solution, drops	0.5	%
Hydroxypropyl methylcellulose 2910	Nasal; spray, metered	0.1	%
Hydroxypropyl methylcellulose 2910	Ophthalmic; solution	0.5	%
Hydroxypropyl methylcellulose 2910	Ophthalmic; suspension	0.5	%
Hydroxypropyl methylcellulose 2910	Ophthalmic; suspension, drops	0.5	%
Hydroxypropyl-*b*-cyclodextrin	IV(infusion); injection	0.4	%
Insulin beef	Subcutaneous; injection	0.1	%
Insulin pork	Subcutaneous; injection	0.1	%
Iodoxamic acid	Intravenous; infusion	7.61	%
Iodoxamic acid	Intravenous; injection	31	%
Isoleucine	IV(infusion); solution, injection	21	%
Isoleucine	IV(infusion); injection	90	%
Isopropyl myristate	Auricular (otic); suspension	0.024	%
Isotonic sodium chloride solution	Intravenous; injection	0.9	%
Lactic acid	IM–IV–SC; injection	0.012	%
Lactic acid	Intracardiac; injection	0.012	%
Lactic acid	AN, infiltration; injection	0.1184	%
Lactic acid	Nerve block; injection	0.1184	%
Lactic acid	IV(infusion); solution, injection	0.119	%
Lactic acid	Subcutaneous; injection	0.34	%
Lactic acid	Intravenous; injectable	0.413	%
Lactic acid	Intravenous; injection	0.71	%
Lactic acid	IM–IV; injection	1.1578	%
Lactic acid	IV(infusion); injection	32.2	%
DL-Lactic acid	IV(infusion); injection	2.82	%
L-Lactic acid	Intravenous; injection	0.3	%
L-Lactic acid	Subcutaneous; injection	0.3	%
L-Lactic acid	Intravenous; injectable	0.4	%
Lactose	IV(infusion); solution, injection	0.45	%
Lactose	Subcutaneous; powder, for injection solution, lyophilized	0.5	%
Lactose	Intramuscular; powder, for injection solution, lyophilized	1	%
Lactose	Intravenous; powder, for injection solution, lyophilized	1	%
Lactose	Intramuscular; powder, for injection solution	2	%
Lactose	Subcutaneous; powder, for injection solution	2	%
Lactose	Intravenous; powder, for injection solution	5	%
Lactose	Inhalation; powder	9	%
Lactose	IM–IV–SC; powder, for injection solution	13.3	%
Lactose	Intracavitary; powder, for injection solution, lyophilized	19.38	%

Ingredient	Dosage Form	Qty	Unit
Lactose	Inhalation; capsule	20	mg
Lactose	Inhalation; capsule, hard gelatin	25	mg
Lactose	Intravenous; injection	50	%
Lactose monohydrate	Respiratory (inhalation); powder, for inhalation	2	%
Lactose monohydrate	IM–SC; injection	2.1	%
Lactose monohydrate	IM–IV; powder	2.75	%
Lactose monohydrate	Intracavitary; powder, for injection solution, lyophilized	4.54	%
Lactose monohydrate	IV–SC; injection	4.9	%
Lactose monohydrate	Intramuscular; injection	5	%
Lactose monohydrate	IM–IV–SC; powder, for injection solution, lyophilized	10.7	%
Lactose monohydrate	IV(infusion); powder, for injection solution	20	%
Lactose monohydrate	Respiratory (inhalation); capsule	25	mg
Lactose monohydrate	Intravenous; powder, for injection solution, lyophilized	69	%
Lactose monohydrate	IV(infusion); powder, for injection solution, lyophilized	90	%
Lactose, anhydrous	IM–IV; injectable	2.5	%
Lactose, anhydrous	IM–IV; powder, for injection solution	2.5	%
Lactose, anhydrous	IV(infusion); powder, for injection solution	2.5	%
Lactose, anhydrous	Intracavitary; powder, for injection solution, lyophilized	4.75	%
Lactose, hydrous	Intramuscular; powder, for injection solution, lyophilized	1.05	%
Lactose, hydrous	IM–IV; injection	2.5	%
Lactose, hydrous	IM–IV; powder, for injection solution	2.5	%
Lactose, hydrous	IV(infusion); powder, for injection solution	20	%
Lactose, hydrous	Intravenous; injection	25	%
Lactose, hydrous	Intravenous; powder, for injection solution	75	%
Lanolin	Ophthalmic; ointment	2	%
Lanolin alcohols	Ophthalmic; ointment	10	%
Lanolin, anhydrous	Ophthalmic; ointment	3	%
Lauralkonium chloride	Ophthalmic; solution, drops	0.005	%
Lecithin	Inhalation; aerosol, metered	0.0002	%
Lecithin	Intramuscular; injection	2.3	%
Lecithin, egg	Intravenous; emulsion, injection	1.2	%
Lecithin, egg	Intravenous; injectable	1.2	%
Lecithin, hydrogenated	Auricular (otic); suspension, liquid	1.5	%
Lecithin, hydrogenated soy	Inhalation; aerosol, metered	0.28	%
Lecithin, hydrogenated soy	Intravenous; injection, suspension, liposomal	0.958	%
Lecithin, hydrogenated soy	Intravenous; injection, powder, lyophilized, for liposomal suspension	21.3	%
Lecithin, soybean	Inhalation; aerosol, metered	0.1	%
Lecithin, soybean	Intravenous; powder, for injection solution, lyophilized	11.25	%
Leucine	IV(infusion); solution, injection	27	%
Leucine	IV(infusion); injection	52.6	%
Lysine	IV(infusion); solution, injection	22	%
Lysine	IV(infusion); injection	61	%
Lysine acetate	IV(infusion); injection	0.756	%

Ingredient	Dosage Form	Qty	Unit
Lysine acetate	IV(infusion); solution, injection	31	%
Magnesium chloride	Ophthalmic; solution, drops	0.0065	%
Magnesium chloride	Intraocular; solution	0.03	%
Magnesium chloride	Ophthalmic; powder, for solution	0.03	%
Magnesium chloride	Subcutaneous; powder, for injection solution, lyophilized	0.125	%
Magnesium chloride	Intraperitoneal; solution	0.508	%
Magnesium chloride	IV(infusion); injection	10.2	%
Magnesium stearate	Implantation; injection	0.0015	%
Magnesium stearate	Intravitreal; injection	0.0015	%
Magnesium stearate	Intravitreal; implant	0.0048	mg
Magnesium stearate	Subcutaneous; implant	0.5	mg
Mannitol	Respiratory (inhalation); powder, for inhalation	0.051	%
Mannitol	IM–SC; powder, for injection solution	2	%
Mannitol	Ophthalmic; suspension	2.4	%
Mannitol	IM–IV; injection	2.5	%
Mannitol	Intramuscular; powder, for injection solution, lyophilized, with additives	3.6	%
Mannitol	Subcutaneous; injectable	3.6	%
Mannitol	Subcutaneous; suspension, injection	3.64	%
Mannitol	Ophthalmic; suspension, drops	4	%
Mannitol	Subcutaneous; powder, for injection solution, lyophilized, with additives	4	%
Mannitol	Intravenous; solution	4.15	%
Mannitol	Subcutaneous; solution, injection	4.3	%
Mannitol	Ophthalmic; solution, gel forming, extended release	4.35	%
Mannitol	Subcutaneous; injection	4.5	%
Mannitol	Ophthalmic; solution, drops	4.6	%
Mannitol	IV(infusion); solution, injection	4.7	%
Mannitol	Intravenous; solution, injection	4.95	%
Mannitol	Intramuscular; powder, for injection suspension, lyophilized	5.19	%
Mannitol	Ophthalmic; powder, for solution	5.6	%
Mannitol	Intravenous; liquid, concentrate, injection	6.13	%
Mannitol	IV(infusion); powder, for injection solution, lyophilized, with additives	7.5	%
Mannitol	Intramuscular; powder, for injection solution, lyophilized	8.5	%
Mannitol	Subcutaneous; powder, for injection solution	9	%
Mannitol	Subcutaneous; powder, for injection suspension, lyophilized	10	%
Mannitol	Intramuscular; injection	10.66	%
Mannitol	Intramuscular; powder, for injection solution	11.9292	%
Mannitol	Intravenous; injection	13	%
Mannitol	Intramuscular; injection, microspheres	13.49	%
Mannitol	Subcutaneous; powder, for injection solution, lyophilized	16.44	%
Mannitol	IV(infusion); injection	20	%
Mannitol	Ophthalmic; solution	23	%
Mannitol	IM–IV; powder, for injection solution	30	%
Mannitol	Intravenous; powder, for injection solution	34	%

Ingredient	Dosage Form	Qty	Unit
Mannitol	Intravenous; injectable	45	%
Mannitol	Intravenous; powder	45	%
Mannitol	Intravenous; powder, for injection solution, lyophilized	45	%
Mannitol	IV(infusion); powder, for injection solution, lyophilized	50	%
Mannitol	IV(infusion); powder, for injection solution	75	%
Medronate disodium	Intravenous; powder, for injection solution	0.01	%
Medronate disodium	Intravenous; injection	1	%
Medronic acid	Intravenous; powder, for injection solution	1	%
Medronic acid	Intravenous; injection	2.5	%
Meglumine	Intravenous; infusion	2.3	%
Meglumine	IV(infusion); injection	7.238	%
Meglumine	Intramuscular; injection	15.924	%
Meglumine	Intravenous; injection	15.924	%
Menthol	Inhalation; aerosol, metered	0.0502	%
Metaphosphoric acid	IV(infusion); injection	0.13	%
Methanesulfonic acid	IV(infusion); powder, for injection solution, lyophilized	8.07	%
Methionine	Intrathecal; injectable	0.005	%
Methionine	Subcutaneous; powder, for injection solution, lyophilized	0.01	%
Methionine	Subcutaneous; injection	0.015	%
Methionine	Intramuscular; solution, injection	0.0443	%
Methionine	Subcutaneous; solution, injection	0.0443	%
Methionine	Subcutaneous; suspension, injection	0.15	%
Methionine	Intravenous; injection	0.3	%
Methionine	IV(infusion); solution, injection	16	%
Methionine	IV(infusion); injection	49.2	%
Methyl boronic acid	Intravenous; injection	0.2	%
Methylcellulose	Intra-articular; injection	0.1	%
Methylcellulose	Intramuscular; injection	0.1	%
Methylcellulose	Ophthalmic; solution	0.1641	%
Methylcellulose 4000	Ophthalmic; solution	0.5	%
Methylene blue	Intravenous; injection	1	%
Methylparaben	Auricular (otic); suspension	0.0014	%
Methylparaben	Nasal; solution	0.033	%
Methylparaben	Ophthalmic; ointment	0.05	%
Methylparaben	Ophthalmic; solution	0.05	%
Methylparaben	Ophthalmic; solution, drops	0.05	%
Methylparaben	Ophthalmic; suspension	0.05	%
Methylparaben	Ophthalmic; suspension, drops	0.05	%
Methylparaben	Inhalation; solution	0.07	%
Methylparaben	AN, infiltration; injection	0.1	%
Methylparaben	Caudal block; injection	0.1	%
Methylparaben	Epidural; injection	0.1	%
Methylparaben	Intradermal; injection	0.1	%

Ingredient	Dosage Form	Qty	Unit
Methylparaben	IV(infusion); powder, for injection solution	0.1	%
Methylparaben	Nerve block; injection	0.1	%
Methylparaben	Peridural; injection	0.1	%
Methylparaben	IM–IV; injectable	0.12	%
Methylparaben	N/A; liquid	0.12	%
Methylparaben	IM–IV; solution	0.126	%
Methylparaben	Intralesional; injection	0.15	%
Methylparaben	Soft tissue; injection	0.15	%
Methylparaben	Subcutaneous; suspension, injection	0.16	%
Methylparaben	IM–SC; injection	0.18	%
Methylparaben	Intrabursal; injection	0.18	%
Methylparaben	Intravenous; injectable	0.18	%
Methylparaben	IV–SC; injection	0.18	%
Methylparaben	Subcutaneous; injection	0.18	%
Methylparaben	Intra-articular; injection	0.24	%
Methylparaben	Intramuscular; injection	0.24	%
Methylparaben	IM–IV–SC; injection	0.44	%
Methylparaben	IV(infusion); injection	0.44	%
Methylparaben	N/A; not applicable	0.45	mg
Methylparaben	Nasal; spray, metered	0.7	%
Methylparaben	IM–IV; injection	0.75	%
Methylparaben	Intravenous; powder, for injection solution	1.5	%
Methylparaben	Intravenous; injection	1.8	%
Methylparaben	Irrigation; solution	2	%
Mineral oil	Ophthalmic; suspension	0.1	%
Mineral oil	Auricular (otic); suspension	0.5	%
Mineral oil	Ophthalmic; ointment	59.5	%
Mineral oil	Dental; paste	457.95	mg
Myristyl-gamma-picolinium chloride	Intra-articular; injection	0.019	%
Myristyl-gamma-picolinium chloride	Intralesional; injection	0.019	%
Myristyl-gamma-picolinium chloride	Intramuscular; injection	0.019	%
Myristyl-gamma-picolinium chloride	Soft tissue; injection	0.019	%
Myristyl-gamma-picolinium chloride	Intralesional; injection, sustained action	0.0195	%
Myristyl-gamma-picolinium chloride	Intramuscular; injection, sustained action	0.0195	%
Myristyl-gamma-picolinium chloride	Intrasynovial; injection, sustained action	0.0195	%
Myristyl-gamma-picolinium chloride	Soft tissue; injection, sustained action	0.0195	%
N-(carbamoyl-methoxy PEG-40)-1,2-distearoyl-cephalin sodium	Intravenous; injection, suspension, liposomal	0.319	%
N, N-dimethylacetamide	Intravenous; injection	1.8	%
Niacinamide	IM–IV; injection	2.5	%
Nioxime	Intravenous; injection	0.2	%
Nitric acid	Inhalation; aerosol, metered	1.67	%
N-lauroylsarcosine	Ophthalmic; suspension, drops	0.03	%
nonoxynol-9	Ophthalmic; solution	0.125	%

Ingredient	Dosage Form	Qty	Unit
Norflurane	Inhalation; aerosol, metered	7.5	%
Norflurane	Respiratory (inhalation); aerosol, metered	89.76	%
Octanoic acid	Intravenous; injection	0.012	%
Octoxynol-40	Ophthalmic; solution	0.01	%
Oleic acid	Respiratory (inhalation); aerosol, metered	0.0003	%
Oleic acid	Nasal; aerosol, metered	0.132	%
Oleic acid	Inhalation; inhalant	0.16	%
Oleic acid	Inhalation; aerosol, metered	0.267	%
Oxidronate sodium	Intravenous; injection	0.2	%
Oxyquinoline	Intravenous; injection	0.005	%
Pectin	Dental; paste	180	mg
PEG vegetable oil	IV(infusion); injection	5	%
PEG vegetable oil	IM–SC; injection	7	%
PEG-40 sorbitan diisostearate	Dental; solution	2.4	%
Pentetate pentasodium	Intravenous; injection	0.5	%
Pentetic acid	Intravenous; injection	0.2	%
Peppermint	Dental; solution	0.5	%
Peppermint oil	Dental; solution	0.525	%
Petrolatum	Ophthalmic; ointment	85	%
Petrolatum, white	Dental; paste	64	mg
Petrolatum, white	Ophthalmic; ointment	89	%
Phenethyl alcohol	Nasal; solution	0.2	%
Phenethyl alcohol	Auricular (otic); solution	0.25	%
Phenethyl alcohol	Nasal; spray, metered	0.254	%
Phenethyl alcohol	Ophthalmic; solution	0.5	%
Phenol	Subcutaneous; suspension, injection	0.15	%
Phenol	Subcutaneous; injectable	0.18	%
Phenol	Intradermal; injection	0.25	%
Phenol	IM–IV–SC; injection	0.45	%
Phenol	Intramuscular; solution, injection	0.45	%
Phenol	IM–SC; injection	0.5	%
Phenol	IM–SC; injection, sustained action	0.5	%
Phenol	Intra-articular; injection	0.5	%
Phenol	Intralesional; injection	0.5	%
Phenol	Intramuscular; injectable	0.5	%
Phenol	Intramuscular; injection, sustained action	0.5	%
Phenol	Intrasynovial; injection	0.5	%
Phenol	Intravenous; injectable	0.5	%
Phenol	Intravenous; injection	0.5	%
Phenol	Subcutaneous; injection	0.5	%
Phenol	Subcutaneous; solution, injection	0.5	%
Phenol	IM–IV; injection	1	%
Phenol	IV(infusion); injection	1	%

Ingredient	Dosage Form	Qty	Unit
Phenol	Intramuscular; injection	1.3333	%
Phenol, liquefied	Subcutaneous; injection	0.065	%
Phenol, liquefied	Subcutaneous; suspension, injection	0.073	%
Phenol, liquefied	IM–SC; injection	0.2	%
Phenol, liquefied	Intravenous; injection	0.28	%
Phenol, liquefied	IM–IV; injection	0.5	%
Phenol, liquefied	IV–SC; liquid	0.5	%
Phenylalanine	IV(infusion); solution, injection	17	%
Phenylalanine	IV(infusion); injection	52.6	%
Phenylmercuric acetate	Ophthalmic; ointment	0.0008	%
Phenylmercuric nitrate	Ophthalmic; ointment	0.002	%
Phenylmercuric nitrate	Ophthalmic; solution	0.002	%
Phosphatidyl glycerol, egg	Intravenous; powder, for injection solution, lyophilized	4.875	%
Phospholipid	IV(infusion); injection	1.2	%
Phospholipid	IV(infusion); emulsion, injection	12	%
Phospholipid, egg	IV(infusion); injection	1.2	%
Phosphoric acid	Subcutaneous; powder, for injection solution, lyophilized, with additives	0.1398	%
Phosphoric acid	Subcutaneous; injection	0.205	%
Phosphoric acid	Intramuscular; powder, for injection solution, lyophilized	0.233	%
Phosphoric acid	Subcutaneous; powder, for injection solution, lyophilized	0.233	%
Phosphoric acid	IV(infusion); injection	11.5	%
Plastibase-50W	Dental; paste	549	mg
Poloxamer 188	Subcutaneous; injection	0.015	%
Poloxamer 188	Ophthalmic; solution	0.1	%
Poloxamer 188	Ophthalmic; solution, drops	0.1	%
Poloxamer 188	Intravenous; powder, for injection solution	0.22	%
Poloxamer 188	Subcutaneous; solution, injection	0.3	%
Poloxamer 188	Intravenous; injection	0.6	%
Poloxamer 407	Ophthalmic; solution, drops	0.16	%
Poloxamer 407	Ophthalmic; solution	0.2	%
Poly(bis(*p*-carboxyphenoxy)propane anhydride): sebacic acid	Implantation; wafer	192.3	mg
Polycarbophil	Ophthalmic; solution	0.9	%
Polyethylene	Dental; paste	40	mg
Polyethylene glycol 1540	Dental; gel	5	%
Polyethylene glycol 200	Intramuscular; injection	30	%
Polyethylene glycol 300	IM–IV; injection	50	%
Polyethylene glycol 300	Intramuscular; injection	50	%
Polyethylene glycol 300	Intravenous; injection	65	%
Polyethylene glycol 300	IV(infusion); injection	65	%
Polyethylene glycol 3350	Nasal; spray, metered	1.5	%
Polyethylene glycol 3350	Subcutaneous; suspension, injection	2.875	%
Polyethylene glycol 3350	Intralesional; injection, sustained action	2.9	%

Ingredient	Dosage Form	Qty	Unit
Polyethylene glycol 3350	Intramuscular; injection, sustained action	2.9	%
Polyethylene glycol 3350	Intrasynovial; injection, sustained action	2.9	%
Polyethylene glycol 3350	Soft tissue; injection, sustained action	2.9	%
Polyethylene glycol 3350	Intralesional; suspension, injection	2.91	%
Polyethylene glycol 3350	Intramuscular; suspension, injection	2.91	%
Polyethylene glycol 3350	Intrasynovial; suspension, injection	2.91	%
Polyethylene glycol 3350	Soft tissue; suspension, injection	2.91	%
Polyethylene glycol 3350	Intra-articular; injection	3	%
Polyethylene glycol 3350	Intralesional; injection	3	%
Polyethylene glycol 3350	Intramuscular; injection	3	%
Polyethylene glycol 3350	Intrasynovial; injection	3	%
Polyethylene glycol 3350	Soft tissue; injection	3	%
Polyethylene glycol 400	Ophthalmic; ointment	4.997	%
Polyethylene glycol 400	Intravenous; injection	11.25	%
Polyethylene glycol 400	IV(infusion); injection	11.25	%
Polyethylene glycol 400	IM–IV; solution, injection	18	%
Polyethylene glycol 400	Nasal; spray, metered	20	%
Polyethylene glycol 400	IM–IV; injection	20.3	%
Polyethylene glycol 4000	Intra-articular; injection	3	%
Polyethylene glycol 4000	Intralesional; injection	3	%
Polyethylene glycol 4000	Intramuscular; injection	3	%
Polyethylene glycol 4000	Intrasynovial; injection	3	%
Polyethylene glycol 600	Intravenous; injection	5	%
Polyethylene glycol 600	Intravenous; solution, injection	5	%
Polyethylene glycol 8000	Ophthalmic; solution	2	%
Polyglactin	Subcutaneous; powder, for injection suspension	13.26	%
Polyglactin	Intramuscular; injection	14.5	%
Polyglactin	Intramuscular; powder, for injection solution, lyophilized	17	%
Polyglactin	Subcutaneous; injection	21.15	%
Polyglactin	Implantation; pellet, implant	25.2	mg
Polyglactin	Subcutaneous; pellet, implant	25.2	mg
Polyglactin	Intramuscular; injection, microspheres	56.64	%
Polylactide	Intramuscular; powder, for injection suspension, lyophilized	26.48	%
Polyols	Dental; gel	65.82	%
Polyoxyethylene fatty acid esters	IM–SC; injection	7	%
Polyoxyl 35 castor oil	Ophthalmic; solution	5	%
Polyoxyl 35 castor oil	Intravesical; solution	50	%
Polyoxyl 35 castor oil	IV(infusion); solution, injection	52.75	%
Polyoxyl 35 castor oil	IV(infusion); injection	65	%
Polyoxyl 40 castor oil	IM–SC; injection	7	%
Polyoxyl 40 hydrogenated castor oil	Ophthalmic; solution, drops	0.5	%
Polyoxyl 40 hydrogenated castor oil	Dental; solution	1	%
Polyoxyl 40 stearate	Ophthalmic; suspension	0.5	%

Ingredient	Dosage Form	Qty	Unit
Polyoxyl 40 stearate	Auricular (otic); suspension	1	%
Polyoxyl 40 stearate	Ophthalmic; solution	7	%
Polyoxyl 400 stearate	Nasal; spray, metered	15	%
Polyoxyl 60 castor oil	IV(infusion); injection	20	%
Polyoxyl stearate	Auricular (otic); suspension	0.006	%
Polypropylene glycol	Ophthalmic; solution	15	%
Polypropylene glycol	IM–IV; injectable	40	%
Polyquaternium-1	Ophthalmic; solution, drops	0.0005	%
Polysorbate 20	IM–SC; injection	0.0005	%
Polysorbate 20	Subcutaneous; injection	0.001	%
Polysorbate 20	Subcutaneous; injectable	0.002	%
Polysorbate 20	Intramuscular; powder, for injection solution, lyophilized	0.01	%
Polysorbate 20	Subcutaneous; powder, for injection solution, lyophilized	0.01	%
Polysorbate 20	Intramuscular; solution, injection	0.0177	%
Polysorbate 20	Ophthalmic; suspension	0.05	%
Polysorbate 20	Subcutaneous; liquid	0.05	%
Polysorbate 20	Intravenous; injection	0.4	%
Polysorbate 20	Intravenous; solution, injection	0.4	%
Polysorbate 20	Subcutaneous; solution, injection	0.4	%
Polysorbate 20	Auricular (otic); suspension, liquid	1	%
Polysorbate 20	IV(infusion); injection	2.4	%
Polysorbate 20	Nasal; spray, metered	2.5	%
Polysorbate 60	Ophthalmic; ointment	15	%
Polysorbate 80	Nasal; spray	0.004	%
Polysorbate 80	Ophthalmic; solution, gel forming, extended release	0.05	%
Polysorbate 80	Auricular (otic); solution, drops	0.1	%
Polysorbate 80	Intramuscular; injection, microspheres	0.1	%
Polysorbate 80	Nasal; solution	0.1	%
Polysorbate 80	Ophthalmic; suspension	0.1	%
Polysorbate 80	Ophthalmic; suspension, drops	0.1	%
Polysorbate 80	Intralesional; suspension, injection	0.194	%
Polysorbate 80	Intramuscular; suspension, injection	0.194	%
Polysorbate 80	Intrasynovial; suspension, injection	0.194	%
Polysorbate 80	Soft tissue; suspension, injection	0.194	%
Polysorbate 80	Auricular (otic); solution	0.2	%
Polysorbate 80	Intralesional; injection	0.2	%
Polysorbate 80	Intramuscular; powder, for injection solution, lyophilized	0.2	%
Polysorbate 80	Intrasynovial; injection	0.2	%
Polysorbate 80	Ophthalmic; solution	0.2	%
Polysorbate 80	Soft tissue; injection	0.2	%
Polysorbate 80	Subcutaneous; suspension, injection	0.3	%
Polysorbate 80	Intra-articular; injection	0.4	%
Polysorbate 80	Ophthalmic; emulsion	1	%

Ingredient	Dosage Form	Qty	Unit
Polysorbate 80	Ophthalmic; solution, drops	1	%
Polysorbate 80	Intravenous; powder, for injection solution, lyophilized	2.5	%
Polysorbate 80	Auricular (otic); suspension	5	%
Polysorbate 80	Intramuscular; solution, injection	5	%
Polysorbate 80	IV(infusion); injection	8	%
Polysorbate 80	Intravenous; injectable	10	%
Polysorbate 80	Intravenous; injection	10	%
Polysorbate 80	Intravenous; solution, injection	10	%
Polysorbate 80	IV(infusion); solution, injection	10	%
Polysorbate 80	Nasal; spray, metered	10	%
Polysorbate 80	Intramuscular; injection	12	%
Polysorbate 80	IV(infusion); powder, for injection solution, lyophilized	12.5	%
Polyvinyl alcohol	Intravitreal; implant	0.119	mg
Polyvinyl alcohol	Intraocular; solution	1.4	%
Polyvinyl alcohol	Ophthalmic; solution	1.4	%
Polyvinyl alcohol	Ophthalmic; solution, drops	1.4	%
Polyvinyl alcohol	Ophthalmic; suspension	1.4	%
Polyvinyl alcohol	Ophthalmic; suspension, drops	1.4	%
Polyvinyl alcohol	Auricular (otic); suspension, liquid	20	%
Potassium acetate	Ophthalmic; powder, for solution	4	%
Potassium chloride	AN, infiltration; injection	0.03	%
Potassium chloride	Caudal block; injection	0.03	%
Potassium chloride	Epidural; injection	0.03	%
Potassium chloride	Nerve block; injection	0.03	%
Potassium chloride	Intraocular; solution	0.075	%
Potassium chloride	Ophthalmic; powder, for solution	0.075	%
Potassium chloride	Ophthalmic; solution, drops	0.14	%
Potassium chloride	Intravenous; solution, injection	0.382	%
Potassium chloride	Ophthalmic; solution	22.2	%
Potassium metabisulfite	IV(infusion); injection	0.06	%
Potassium metabisulfite	Auricular (otic); solution, drops	0.1	%
Potassium metabisulfite	IM–IV; injection	0.1	%
Potassium metabisulfite	Auricular (otic); solution	0.11	%
Potassium metabisulfite	IV(infusion); solution, injection	5	%
Potassium phosphate, dibasic	Subcutaneous; powder, for injection solution, lyophilized	0.192	%
Potassium phosphate, dibasic	Intra-articular; injection	0.6	%
Potassium phosphate, dibasic	Intramuscular; injection	0.6	%
Potassium phosphate, dibasic	Subcutaneous; injection	1.36	%
Potassium phosphate, dibasic	IV(infusion); injection	55.2	%
Potassium phosphate, monobasic	Intravenous; injection	0.0153	%
Potassium phosphate, monobasic	Ophthalmic; solution, drops	0.065	%
Potassium phosphate, monobasic	IM–IV; injection	0.096	%
Potassium phosphate, monobasic	Intramuscular; injectable	0.096	%

Ingredient	Dosage Form	Qty	Unit
Potassium phosphate, monobasic	Intravenous; injectable	0.096	%
Potassium phosphate, monobasic	Subcutaneous; powder, for injection solution, lyophilized	0.122	%
Potassium phosphate, monobasic	Nasal; spray	0.14	%
Potassium phosphate, monobasic	Auricular (otic); solution	0.2	%
Potassium phosphate, monobasic	Ophthalmic; solution	0.2	%
Potassium phosphate, monobasic	Intra-articular; injection	0.3	%
Potassium phosphate, monobasic	Intramuscular; injection	0.3	%
Potassium phosphate, monobasic	Ophthalmic; suspension	0.44	%
Potassium phosphate, monobasic	IV(infusion); solution, injection	1.361	%
Potassium phosphate, monobasic	AN, infiltration; injection	2.7218	%
Potassium phosphate, monobasic	Nerve block; injection	2.7218	%
Potassium sorbate	Nasal; spray, metered	0.0084	%
Potassium sorbate	Ophthalmic; solution	0.47	%
Povidone K17	Subcutaneous; suspension, injection	0.5	%
Povidone K29-32	Ophthalmic; solution	1.8	%
Povidone K30	Ophthalmic; suspension	0.6	%
Povidone K90	Ophthalmic; solution, drops	1.2	%
Proline	IV(infusion); solution, injection	34	%
Proline	IV(infusion); injection	80	%
Propylene glycol	Ophthalmic; solution, drops	0.75	%
Propylene glycol	Ophthalmic; suspension, drops	1	%
Propylene glycol	Dental; solution	2	%
Propylene glycol	Extracorporeal; solution	5	%
Propylene glycol	Ophthalmic; suspension	5	%
Propylene glycol	Photopheresis; solution	5	%
Propylene glycol	Auricular (otic); suspension	10	%
Propylene glycol	Ophthalmic; solution	10	%
Propylene glycol	Nasal; spray, metered	20	%
Propylene glycol	Inhalation; solution	25	%
Propylene glycol	Intravenous; injectable	30	%
Propylene glycol	Intravenous; solution, injection	30	%
Propylene glycol	IV(infusion); solution, injection	30	%
Propylene glycol	Intramuscular; injection	40	%
Propylene glycol	Intramuscular; solution, injection	40	%
Propylene glycol	IM–IV; solution, injection	41.6	%
Propylene glycol	Intravenous; injection	50	%
Propylene glycol	Intravenous; solution, concentrate	50.3325	%
Propylene glycol	IV(infusion); injection	51.8	%
Propylene glycol	Auricular (otic); solution, drops	80	%
Propylene glycol	IM–IV; injection	82.043	%
Propylene glycol	Auricular (otic); solution	94.925	%
Propylene glycol diacetate	Auricular (otic); solution, drops	3	%
Propylene glycol diacetate	Auricular (otic); solution	65	%

Ingredient	Dosage Form	Qty	Unit
Propylparaben	Auricular (otic); suspension	0.0006	%
Propylparaben	AN, infiltration; injection	0.01	%
Propylparaben	Ophthalmic; ointment	0.01	%
Propylparaben	Ophthalmic; suspension	0.01	%
Propylparaben	Ophthalmic; suspension, drops	0.01	%
Propylparaben	N/A; liquid	0.012	%
Propylparaben	IM–IV; injectable	0.015	%
Propylparaben	Ophthalmic; solution	0.015	%
Propylparaben	Ophthalmic; solution, drops	0.015	%
Propylparaben	Subcutaneous; suspension, injection	0.015	%
Propylparaben	IM–IV; solution	0.0158	%
Propylparaben	Nasal; solution	0.017	%
Propylparaben	IM–SC; injection	0.02	%
Propylparaben	Intrabursal; injection	0.02	%
Propylparaben	Intralesional; injection	0.02	%
Propylparaben	Intravenous; injectable	0.02	%
Propylparaben	IV–SC; injection	0.02	%
Propylparaben	Soft tissue; injection	0.02	%
Propylparaben	Subcutaneous; injection	0.02	%
Propylparaben	Nerve block; injection	0.035	%
Propylparaben	Inhalation; solution	0.0375	%
Propylparaben	IV(infusion); injection	0.056	%
Propylparaben	N/A; not applicable	0.06	mg
Propylparaben	Intravenous; powder, for injection solution	0.08	%
Propylparaben	Intra-articular; injection	0.16	%
Propylparaben	Intramuscular; injection	0.16	%
Propylparaben	IM–IV; injection	0.2	%
Propylparaben	Intravenous; injection	0.2	%
Propylparaben	Nasal; spray, metered	0.3	%
Propylparaben	IM–IV–SC; injection	20	%
Protamine sulfate	Subcutaneous; suspension, injection	0.033	%
Protamine sulfate	Subcutaneous; injection	0.036	%
Protamine sulfate	Intradermal; injection	0.125	%
Saccharin	Inhalation; aerosol, metered	0.1127	%
Saccharin sodium	Inhalation; aerosol, metered	0.045	%
Saccharin sodium	IM–IV; injection	0.09	%
Saccharin sodium	Intramuscular; injection	0.09	%
Saccharin sodium	Intravenous; injection	0.09	%
Saccharin sodium	IV(infusion); injection	0.09	%
Saccharin sodium	Dental; solution	0.15	%
Saccharin sodium	Dental; gel	0.3	%
Saccharin sodium, anhydrous	IM–IV; injection	0.09	%
Saccharin sodium, anhydrous	IV(infusion); injection	0.09	%

Ingredient	Dosage Form	Qty	Unit
Serine	IV(infusion); solution, injection	18	%
Serine	IV(infusion); injection	50	%
Sesame oil	Intramuscular; injection	70	%
Silastic brand medical grade tubing	Implantation; rod	13	mg
Silastic medical adhesive, silicone type A	Implantation; pellet, implant	13	mg
Silicon dioxide	Dental; gel	19	%
Silicon dioxide, colloidal	Endocervical; gel	8	%
Silicone	Intrauterine; suppository, insert, controlled release	60	mg
Sodium acetate	Intravenous; solution, injection	0.0204	%
Sodium acetate	Auricular (otic); solution, drops	0.0267	%
Sodium acetate	Auricular (otic); suspension	0.042	%
Sodium acetate	Intravenous; injectable	0.05	%
Sodium acetate	Auricular (otic); solution	0.075	%
Sodium acetate	Subcutaneous; injection	0.14	%
Sodium acetate	Subcutaneous; liquid	0.1455	%
Sodium acetate	Subcutaneous; solution, injection	0.1592	%
Sodium acetate	Intradermal; injection	0.16	%
Sodium acetate	Extracorporeal; solution	0.175	%
Sodium acetate	Photopheresis; solution	0.175	%
Sodium acetate	IM–SC; injection	0.2	%
Sodium acetate	IV–SC; injection	0.2	%
Sodium acetate	IV–SC; liquid	0.2	%
Sodium acetate	Ophthalmic; solution	0.35	%
Sodium acetate	Intraocular; solution	0.39	%
Sodium acetate	Ophthalmic; powder, for solution	0.39	%
Sodium acetate	Intramuscular; injection	0.4	%
Sodium acetate	IM–IV–SC; injection	0.65	%
Sodium acetate	IM–IV; injection	0.969	%
Sodium acetate	Ophthalmic; solution, drops	1.279	%
Sodium acetate	IV(infusion); solution, injection	1.7	%
Sodium acetate	Auricular (otic); suspension, liquid	6.8	%
Sodium acetate	Intravenous; injection	12.25	%
Sodium acetate	IV(infusion); injection	59.4	%
Sodium acetate, anhydrous	Intravenous; injectable	0.005	%
Sodium acetate, anhydrous	Subcutaneous; powder, for injection solution, lyophilized	0.01	%
Sodium acetate, anhydrous	IM–SC; injection	0.07	%
Sodium acetate, anhydrous	Subcutaneous; injection	0.16	%
Sodium acetate, anhydrous	Intramuscular; injection	0.471	%
Sodium acetate, anhydrous	IV(infusion); injection	6.25	%
Sodium acetate, anhydrous	Intravenous; solution	17.7	%
Sodium ascorbate	Intravenous; injection	1	%
Sodium ascorbate	Intravenous; solution, injection	1	%
Sodium benzoate	Intravenous; injectable	0.07	%

Ingredient	Dosage Form	Qty	Unit
Sodium benzoate	Dental; gel	0.08	%
Sodium benzoate	Intramuscular; solution, injection	4.8	%
Sodium benzoate	Intramuscular; injection	5	%
Sodium benzoate	IV(infusion); injection	5	%
Sodium benzoate	IM–IV; injection	10	%
Sodium bicarbonate	Intrathecal; injection	0.005	%
Sodium bicarbonate	Intravenous; injection	0.005	%
Sodium bicarbonate	Subcutaneous; powder, for injection solution	0.016	%
Sodium bicarbonate	Intravitreal; injection	0.178	%
Sodium bicarbonate	IV(infusion); powder, for injection solution, lyophilized	0.18	%
Sodium bicarbonate	Intravenous; powder, for injection solution	2.1	%
Sodium bicarbonate	Intramuscular; powder, for injection solution	3	%
Sodium bicarbonate	Intramuscular; injection	3.5	%
Sodium bicarbonate	Intraperitoneal; powder, for injection solution	60	%
Sodium bicarbonate	IM–IV; powder, for injection solution, lyophilized	61.9	%
Sodium bicarbonate	IV(infusion); powder, for injection solution	81.94	%
Sodium bicarbonate	IV(infusion); injection	83	%
Sodium bisulfate	Inhalation; solution	0.011	%
Sodium bisulfate	IM–IV–SC; injection	0.1	%
Sodium bisulfate	IM–IV; injection	0.32	%
Sodium bisulfite	Auricular (otic); suspension	0.001	%
Sodium bisulfite	IV(infusion); solution, injection	0.024	%
Sodium bisulfite	Ophthalmic; suspension	0.06	%
Sodium bisulfite	Inhalation; inhalant	0.075	%
Sodium bisulfite	Auricular (otic); solution	0.1	%
Sodium bisulfite	Auricular (otic); solution, drops	0.1	%
Sodium bisulfite	Intracardiac; injection	0.1	%
Sodium bisulfite	Ophthalmic; solution	0.1	%
Sodium bisulfite	Ophthalmic; solution, drops	0.1	%
Sodium bisulfite	Soft tissue; injection	0.1	%
Sodium bisulfite	Subcutaneous; injection	0.15	%
Sodium bisulfite	AN, infiltration; injection	0.2	%
Sodium bisulfite	Inhalation; solution	0.2	%
Sodium bisulfite	Intra-articular; injection	0.32	%
Sodium bisulfite	Intralesional; injection	0.32	%
Sodium bisulfite	Intrasynovial; injection	0.32	%
Sodium bisulfite	IM–IV–SC; injection	0.5	%
Sodium bisulfite	IM–IV; injection	0.66	%
Sodium bisulfite	Irrigation; injection	0.66	%
Sodium bisulfite	Intramuscular; injection	1.35	%
Sodium bisulfite	Intraperitoneal; injection	1.35	%
Sodium bisulfite	Nerve block; injection	2.2	%
Sodium bisulfite	Intravenous; injection	5	%

Ingredient	Dosage Form	Qty	Unit
Sodium bisulfite	Intravenous; solution, injection	5	%
Sodium bisulfite	IM–IV; powder, for injection solution	5.18	%
Sodium bisulfite	IV(infusion); injection	10	%
Sodium borate	Ophthalmic; suspension, drops	0.0285	%
Sodium borate	Auricular (otic); solution	0.3	%
Sodium borate	Ophthalmic; solution	0.543	%
Sodium borate	Ophthalmic; solution, drops	1.1	%
Sodium borate decahydrate	Ophthalmic; solution, drops	0.084	%
Sodium borate decahydrate	Ophthalmic; solution	0.15	%
Sodium carbonate	Intravitreal; injection	0.0082	%
Sodium carbonate	Intravenous; injection	0.046	%
Sodium carbonate	IV(infusion); powder, for injection solution, lyophilized	0.177	%
Sodium carbonate	Ophthalmic; solution	1	%
Sodium carbonate	IM–IV; injection	1.64	%
Sodium carbonate	IV(infusion); injection	24.1	%
Sodium carbonate	IV(infusion); powder, for injection solution	63	%
Sodium carbonate	IM–IV; powder, for injection solution	70.8	%
Sodium carbonate decahydrate	Intravenous; injection	12.428	%
Sodium chlorate	IV(infusion); injection	15.4	%
Sodium chloride	Intratracheal; suspension	0.088	%
Sodium chloride	Intra-arterial; powder, for injection solution	0.135	%
Sodium chloride	Intrathecal; powder, for injection solution	0.135	%
Sodium chloride	Subcutaneous; liquid	0.146	%
Sodium chloride	Intravascular; injection	0.187	%
Sodium chloride	Intralesional; suspension, injection	0.22	%
Sodium chloride	Intramuscular; suspension, injection	0.22	%
Sodium chloride	Intrasynovial; suspension, injection	0.22	%
Sodium chloride	Soft tissue; suspension, injection	0.22	%
Sodium chloride	Intramuscular; powder, for injection solution, lyophilized, with additives	0.24	%
Sodium chloride	AN, sympathetic NBLK; injection	0.3	%
Sodium chloride	Intrabursal; injection	0.32	%
Sodium chloride	Auricular (otic); solution, drops	0.362	%
Sodium chloride	Dental; injection	0.6	%
Sodium chloride	Nasal; solution	0.668	%
Sodium chloride	IV–SC; powder, for injection solution	0.68	%
Sodium chloride	Ophthalmic; suspension, drops	0.68	%
Sodium chloride	Intracardiac; injection	0.7	%
Sodium chloride	Intradermal; injection	0.7	%
Sodium chloride	Intraocular; solution	0.7	%
Sodium chloride	IV–SC; liquid	0.7	%
Sodium chloride	IM–IV; solution, injection	0.75	%
Sodium chloride	Intravitreal; injection	0.774	%
Sodium chloride	AN, CNBLK intrathecal; injection	0.8	%

Ingredient	Dosage Form	Qty	Unit
Sodium chloride	Extracorporeal; solution	0.8	%
Sodium chloride	Subcutaneous; suspension, injection	0.8	%
Sodium chloride	Photopheresis; solution	0.8	%
Sodium chloride	Peridural; injection	0.807	%
Sodium chloride	Intracavitary; injection	0.82	%
Sodium chloride	Infiltration; solution, injection	0.85	%
Sodium chloride	Intralesional; injection	0.85	%
Sodium chloride	Ophthalmic; suspension	0.85	%
Sodium chloride	Soft tissue; injection	0.85	%
Sodium chloride	Subcutaneous; injectable	0.85	%
Sodium chloride	AN, infiltration; injection	0.855	%
Sodium chloride	Caudal block; injection	0.9	%
Sodium chloride	Epidural; injection	0.9	%
Sodium chloride	Epidural; solution, injection	0.9	%
Sodium chloride	Extracorporeal; injection	0.9	%
Sodium chloride	IM–IV–SC; injection	0.9	%
Sodium chloride	IM–IV; injectable	0.9	%
Sodium chloride	IM–IV; solution	0.9	%
Sodium chloride	IM–SC; injection	0.9	%
Sodium chloride	Intra-arterial; solution	0.9	%
Sodium chloride	Intra-articular; injection	0.9	%
Sodium chloride	Intralesional; injection, sustained action	0.9	%
Sodium chloride	Intramuscular; injection, sustained action	0.9	%
Sodium chloride	Intramuscular; solution, injection	0.9	%
Sodium chloride	Intrasynovial; injection	0.9	%
Sodium chloride	Intrasynovial; injection, sustained action	0.9	%
Sodium chloride	Intrathecal; injectable	0.9	%
Sodium chloride	Intrathecal; solution, injection	0.9	%
Sodium chloride	Intravenous bolus; solution, injection	0.9	%
Sodium chloride	Intravenous; injectable	0.9	%
Sodium chloride	Intravenous; solution	0.9	%
Sodium chloride	Intravenous; solution, injection	0.9	%
Sodium chloride	Intravitreal; injectable	0.9	%
Sodium chloride	IV(infusion); solution, injection	0.9	%
Sodium chloride	IV(infusion); suspension, injection	0.9	%
Sodium chloride	Nasal; spray	0.9	%
Sodium chloride	Nerve block; injection	0.9	%
Sodium chloride	Nerve block; solution, injection	0.9	%
Sodium chloride	Ophthalmic; powder, for solution	0.9	%
Sodium chloride	Ophthalmic; solution, drops	0.9	%
Sodium chloride	Soft tissue; injection, sustained action	0.9	%
Sodium chloride	Subarachnoid; solution, injection	0.9	%
Sodium chloride	Subcutaneous; injection	0.9	%

Ingredient	Dosage Form	Qty	Unit
Sodium chloride	IV–SC; injection	1	%
Sodium chloride	Respiratory (inhalation); solution, aerosol, for inhalation	1.125	%
Sodium chloride	Intratracheal; injection	1.2	%
Sodium chloride	Intratumor; injection	1.2	%
Sodium chloride	Nasal; spray, metered	1.9	%
Sodium chloride	Respiratory (inhalation); solution	2.7	%
Sodium chloride	Respiratory (inhalation); solution, for inhalation	2.7	%
Sodium chloride	Inhalation; solution	3.16	%
Sodium chloride	Intramuscular; injection	4.5	%
Sodium chloride	Subcutaneous; solution, injection	4.5	%
Sodium chloride	Intratracheal; powder, for suspension	4.676	%
Sodium chloride	Intra-arterial; injection	4.9	%
Sodium chloride	Intrathecal; injection	4.9	%
Sodium chloride	Auricular (otic); solution	9	%
Sodium chloride	Auricular (otic); suspension, liquid	9	%
Sodium chloride	IM–IV; powder, for injection solution	9	%
Sodium chloride	Intrathecal; injection, suspension, liposomal	9	%
Sodium chloride	Submucosal; solution, injection	16	%
Sodium chloride	IM–IV; powder, for injection solution, lyophilized	18	%
Sodium chloride	Intramuscular; powder, for injection solution	22.6	%
Sodium chloride	Intraperitoneal; powder, for injection solution	22.6	%
Sodium chloride	Intrapleural; powder, for injection solution	22.6	%
Sodium chloride	Intravenous; powder, for injection solution, lyophilized	45	%
Sodium chloride	IV(infusion); powder, for injection solution	45	%
Sodium chloride	Intravenous; powder, for injection solution	45.2	%
Sodium chloride	Intraperitoneal; solution	53.5	%
Sodium chloride	Ophthalmic; solution	55	%
Sodium chloride	Subcutaneous; implant	77	mg
Sodium chloride	IM–IV; injection	90	%
Sodium chloride	Intravenous; injection	90	%
Sodium chloride	IV(infusion); injection	90	%
Sodium chlorite	Ophthalmic; solution, drops	0.005	%
Sodium cholesteryl sulfate	IV(infusion); powder, for injection suspension, lyophilized	5.676	%
Sodium citrate	Intracavitary; powder, for injection solution, lyophilized	0.0053	%
Sodium citrate	IM–IV; solution	0.025	%
Sodium citrate	Intravenous; injectable	0.025	%
Sodium citrate	Nasal; spray, metered	0.032	%
Sodium citrate	AN, infiltration; injection	0.0395	%
Sodium citrate	Nerve block; injection	0.0395	%
Sodium citrate	Intravenous; solution, injection	0.065	%
Sodium citrate	Respiratory (inhalation); powder, for inhalation	0.138	%
Sodium citrate	Intracavitary; injection	0.15	%
Sodium citrate	Ophthalmic; powder, for solution	0.17	%

Ingredient	Dosage Form	Qty	Unit
Sodium citrate	IM–SC; injection	0.228	%
Sodium citrate	Ophthalmic; suspension	0.3	%
Sodium citrate	Intravascular; injection	0.32	%
Sodium citrate	Intraocular; solution	0.4	%
Sodium citrate	Nasal; spray	0.44	%
Sodium citrate	Ophthalmic; suspension, drops	0.45	%
Sodium citrate	Inhalation; solution	0.6	%
Sodium citrate	IV(infusion); solution, injection	0.6	%
Sodium citrate	Intramuscular; injectable	0.6214	%
Sodium citrate	Intramuscular; powder, for injection solution, lyophilized	0.645	%
Sodium citrate	Subcutaneous; powder, for injection solution, lyophilized	0.645	%
Sodium citrate	Intracardiac; injection	0.8	%
Sodium citrate	Intravenous; solution	0.8295	%
Sodium citrate	IM–IV–SC; injection	0.94	%
Sodium citrate	Intralesional; injection	1	%
Sodium citrate	Intrasynovial; injection	1	%
Sodium citrate	Soft tissue; injection	1	%
Sodium citrate	Intramuscular; solution, injection	1.301	%
Sodium citrate	Subcutaneous; solution, injection	1.301	%
Sodium citrate	IM–IV; injectable	1.35	%
Sodium citrate	Auricular (otic); solution	2	%
Sodium citrate	Ophthalmic; solution	2	%
Sodium citrate	Epidural; injection	2.2	%
Sodium citrate	Intra-articular; injection	2.2	%
Sodium citrate	Irrigation; injection	2.2	%
Sodium citrate	Ophthalmic; solution, drops	2.2	%
Sodium citrate	Intramuscular; powder, for injection solution	4.62	%
Sodium citrate	Intrapleural; powder, for injection solution	4.62	%
Sodium citrate	Intrathecal; powder, for injection solution	4.62	%
Sodium citrate	Intramuscular; injection	6.6	%
Sodium citrate	Intraperitoneal; injection	6.6	%
Sodium citrate	IV(infusion); powder, for injection solution	8	%
Sodium citrate	IV(infusion); powder, for injection solution, lyophilized	14	%
Sodium citrate	Intravenous; powder, for injection solution, lyophilized	16.35	%
Sodium citrate	Intravenous; powder, for injection solution	16.4	%
Sodium citrate	Intravenous; injection	30	%
Sodium citrate	IM–IV; injection	40	%
Sodium citrate	IV(infusion); injection	40	%
Sodium citrate	Nasal; solution	70	%
Sodium citrate, anhydrous	Nasal; spray, metered	0.0007	%
Sodium citrate, anhydrous	Intra-articular; injection	1	%
Sodium citrate, anhydrous	Intrabursal; injection	1	%
Sodium citrate, anhydrous	Intravenous; powder, for injection solution	6.99	%

Ingredient	Dosage Form	Qty	Unit
Sodium citrate, anhydrous	IM–IV; injection	16	%
Sodium citrate, anhydrous	IV(infusion); injection	16	%
Sodium desoxycholate	IV(infusion); powder, for injection solution	4.1	%
Sodium dithionite	IM–IV–SC; injection	0.1	%
Sodium dithionite	IV(infusion); injection	2	%
Sodium dithionite	Intravenous; injection	3	%
Sodium formaldehyde sulfoxylate	IM–IV; injection	0.1	%
Sodium formaldehyde sulfoxylate	IM–SC; injection	0.1	%
Sodium formaldehyde sulfoxylate	Intramuscular; injection	0.2	%
Sodium formaldehyde sulfoxylate	IV(infusion); injection	1.1	%
Sodium gluconate	IV(infusion); powder, for injection solution, lyophilized	0.1	%
Sodium gluconate	Intravenous; injection	2.3	%
Sodium hydroxide	Nasal; spray, metered	0.004	%
Sodium hydroxide	Intravenous; solution, injection	0.035	%
Sodium hydroxide	AN, infiltration; injection	0.0706	%
Sodium hydroxide	Nerve block; injection	0.0706	%
Sodium hydroxide	Ophthalmic; solution	0.1	%
Sodium hydroxide	IM–IV; solution, injection	0.134	%
Sodium hydroxide	Subcutaneous; suspension, injection	0.22	%
Sodium hydroxide	Ophthalmic; emulsion	0.397	%
Sodium hydroxide	Subcutaneous; injectable	0.42	%
Sodium hydroxide	IM–IV; powder, for injection solution	0.701	%
Sodium hydroxide	Auricular (otic); solution	0.8	%
Sodium hydroxide	IV(infusion); powder, for injection solution, lyophilized	1.565	%
Sodium hydroxide	IV(infusion); solution, injection	2.83	%
Sodium hydroxide	Intramuscular; injection	3.145	%
Sodium hydroxide	Subcutaneous; injection	3.145	%
Sodium hydroxide	Inhalation; solution	8	%
Sodium hydroxide	IV(infusion); powder, for injection solution	9	%
Sodium hydroxide	Intravenous; injection	10	%
Sodium hydroxide	IM–IV; injection	10.68	%
Sodium hydroxide	IV(infusion); injection	13	%
Sodium hydroxide	Intravenous; powder, for injection solution	13.655	%
Sodium hydroxide	Intravenous; powder, for injection solution, lyophilized	19.27	%
Sodium hypochlorite	IV(infusion); injection	1	%
Sodium iodide	Intravenous; injection	1	%
Sodium iodide	Intravenous; powder, for injection solution	5	%
Sodium lactate	Caudal block; injection	0.0001	%
Sodium lactate	Intravenous; injection	0.17	%
Sodium lactate	Nerve block; injection	0.17	%
Sodium lactate	Intravenous; powder, for injection solution, lyophilized	1.87	%
Sodium lactate	Intraperitoneal; solution	44.8	%
L-Sodium lactate	IM–IV–SC; injection	0.18	%

Ingredient	Dosage Form	Qty	Unit
L-Sodium lactate	Intracardiac; injection	0.18	%
L-Sodium lactate	IV(infusion); injection	0.18	%
Sodium lauryl sulfate	Dental; gel	1.47	%
Sodium metabisulfite	Intravenous; emulsion, injection	0.025	%
Sodium metabisulfite	Intravenous; solution, injection	0.05	%
Sodium metabisulfite	Intracardiac; injection	0.09	%
Sodium metabisulfite	Ophthalmic; suspension, drops	0.1	%
Sodium metabisulfite	IM–IV–SC; injection	0.15	%
Sodium metabisulfite	Caudal block; injection	0.183	%
Sodium metabisulfite	Epidural; injection	0.183	%
Sodium metabisulfite	Intra-articular; injection	0.2	%
Sodium metabisulfite	Intrabursal; injection	0.2	%
Sodium metabisulfite	Ophthalmic; solution	0.2	%
Sodium metabisulfite	Ophthalmic; solution, drops	0.25	%
Sodium metabisulfite	Subcutaneous; injection	0.3016	%
Sodium metabisulfite	Intravenous; injection	0.32	%
Sodium metabisulfite	AN, infiltration; injection	0.5	%
Sodium metabisulfite	Nerve block; injection	0.5	%
Sodium metabisulfite	Intraperitoneal; injection	0.66	%
Sodium metabisulfite	Inhalation; solution	1	%
Sodium metabisulfite	IV(infusion); injection	1.1	%
Sodium metabisulfite	Submucosal; solution, injection	5	%
Sodium metabisulfite	IV(infusion); solution, injection	22	%
Sodium metabisulfite	IM–IV; injection	27.5	%
Sodium metabisulfite	Intramuscular; injection	27.5	%
Sodium nitrate	Ophthalmic; solution	1.18	%
Sodium phosphate	Nerve block; injection	0.02	%
Sodium phosphate	Intramuscular; powder, for injection solution	0.1	%
Sodium phosphate	IM–IV; solution, injection	0.17	%
Sodium phosphate	Nasal; solution	0.189	%
Sodium phosphate	Intradermal; injection	0.2	%
Sodium phosphate	Ophthalmic; suspension	0.2	%
Sodium phosphate	Ophthalmic; solution, drops	0.29	%
Sodium phosphate	IM–IV; injection	0.3	%
Sodium phosphate	Subcutaneous; injection	0.378	%
Sodium phosphate	Intramuscular; injection	0.425	%
Sodium phosphate	IV(infusion); injection	0.79	%
Sodium phosphate	Ophthalmic; solution	0.81	%
Sodium phosphate	Intravenous; powder, for injection solution	1	%
Sodium phosphate	Intravenous; injection	1.6	%
Sodium phosphate	IM–IV; powder, for injection solution	2.475	%
Sodium phosphate dihydrate	Ophthalmic; solution	0.03	%
Sodium phosphate dihydrate	Subcutaneous; powder, for injection solution, lyophilized	0.13	%

Ingredient	Dosage Form	Qty	Unit
Sodium phosphate dihydrate	Subcutaneous; injection	0.24	%
Sodium phosphate, dibasic	Subcutaneous; suspension, injection	0.0588	%
Sodium phosphate, dibasic	Intralesional; suspension, injection	0.142	%
Sodium phosphate, dibasic	Intramuscular; suspension, injection	0.142	%
Sodium phosphate, dibasic	Intrasynovial; suspension, injection	0.142	%
Sodium phosphate, dibasic	Soft tissue; suspension, injection	0.142	%
Sodium phosphate, dibasic	Intradermal; injection	0.2	%
Sodium phosphate, dibasic	Ophthalmic; solution	0.29	%
Sodium phosphate, dibasic	Subcutaneous; powder, for injection solution, lyophilized	0.298	%
Sodium phosphate, dibasic	Ophthalmic; suspension	0.43	%
Sodium phosphate, dibasic	Intravenous; injection	0.76	%
Sodium phosphate, dibasic	IM–IV; injectable	1.74	%
Sodium phosphate, dibasic, anhydrous	Nasal; spray	0.011	%
Sodium phosphate, dibasic, anhydrous	Intramuscular; powder, for injection solution, lyophilized	0.03	%
Sodium phosphate, dibasic, anhydrous	Subcutaneous; powder, for injection solution, lyophilized	0.03	%
Sodium phosphate, dibasic, anhydrous	Subcutaneous; injectable	0.104	%
Sodium phosphate, dibasic, anhydrous	Intramuscular; injectable	0.24	%
Sodium phosphate, dibasic, anhydrous	Intravenous; injectable	0.24	%
Sodium phosphate, dibasic, anhydrous	Ophthalmic; suspension	0.25	%
Sodium phosphate, dibasic, anhydrous	Intramuscular; injection	0.29	%
Sodium phosphate, dibasic, anhydrous	Intravenous; solution, injection	0.76	%
Sodium phosphate, dibasic, anhydrous	Auricular (otic); solution, drops	0.7954	%
Sodium phosphate, dibasic, anhydrous	Ophthalmic; solution	1.28	%
Sodium phosphate, dibasic, anhydrous	Ophthalmic; solution, drops	1.4	%
Sodium phosphate, dibasic, anhydrous	Intravenous; powder, for injection solution, lyophilized	1.5	%
Sodium phosphate, dibasic, anhydrous	IM–IV; injectable	1.746	%
Sodium phosphate, dibasic, anhydrous	IV(infusion); injection	4	%
Sodium phosphate, dibasic, anhydrous	IM–IV; injection	13.92	%
Sodium phosphate, dibasic, anhydrous	IM–IV; powder, for injection solution	13.92	%
Sodium phosphate, dibasic, anhydrous	IV(Infusion); powder, for injection solution	13.92	%
Sodium phosphate, dibasic, anhydrous	Intravenous; injection	21.3	%
Sodium phosphate, dibasic, dihydrate	Subcutaneous; powder, for injection solution, lyophilized	0.111	%
Sodium phosphate, dibasic, dihydrate	Subcutaneous; injection	0.1665	%
Sodium phosphate, dibasic, dihydrate	Subcutaneous; injectable	0.18	%
Sodium phosphate, dibasic, dihydrate	Nasal; spray, metered	0.3	%
Sodium phosphate, dibasic, dihydrate	Ophthalmic; solution	1.081	%
Sodium phosphate, dibasic, dihydrate	Ophthalmic; solution, drops	1.201	%
Sodium phosphate, dibasic, dodecahydrate	Nasal; spray, metered	14.3	%
Sodium phosphate, dibasic, heptahydrate	AN, infiltration; injection	0.02	%
Sodium phosphate, dibasic, heptahydrate	Nerve block; injection	0.02	%
Sodium phosphate, dibasic, heptahydrate	IM–SC; injection	0.0268	%
Sodium phosphate, dibasic, heptahydrate	Nasal; solution	0.0452	%
Sodium phosphate, dibasic, heptahydrate	Intramuscular; injection, sustained action	0.067	%

Ingredient	Dosage Form	Qty	Unit
Sodium phosphate, dibasic, heptahydrate	Intravitreal; injectable	0.12	%
Sodium phosphate, dibasic, heptahydrate	Subcutaneous; injectable	0.188	%
Sodium phosphate, dibasic, heptahydrate	Subcutaneous; powder, for injection solution, lyophilized	0.209	%
Sodium phosphate, dibasic, heptahydrate	Subcutaneous; injection	0.378	%
Sodium phosphate, dibasic, heptahydrate	Subcutaneous; suspension, injection	0.378	%
Sodium phosphate, dibasic, heptahydrate	Intravenous; injection	0.43	%
Sodium phosphate, dibasic, heptahydrate	Ophthalmic; suspension, drops	0.431	%
Sodium phosphate, dibasic, heptahydrate	Nasal; spray, metered	0.486	%
Sodium phosphate, dibasic, heptahydrate	Auricular (otic); solution	0.5	%
Sodium phosphate, dibasic, heptahydrate	Intramuscular; powder, for injection solution	0.543	%
Sodium phosphate, dibasic, heptahydrate	Subcutaneous; powder, for injection solution	0.543	%
Sodium phosphate, dibasic, heptahydrate	IM–IV; solution, injection	0.566	%
Sodium phosphate, dibasic, heptahydrate	Ophthalmic; suspension	0.866	%
Sodium phosphate, dibasic, heptahydrate	Ophthalmic; solution	1.206	%
Sodium phosphate, dibasic, heptahydrate	IV(infusion); powder, for injection solution	1.58	%
Sodium phosphate, dibasic, heptahydrate	Ophthalmic; solution, drops	2.5	%
Sodium phosphate, dibasic, heptahydrate	Intravenous; powder, for injection solution	2.9	%
Sodium phosphate, dibasic, heptahydrate	IM–IV; powder	3.627	%
Sodium phosphate, dibasic, heptahydrate	Intramuscular; powder, for injection solution, lyophilized	4.8	%
Sodium phosphate, dibasic, heptahydrate	IM–IV; injection	6.96	%
Sodium phosphate, dibasic, heptahydrate	IV(infusion); injection	10.3	%
Sodium phosphate, dibasic, heptahydrate	IM–IV; powder, for injection solution	27.927	%
Sodium phosphate, monobasic	Ophthalmic; solution, drops	0.01	%
Sodium phosphate, monobasic	Subcutaneous; powder, for injection solution, lyophilized	0.022	%
Sodium phosphate, monobasic	Subcutaneous; suspension, injection	0.0694	%
Sodium phosphate, monobasic	IM–IV; injectable	0.16	%
Sodium phosphate, monobasic	Ophthalmic; solution	0.19	%
Sodium phosphate, monobasic	Intramuscular; injection	0.5747	%
Sodium phosphate, monobasic	Intralesional; suspension, injection	0.68	%
Sodium phosphate, monobasic	Intramuscular; suspension, injection	0.68	%
Sodium phosphate, monobasic	Intrasynovial; suspension, injection	0.68	%
Sodium phosphate, monobasic	Soft tissue; suspension, injection	0.68	%
Sodium phosphate, monobasic	IV(infusion); powder, for injection solution	1.32	%
Sodium phosphate, monobasic	IM–IV; injection	1.472	%
Sodium phosphate, monobasic, anhydrous	Intravascular; injection	0.0125	%
Sodium phosphate, monobasic, anhydrous	Nasal; spray, metered	0.019	%
Sodium phosphate, monobasic, anhydrous	Ophthalmic; suspension, drops	0.056	%
Sodium phosphate, monobasic, anhydrous	Subcutaneous; powder, for injection solution	0.08	%
Sodium phosphate, monobasic, anhydrous	Subcutaneous; powder, for injection solution, lyophilized	0.11	%
Sodium phosphate, monobasic, anhydrous	Auricular (otic); solution, drops	0.128	%
Sodium phosphate, monobasic, anhydrous	Intramuscular; injection	0.5	%
Sodium phosphate, monobasic, anhydrous	Intramuscular; powder, for injection solution	0.5	%
Sodium phosphate, monobasic, anhydrous	Intravenous; injection	0.5	%
Sodium phosphate, monobasic, anhydrous	IV(infusion); injection	0.5	%

Ingredient	Dosage Form	Qty	Unit
Sodium phosphate, monobasic, anhydrous	IM–IV; solution, injection	0.62	%
Sodium phosphate, monobasic, anhydrous	Ophthalmic; suspension	0.65	%
Sodium phosphate, monobasic, anhydrous	Intravenous; powder, for injection solution	0.71	%
Sodium phosphate, monobasic, anhydrous	Ophthalmic; solution	0.725	%
Sodium phosphate, monobasic, anhydrous	Ophthalmic; solution, drops	0.78	%
Sodium phosphate, monobasic, anhydrous	Intramuscular; powder, for injection solution, lyophilized	1.2	%
Sodium phosphate, monobasic, anhydrous	IM–IV; injection	1.28	%
Sodium phosphate, monobasic, anhydrous	IM–IV; powder, for injection solution	1.28	%
Sodium phosphate, monobasic, anhydrous	IV(infusion); powder, for injection solution	1.28	%
Sodium phosphate, monobasic, anhydrous	Subcutaneous; injection	3.31	%
Sodium phosphate, monobasic, anhydrous	Intravenous; solution	4	%
Sodium phosphate, monobasic, dihydrate	Subcutaneous; powder, for injection solution, lyophilized	0.045	%
Sodium phosphate, monobasic, dihydrate	IV(infusion); powder, for injection solution	0.16	%
Sodium phosphate, monobasic, dihydrate	Intravenous; injection	0.76	%
Sodium phosphate, monobasic, dihydrate	Ophthalmic; solution, drops	1.053	%
Sodium phosphate, monobasic, dihydrate	Ophthalmic; solution	1.158	%
Sodium phosphate, monobasic, dihydrate	Nasal; spray, metered	4.2	%
Sodium phosphate, monobasic, monohydrate	Subcutaneous; injectable	0.036	%
Sodium phosphate, monobasic, monohydrate	Intravenous; powder, for injection solution	0.0495	%
Sodium phosphate, monobasic, monohydrate	Subcutaneous; injection	0.0675	%
Sodium phosphate, monobasic, monohydrate	Intravitreal; injectable	0.077	%
Sodium phosphate, monobasic, monohydrate	Intravenous; solution, injection	0.18	%
Sodium phosphate, monobasic, monohydrate	IM–IV; powder	0.202	%
Sodium phosphate, monobasic, monohydrate	IM–IV; injection	0.5	%
Sodium phosphate, monobasic, monohydrate	IV(infusion); injection	0.5	%
Sodium phosphate, monobasic, monohydrate	Ophthalmic; suspension	0.538	%
Sodium phosphate, monobasic, monohydrate	Ophthalmic; solution	0.54	%
Sodium phosphate, monobasic, monohydrate	Ophthalmic; solution, drops	0.721	%
Sodium phosphate, monobasic, monohydrate	IV(infusion); powder, for injection solution	1.3606	%
Sodium phosphate, monobasic, monohydrate	IM–IV; powder, for injection solution	1.555	%
Sodium phosphate, monobasic, monohydrate	Intravenous; injection	6.21	%
Sodium phosphate, monobasic, monohydrate	N/A; not applicable	600	mg
Sodium pyrophosphate	Intravenous; injection	1.2	%
Sodium succinate	Intravenous; injection, powder, lyophilized, for liposomal suspension	2.7	%
Sodium sulfate	Ophthalmic; solution	0.226	%
Sodium sulfate	Ophthalmic; suspension	1.2	%
Sodium sulfate decahydrate	Ophthalmic; solution, drops	0.09	%
Sodium sulfate, anhydrous	Inhalation; solution	0.025	%
Sodium sulfate, anhydrous	Ophthalmic; solution	0.152	%
Sodium sulfate, anhydrous	Ophthalmic; solution, drops	0.17	%
Sodium sulfate, anhydrous	Ophthalmic; suspension	1.2	%
Sodium sulfite	Auricular (otic); solution	0.02	%
Sodium sulfite	Intramuscular; injection	0.05	%
Sodium sulfite	Subcutaneous; injection	0.09	%

Ingredient	Dosage Form	Qty	Unit
Sodium sulfite	Epidural; injection	0.1	%
Sodium sulfite	Inhalation; solution	0.1	%
Sodium sulfite	Intra-articular; injection	0.1	%
Sodium sulfite	Intravenous; injection	0.1	%
Sodium sulfite	IM–IV; injection	0.2	%
Sodium sulfite	Ophthalmic; solution, drops	0.2	%
Sodium tartrate	IM–IV; injection	1.2	%
Sodium tartrate	Intravenous; injection	1.2	%
Sodium tartrate	IV(infusion); injection	1.2	%
Sodium tartrate	Intramuscular; injection	1.41	%
Sodium thioglycolate	Subcutaneous; injection	0.66	%
Sodium thiosulfate	Ophthalmic; solution, drops	0.31	%
Sodium thiosulfate	Ophthalmic; suspension, drops	0.314	%
Sodium thiosulfate	Ophthalmic; suspension	0.32	%
Sodium thiosulfate	Ophthalmic; solution	5	%
Sodium thiosulfate, anhydrous	Intravenous; solution	0.19	%
Sorbic acid	Ophthalmic; solution	0.2	%
Sorbitan trioleate	Nasal; aerosol, metered	0.0175	%
Sorbitan trioleate	Inhalation; aerosol, metered	0.0694	%
Sorbitol	Ophthalmic; solution, drops	0.25	%
Sorbitol	Nasal; solution	2.5	%
Sorbitol	Nasal; spray, metered	2.86	%
Sorbitol	Intravenous; solution, injection	7.14	%
Sorbitol	IV(infusion); solution, injection	7.14	%
Sorbitol	Intravenous; injection	30	%
Sorbitol	Intra-articular; injection	45	%
Sorbitol	Intralesional; injection	45	%
Sorbitol	Intrasynovial; injection	45	%
Sorbitol solution	Intravenous; injection	7.14	%
Sorbitol solution	Intravenous; solution, injection	7.14	%
Sorbitol solution	IV(infusion); solution, injection	7.14	%
Sorbitol solution	Intramuscular; injection	25	%
Sorbitol solution	Ophthalmic; solution, drops	39.9996	%
Soybean oil	Intravenous; emulsion, injection	10	%
Soybean oil	Intravenous; injectable	10	%
Stannous chloride	IV(infusion); powder, for injection solution, lyophilized	0.003	%
Stannous chloride	Intravenous; powder, for injection solution	0.025	%
Stannous chloride	IV(infusion); injection	0.05	%
Stannous chloride	Intravenous; injection	0.34	%
Stannous chloride, anhydrous	Intravenous; injection	0.005	%
Stannous fluoride	Intravenous; injection	0.073	%
Stannous tartrate	Intravenous; injection	0.008	%
Starch	Intramuscular; injection	0.6	%

Ingredient	Dosage Form	Qty	Unit
Stearic acid	Implantation; pellet	0.2	mg
Stearic acid	Subcutaneous; implant	1.04	mg
Sucrose	Subcutaneous; powder, for injection solution, lyophilized, with additives	4.104	%
Sucrose	Intramuscular; solution, injection	4.425	%
Sucrose	Subcutaneous; solution, injection	4.425	%
Sucrose	IV(infusion); powder, for injection solution, lyophilized	5.4	%
Sucrose	Intramuscular; powder, for injection solution, lyophilized	6.84	%
Sucrose	Subcutaneous; powder, for injection solution, lyophilized	6.84	%
Sucrose	Intravenous; powder, for injection solution, lyophilized	7.78	%
Sucrose	Intravenous; solution, liposome, injection	8.5	%
Sucrose	Subcutaneous; injection	9	%
Sucrose	Intravenous; injection, suspension, liposomal	9.4	%
Sucrose	Intravenous; injection	19.5	%
Sucrose	Intravenous; injection, powder, lyophilized, for liposomal suspension	90	%
Sulfur dioxide	IV(infusion); solution, injection	0.15	%
Sulfuric acid	Ophthalmic; solution, drops	0.02	%
Sulfuric acid	Auricular (otic); suspension	0.023	%
Sulfuric acid	Nasal; spray	0.4	%
Sulfuric acid	Intramuscular; injection	2.098	%
Sulfuric acid	Intravenous; injection	2.098	%
Sulfuric acid	IV(infusion); injection	2.12	%
Sulfuric acid	Inhalation; solution	12.5	%
Sulfuric acid	IM–IV; injection	56.6	%
Tartaric acid	Intravenous; injection	0.2	%
Tartaric acid	Intravenous; solution, injection	0.2	%
Tartaric acid	Intramuscular; injection	0.35	%
Tartaric acid	IV(infusion); powder, for injection solution, lyophilized	2	%
Tetrofosmin	IV(infusion); powder, for injection solution, lyophilized	0.023	%
Theophylline, anhydrous	Intravenous; injection	1.973	%
Theophylline, anhydrous	IV(infusion); injection	2.053	%
Thimerosal	Intramuscular; injection, sustained action	0.002	%
Thimerosal	Ophthalmic; suspension	0.004	%
Thimerosal	Intramuscular; injection	0.0084	%
Thimerosal	Auricular (otic); suspension	0.01	%
Thimerosal	Ophthalmic; solution	0.01	%
Thimerosal	Ophthalmic; solution, drops	0.01	%
Thimerosal	Subcutaneous; injection	0.01	%
Thimerosal	Ophthalmic; suspension, drops	1	%
Thioglycerol	Nerve block; injection	0.0001	%
Thioglycerol	IM–IV; injection	0.5	%
Thioglycerol	Intramuscular; injection	1	%
Thioglycerol	Intravenous; injection	1	%
Threonine	IV(infusion); solution, injection	12	%

Ingredient	Dosage Form	Qty	Unit
Threonine	IV(infusion); injection	45	%
Thymol	Inhalation; liquid	0.01	%
Tin	Intravenous; injection	0.0083	%
Titanium dioxide	Ophthalmic; suppository, insert, controlled release	0.4	mg
Titanium dioxide	Intrauterine; suppository, insert, controlled release	1	mg
Tocophersolan	Ophthalmic; solution, drops	0.5	%
Tricaprylin	Epidural; injection, suspension, liposomal	0.03	%
Trichloromonofluoromethane	Nasal; aerosol, metered	0.9	%
Trichloromonofluoromethane	Inhalation; aerosol, metered	33.831	%
Triolein	Epidural; injection, suspension, liposomal	0.01	%
Trisodium citrate dihydrate	Intravenous; injectable	0.023	%
Trisodium citrate dihydrate	IM–IV; injectable	0.025	%
Trisodium citrate dihydrate	IM–IV; solution	0.025	%
Trisodium citrate dihydrate	Ophthalmic; solution	0.14	%
Tromethamine	IV(infusion); injection	0.005	%
Tromethamine	Respiratory (inhalation); solution, for inhalation	0.0121	%
Tromethamine	Intramuscular; injection	0.1	%
Tromethamine	Intra-arterial; injection	0.242	%
Tromethamine	Ophthalmic; solution, drops	0.5	%
Tromethamine	Subcutaneous; injection	0.6	%
Tromethamine	Ophthalmic; solution, gel forming, extended release	0.8	%
Tromethamine	Ophthalmic; solution	0.936	%
Tromethamine	Intravascular; injection	1	%
Tromethamine	Intravenous; injection	1	%
Tromethamine	IM–IV; injectable	1.1	%
Tromethamine	IM–IV; injection, solution	1.211	%
Tromethamine	IV(infusion); powder, for injection suspension, lyophilized	1.213	%
Tryptophan	IV(infusion); solution, injection	4.6	%
Tryptophan	IV(infusion); injection	15.2	%
Tyloxapol	Ophthalmic; solution	0.1	%
Tyloxapol	Ophthalmic; solution, drops	0.1	%
Tyloxapol	Ophthalmic; suspension	0.3	%
Tyloxapol	Ophthalmic; suspension, drops	0.3	%
Tyrosine	IV(infusion); injection	3.4	%
Valine	IV(infusion); solution, injection	20	%
Valine	IV(infusion); injection	84	%
Versetamide	Intravenous; injection	2.54	%
Xanthan gum	Ophthalmic; solution, gel forming, extended release	0.6	%
Zinc	Subcutaneous; injectable	0.0065	%
Zinc	Subcutaneous; injection	0.015	%
Zinc	Subcutaneous; suspension, injection	3.27	%
Zinc acetate	Subcutaneous; powder, for injection suspension	0.23	%
Zinc carbonate	Subcutaneous; powder, for injection suspension	0.16	%

Ingredient	Dosage Form	Qty	Unit
Zinc chloride	Ophthalmic; solution, drops	0.0025	%
Zinc chloride	Subcutaneous; injectable	0.0063	%
Zinc chloride	Subcutaneous; injection	0.015	%
Zinc chloride	Intradermal; injection	0.04	%
Zinc oxide	Subcutaneous; injectable	0.002	%
Zinc oxide	Subcutaneous; suspension, injection	0.0025	%
Zinc oxide	Subcutaneous; injection	0.019	%
Zinc oxide	Respiratory (inhalation); solution, injection	3.114	%

Part II

Manufacturing Formulations

Abciximab Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Abciximab	2.00	g
0.01	M	2	Sodium phosphate	0.01	M
0.15	M	3	Sodium chloride	0.15	M
0.001	%	4	Polysorbate 80	0.001	%
QS	mL	5	Water for injection	QS to 1.00	L

Manufacturing Directions

1. Abciximab is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3.
2. Abciximab binds to the glycoprotein (GP) IIb/IIIa receptor of human platelets and inhibits platelet aggregation. Abciximab also binds to the vitronectin ($alpha_v beta_3$) receptor found on platelets and vessel wall endothelial and smooth muscle cells.
3. The chimeric 7E3 antibody is produced by continuous perfusion in mammalian cell culture. The 47615 Da Fab fragment is purified from cell culture supernatant by a series of steps involving specific viral inactivation and removal procedures, digestion with papain, and column chromatography.
4. It is a clear, colorless sterile nonpyrogenic solution for intravenous (IV) use (pH 7.2). No preservatives are added.

Acetazolamide Injection

Bill of Materials					
Scale/Vial		Item	Material	Qty	UOM
500.00	mg	1	Acetazolamide sodium	500.00	mg
QS	mL	2	Sodium hydroxide[a]	QS	mL
QS	mL	3	Hydrochloric acid[a]	QS	mL

[a] For pH adjustment.

Description

Supplied as a sterile powder requiring reconstitution. The bulk solution is adjusted to pH 9.2 prior to lyophilization.

Acetylcholine Chloride Intraocular Solution

Bill of Materials for Lower Chamber					
Scale/Vial		Item	Material	Qty	UOM
20.00	mg	1	Acetylcholine chloride	20.00	mg
56.00	mg	2	Mannitol	56.00	mg

Description

Acetylcholine chloride intraocular solution is a parasympathomimetic preparation for intraocular use packaged in a vial of two compartments. The reconstituted liquid will be a sterile isotonic solution (275–330 mOsm/kg) containing 20 mg acetylcholine chloride (1:100 solution) and 2.8% mannitol. The pH range is 5.0 to 8.2. Mannitol is used in the process of lyophilizing acetylcholine chloride and is not considered an active ingredient. Diluet includes sodium acetate trihydrate, potassium chloride, magnesium chloride hexahydrate, calcium chloride in sterile water for injection.

Acyclovir Sodium Injection

Bill of Materials per Vial (10 mL)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Acyclovir	500.00	mg
4.90	mg	2	Sodium	49.00	mg
QS	mL	3	Sterile water for injection, USP (for reconstitution)	10.00	mL

Description

Acyclovir sodium for injection is a sterile lyophilized powder for IV administration only. The pH of the reconstituted solution is ca. 11. Further dilution in any appropriate IV solution must be performed before infusion.

Adenosine 5′ Monophosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Adenosine 5′ monophosphate	200.00	g
1.50	%	2	Benzyl alcohol, NF	1.50	%
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	mL

Adenosine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.00	mg	1	Adenosine	3.00	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Water for injection	QS to 1.00	L

Adjust pH to 4.7 to 5.0.

Adrenal Cortex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Adrenal cortex equivalent to 200 mg hydrocortisone reference standard, USP	200.00	mg
1:20,000	—	2	Thimerosal as preservative	1:20,000	—
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium acetate for buffering	QS	mL
QS	mL	5	Acetic acid for buffering	QS	mL

Adrenaline Tartarate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.80	mg	1	Adrenaline bitartrate (1:1000)[a]	1.80	g
1.00	mg	2	Sodium metabisulfite	1.00	g
8.00	mg	3	Sodium chloride NF	8.00	g
QS	L	4	Water for injection, USP	QS to 1.00	L

[a] Contains not less than 0.09% and not more than 0.115% w/v of adrenaline.

Manufacturing Directions

1. Boil item 4 and allow to cool to room temperature; check for suitability by pH and electrical conductivity.
2. Add and mix items 1, 2, and 3 and stir to dissolve all ingredients.
3. Check and record pH 2.9 to 3.6. Sample.
4. Filter through 0.22-μm filter.
5. Fill 1.1 mL into amber ampoules.
6. Heat-sterilize at 121°C for 30 minutes. Sample.
7. Check for clarity. Sample.

Alatrofloxacin Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
7.86	mg	1	Alatrofloxacin mesylate	7.86	g
QS	mL	2	Hydrochloric acid for pH adjustment	QS	mL
QS	mL	3	Sodium hydroxide for pH adjustment	QS	mL
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 0.9 L of item 4 and dissolve item 1 in it.
2. Check and adjust pH to 4.0 (3.7–4.1) by item 2 or 3.

An isotonic form of the above is obtained as follows.

3. Filter and fill 30 mL into a 40-mL vial or ampoule.
4. Autoclave at 115°C for 15 minutes.
5. Finish and sample.

Alatrofloxacin Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.14	mg	1	Alatrofloxacin mesylate	3.14	g
5.00	mg	2	Dextrose, USP	5.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	mL
QS	mL	4	Sodium hydroxide for pH adjustment	QS	mL
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 0.9 L of item 5 and dissolve items 1 and 2 in it.
2. Check and adjust pH to 4.0 (3.7–4.1) by item 3 or 4.

A lyophilized form of the above is obtained as follows:

3. Filter and fill 30 mL into a 40-mL vial.
4. Autoclave at 115°C for 15 minutes.
5. Finish and sample. Final concentration is 3.14 mg/mL.

Alatrofloxacin Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.14	mg	1	Alatrofloxacin mesylate	3.14	g
5.00	mg	2	Lactose, USP	5.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	mL
QS	mL	4	Sodium hydroxide for pH adjustment	QS	mL
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 0.9 L of item 5 and dissolve items 1 and 2 in it.
2. Check and adjust pH to 4.0 (3.7–4.1) by item 3 or 4.
3. Filter and fill 30 mL into a 40-mL vial.
4. Lyophilize for 24 hours under a 0.1-atm vacuum.
5. Autoclave at 115°C for 15 minutes.
6. Finish and sample. Final concentration is 3.14 mg/mL.

Alatrofloxacin Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Trovafloxacin, use alatrofloxacin mesylate	5.00	g
QS	mL	2	Sodium hydroxide[a]	QS	mL
QS	mL	3	Hydrochloric acid[a]	QS	mL
QS	mL	4	Water for injection	QS to 1.00	L

[a] For pH adjustment.

Description

Available in 40- and 60-mL single-use vials as a sterile, preservative-free aqueous concentrate intended for dilution prior to IV administration of doses of 200 or 300 mg of trovafloxacin, respectively. The pH range for the 5 mg/mL aqueous concentrate is 3.5 to 4.3.

Albumin (Human)

Albumin (human), USP, is made from pooled human venous plasma by using the Cohn cold ethanol fractionation process. The approximate sodium content of the product is 145 mEq/L. It contains no preservative. Each 1: 5% vial is heat treated at 60°C for 10 hours against the possibility of transmitting the hepatitis viruses. The product is available in 50- and 100-mL rubber-stoppered single-dose vials.

Albumin 5% Solution

Bill of Materials (Batch Size 1 L)					
Scale/100 mL		Item	Material	Qty	UOM
5.00	g	1	Albumin	50.00	g
QS	mL	2	Sodium caprylate (0.004 M)[a]	QS	mL
QS	mL	3	Sodium *N*-acetyl tryptophanate (0.004 M)[a]	QS	mL
QS	mL	4	Sodium bicarbonate[b]	QS	mL
QS	mL	5	Water for injection	QS to 1.00	L

[a] For stabilization.
[b] For pH adjustment.

Albumin 20% Solution

Bill of Materials (Batch Size 1 L)					
Scale/100 mL		Item	Material	Qty	UOM
20.00	g	1	Albumin	200.00	g
QS	mL	2	Sodium caprylate (0.016 M)	QS	mL
QS	mL	3	Sodium *N*-acetyl tryptophanate (0.016 M)[a]	QS	mL
QS	mL	4	Sodium bicarbonate[b]	QS	mL
QS	mL	5	Water for injection	QS to 1.00	L

[a] For stabilization.
[b] For pH adjustment.

Albumin 25% Solution

Bill of Materials (Batch Size 1 L)					
Scale/100 mL		Item	Material	Qty	UOM
25.00	g	1	Albumin	250.00	g
QS	mL	2	Sodium caprylate (0.02 M)[a]	QS	mL
QS	mL	3	Sodium *N*-acetyl tryptophanate (0.02 M)[a]	QS	mL
QS	mL	4	Sodium bicarbonate[b]	QS	mL
QS	mL	5	Water for injection	QS to 1.00	L

[a] For stabilization.
[b] For pH adjustment 6.9 $\pm$ 0.5.

Albuterol Sulfate Inhalation Solution

Bill of Materials (Batch Size 1 L)					
Scale/3 mL		Item	Material	Qty	UOM
0.63 0.75	mg mg	1	Albuterol use albuterol sulfate	210.00	mg
QS	mg	2	Sodium chloride	QS	mg
QS	mL	3	Sulfuric acid	QS	mL
QS	mL	4	Sterile water for injection	QS to 1.00	L

Adjust pH to 3.5.

Aldesleukin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.10	mg	1	Aldesleukin (18 million IU)	1.10	g
50.00	mg	2	Mannitol	50.00	g
0.18	mg	3	Sodium dodecyl sulfate	0.18	g
0.17	mg	4	Sodium phosphate monobasic	0.17	g
0.89	mg	5	Sodium phosphate dibasic	0.89	g

Note: Each milliliter of product requires 1.2 mL sterile water for injection for reconstitution.

Alemtuzumab Injection

Bill of Materials (Batch Size 1 L)					
Scale/3 mL		Item	Material	Qty	UOM
30.00	mg	1	Alemtuzumab	10.00	g
24.00	mg	2	Sodium chloride	8.00	g
3.50	mg	3	Sodium phosphate dibasic	1.167	g
0.60	mg	4	Potassium chloride	200.00	mg
0.60	mg	5	Potassium phosphate monobasic	200.00	mg
0.30	mg	6	Polysorbate 80	100.00	mg
0.056	mg	7	Disodium edetate	18.667	mg

Alpha-Tocopherol (Vitamin E) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Alpha-tocopherol (Vitamin E)[a]	200.00	g
20.00	mg	2	Benzyl alcohol	20.00	g
QS	mg	3	Sesame oil refined	QS to 1.00	L

[a] Vitamin E is a form of alpha-tocopherol ($C_{29}H_{50}O_2$). It includes the following: *d*- or *dl*-alpha-tocopherol ($C_{29}H_{50}O_2$); *d*- or *dl*-alpha-tocopheryl acetate ($C_{31}H_{52}O_3$); *d*- or *dl*-alpha-tocopheryl acid succinate ($C_{33}H_{54}O_5$). It contains 96% to 102% of $C_{29}H_{50}O_2$, $C_{31}H_{52}O_3$, or $C_{33}H_{54}O_5$.

Alprostadil for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.40	mg	1	Alprostadil	5.40	mg
172.00	mg	2	Lactose	172.00	g
47.00	mg	3	Sodium citrate	47.00	mg
8.40	mg	4	Benzyl alcohol	8.40	mg
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Extra quantity of item 1 to compensate for losses due to adsorption to vial and syringe. Lyophilized powder given is the concentration after reconstitution.

Alteplase Recombinant Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
58 MM	IU	1	Alteplase	100.00	g
3.50	g	2	L-Arginine	3.50	kg
1.00	g	3	Phosphoric acid	1.00	kg
11.00	mg	4	Polysorbate 80	11.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: The specific activity of alteplase is 580,000 IU/mg; 200-mg strength under vacuum.

Amikacin Sulfate Injection (50 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.70	mg	1	Sodium citrate	5.70	g
1.20	mg	2	Sodium metabisulfite	1.20	g
15.60	mg	3	Sulfuric acid for pH adjustment	15.60	g
50.00	mg	4	Amikacin, USP	50.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Nitrogen gas, NF	QS	cy

Amikacin Sulfate Injection (250 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
28.50	mg	1	Sodium citrate	28.50	g
6.00	mg	2	Sodium metabisulfite	6.00	g
73.60	mg	3	Sulfuric acid for pH adjustment	73.60	g
250.00	mg	4	Amikacin, USP	250.00	g
QS	L	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Nitrogen gas, NF	QS	cy

Manufacturing Directions

1. Prepare the solution in a glass-lined or 316 or higher temper-grade stainless steel tank. Protect solution with item 6 throughout the process.
2. Collect ca. 110% of the batch size of item 5 into the tank, heat it to not less than 70°C, then cool to 25°C (20–30°C) while sparging with filtered item 6. Bubble for not less than 30 minutes.
3. Transfer ca. 40% of item 5 from step 2 item into another tank for use in the QS step. Protect tank headspace with filtered item 6.
4. Continue sparging N_2 while adding and dissolving items 1 to 4 one at a time and slowly.
5. Check pH to 4.5 (4–5); adjust if necessary with item 4.
6. Make up volume with item 5 set aside in step 3.
7. Sample for testing.
8. Filter solution through a 0.45-mm or finer membrane into a glass-lined or 316 or higher temper-grade stainless steel tank. Protect solution with item 6.
9. Prior to filling, filter through a 0.22-mm or finer membrane filter.
10. Fill container, protect headspace with item 6, and sterilize using an approved cycle.

Amikacin Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Amikacin, use amikacin sulfate, 33% excess	333.75	g
6.60	mg	2	Sodium metabisulfite (sodium disulfite)	6.60	g
25.00	mg	3	Sodium citrate monohydrate	25.00	g
QS	mL	4	Water for injection	QS to 1.00	L
QS	ft^3	5	Nitrogen gas	QS	
QS	mL	6	Sulfuric acid as buffering agent	QS	
QS	mL	7	Sodium hydroxide, reagent-grade pellets for buffering	QS	

Note: Quantity of amikacin sulfate per liter = 333.75 ∞ 100/% assay (as is basis).

Manufacturing Directions

Important: For general requirements for tests, assays, and equipment, refer to USP.

1. Preparation of water. Check item 4 to be used for solution preparation and verify that it meets a conductivity limit of NMT 1.0 mS/cm and pH range of 5 to 7.
2. Preparation of solution.
   a. Put 700 mL of item 4 into the preparation vessel and bubble N_2 gas to expel dissolved oxygen gas. Monitor the O_2 sensor display (O_2% limit = NMT 1).
   b. Add and dissolve item 1 into the step 2a preparation vessel. Mix well by stirring to make clear solution.
   c. Add and dissolve items 2 and 3 into the solution of step 2b, mix well, and make clear solution.
   d. Check pH (4–5).
   e. Adjust pH by 2 N H_2SO_4/1 N NaOH solution (4–5).
   f. After adjustment of pH, make up volume to 1 L by item 4 and mix during bubbling item 5 until O_2% is less than 1.
   g. Check final pH (4.0–5.2).
3. Preparation of filtration assembly and machine parts for production. Clean and sterilize filtration assembly and machine parts using autoclave as per USP.
4. Prefiltration.
   a. Before starting the primary filtration, check the integrity of filter cartridge.
   b. Integrity test results of filter cartridge by the bubble point test:
      Before filtration bubble point mbar
      After filtration bubble point mbar
      Minimum acceptable bubble point mbar
   c. Transfer the solution from the preparation vessel to mobile vessel through filtration assembly, containing 0.2-mm filter cartridge.
   d. After filtration transfer mobile vessel to solution room.
5. Preparation of ampoules. Use type I 2-mL clear glass ampoules, USP.
   a. Wash the ampoules in the washing machine as per the following parameters and their limits:
      DI water pressure: 2 bar/min
      WFI pressure: 2 bar/min
      Compressed air pressure: 6 bar
      Compressed air pressure after regulator: 2 bar
      Machine speed: 100%
   b. Set the temperature to 330°C (as per latest validation studies).
   c. Sterilize the ampoules by dry heat.
6. Final filtration.
   a. Before starting the final filtration, check the integrity of filter cartridge.
   b. Integrity test results of filter cartridge by the bubble point test:
      Before filtration bubble point mbar
      After filtration bubble point mbar
      Minimum acceptable bubble point mbar
   c. Aseptically connect the N_2 line through sterile N_2 filter to the inlet of mobile vessel. Check the validity of N_2 filter.
   d. Aseptically connect one end of previously sterilized filtration assembly with 0.22-mm pore size filtration cartridge to the outlet of mobile vessel and other end to buffer holding tank on the ampoules filling machine parts.
   e. Filter the solution.
7. Aseptic filling.
   a. Operate previously sterilized ampoules filling machine as per following parameters:
      Adjust the volume to 2.15 mL; O_2 pressure: 4.0 bar; N_2 pressure: 0.4 bar; LPG pressure: 0.4 bar; machine speed (100% max).
   b. Fill 2.15 mL (range 2.1–2.2 mL) amikacin solution from the bulk into each sterile dry clean ampoule and seal it.
8. Terminal sterilization and leak test. Load the inverted ampoules inside the autoclave chamber, run the cycle as per the following parameters:
   Sterilization temperature: 121.1°C
   Exposure time: 20 minutes
9. Optical checking. Check the ampoules under the optical checking machine.

Packaging Material Specifications

Ampoule, 2 mL, flint glass type I.

Amino Acid Parenteral Nutrition Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.10	mg	1	Isoleucine, USP	5.61	g
6.60	mg	2	Leucine, USP	8.50	g
5.10	mg	3	Lysine, use lysine acetate, USP	12.59	g
2.80	mg	4	Methionine, USP	1.46	g
3.10	mg	5	Phenylalanine, USP	2.53	g
3.70	mg	6	Threonine, USP	3.40	g
1.20	mg	7	Tryptophan, USP	1.70	g
5.60	mg	8	Valine, USP	4.25	g
0.44	mg	9	*N*-Acetyl-L-tyrosine	2.30	g
9.00	mg	10	Alanine, USP	8.44	g
6.90	mg	11	Arginine, USP	8.65	g
9.00	mg	12	Glycine, USP	4.25	g
6.10	mg	13	Proline, USP	6.14	g
2.10	mg	14	Histidine base, USP	2.55	g
3.00	mg	15	Serine, USP	4.50	g
0.60	mg	16	Potassium metabisulfite	6.27	g
0.042	mg	17	Glacial acetic acid	5.95	g
QS	mL	18	Water for injection, USP	QS to 1.00	L
QS	mL	19	Nitrogen gas, NF	QS	mL

Manufacturing Directions

1. This solution must be prepared in a glass-lined or 316 or higher temper-grade stainless steel tank.
2. If using the volume method, add item 18 to ca. 85% of the final volume; if using weight method, add all the item 18 at the point of use.
3. Heat item 18 to not less than 70°C, bubble item 19 during the entire manufacturing process.
4. Stop steam supply and begin dissolving amino acids in the following order: arginine, leucine, isoleucine, phenylalanine, histidine, methionine, serine, threonine, valine, proline, lysine acetate, alanine, glycine, and *N*-acetyl-L-tyrosine.
5. Mix until all ingredients are dissolved and solution is uniform.
6. Sample for pH check and adjust to 5.8 (range 5.6–6.2) with item 17.
7. Add and dissolve potassium metabisulfite and tryptophan with mixing.
8. Cool to and maintain temperature of the solution in the mixing tank at 40°C (25–45°C) throughout the remaining process.
9. If using volume method, QS with item 18 to final volume; if using weight method, check final weight of product, add item 18 if necessary to bring specific weight. Mix until solution is uniform.
10. Check and record pH (range 5.6–6.2); again adjust with 20% solution of item 10 if necessary.
11. Prefilter solution through a prefilter unit prepared with approved filter—one prefiltration and one bulk tank microbial sample are taken at this stage for biological test. The size of sample should be large enough for statistical significance.
12. Prior to filling, filter solution through a 0.45-mm or finer membrane connected in a series to a prefilter. Check filtered solution for clarity. Protect product with filtered item 19 in the container headspace during the filling operation.
13. Fill into appropriate containers (250–1000 mL) and seal. During filling pull samples for volume check, develop a statistical sample plan to allow sampling throughout the batch.
14. Maintain N_2 headspace.
15. Autoclave at approved cycle.
16. Sample for final testing.

Amino Acid Parenteral Nutrition Solution (8.5%)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.61	mg	1	Isoleucine, USP	5.61	g
8.50	mg	2	Leucine, USP	8.50	g
8.93	mg	3	Lysine, use lysine acetate, USP	12.59	g
1.46	mg	4	Methionine, USP	1.46	g
2.53	mg	5	Phenylalanine, USP	2.53	g
3.40	mg	6	Threonine, USP	3.40	g
1.70	mg	7	Tryptophan, USP	1.70	g
4.25	mg	8	Valine, USP	4.25	g
2.30	mg	9	*N*-Acetyl-L-tyrosine	2.30	g
8.44	mg	10	Alanine, USP	8.44	g
8.65	mg	11	Arginine, USP	8.65	g
4.25	mg	12	Glycine, USP	4.25	g
6.14	mg	13	Proline, USP	6.14	g
2.55	mg	14	Histidine base, USP	2.55	g
4.50	mg	15	Serine, USP	4.50	g
6.27	mg	16	L-Glutamic acid	6.27	g
5.95	mg	17	L-Aspartic acid	5.95	g
0.20	mg	18	Sodium hydrosulfite, CP	0.20	g
QS		19	Sodium hydroxide pellets for pH adjustment	QS	
QS	mL	20	Water for injection, USP	QS to 1.00	L
QS		21	Nitrogen gas, NF	QS	

Amino Acid Parenteral Nutrition Solution: 10%

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
6.60	mg	1	Isoleucine, USP	6.60	g
10.00	mg	2	Leucine, USP	10.00	g
10.50	mg	3	Lysine, use lysine acetate, USP	14.80	g
1.72	mg	4	Methionine, USP	1.72	g
2.98	mg	5	Phenylalanine, USP	2.98	g
4.00	mg	6	Threonine, USP	4.00	g
2.00	mg	7	Tryptophan, USP	2.00	g
5.00	mg	8	Valine, USP	5.00	g
2.70	mg	9	*N*-Acetyl-L-tyrosine	2.70	g
9.93	mg	10	Alanine, USP	9.93	g
10.18	mg	11	Arginine, USP	10.18	g
5.00	mg	12	Glycine, USP	5.00	g
7.22	mg	13	Proline, USP	7.22	g
3.00	mg	14	Histidine base, USP	3.00	g
5.30	mg	15	Serine, USP	5.30	g
7.38	mg	16	L-Glutamic acid	7.38	g
7.00	mg	17	L-Aspartic acid	7.00	g
0.20	mg	18	Sodium hydrosulfite, CP	0.20	g
QS		19	Sodium hydroxide Pellets for pH adjustment	QS	
QS	mL	20	Water for injection, USP	QS to 1.00	L
QS		21	Nitrogen gas, NF		

Manufacturing Directions

1. Prepare this solution in a glass-lined or 316 or higher temper-grade stainless steel tank.
2. If using the volume method, add item 20 to ca. 85% of the final volume; if using weight method, add all the item 20 at the point of use.
3. Heat item 20 to not less than 70°C; bubble item 21 during the entire manufacturing process.
4. Add items 16 and 17 to the heated item 20 and mix.
5. Stop steam supply and begin dissolving amino acids in the following order: arginine, leucine, isoleucine, phenylalanine, histidine, methionine, serine, threonine, valine, proline, lysine acetate, alanine, glycine, and *N*-acetyl-L-tyrosine.
6. Mix until all ingredients are dissolved and solution is uniform.
7. Sample for pH check and adjust to 5.8 (range 5.6–6.2) with 20% solution of item 19.
8. Add and dissolve sodium hydrosulfite and tryptophan with mixing.
9. Cool to and maintain temperature of the solution in the mixing tank at 40°C (25–45°C) throughout the remaining process.
10. If using volume method, QS with item 20 to final volume; if using weight method, check final weight of product, add item 20 if necessary to bring specific weight. Mix until solution is uniform.
11. Check and record pH (range 5.6–6.2); again adjust with 20% solution of item 10 if necessary.
12. Prefilter solution through a prefilter unit prepared with approved filter—one prefiltration and one bulk tank microbial sample is taken at this stage for biological test. The size of sample should be large enough for statistical significance.
13. Prior to filling, filter solution through 0.45-μm or finer membrane connected in a series to a prefilter. Check filtered solution for clarity. Protect product with filtered item 21 in the container headspace during the filling operation.
14. Fill into appropriate containers (250–1000 mL) and seal. During filling pull samples for volume check, develop a statistical sample plan to allow sampling throughout the batch.
15. Maintain N_2 headspace.
16. Autoclave at approved cycle.
17. Sample for final testing.

Amino Acid Parenteral Injection

Bill of Materials	
Isoleucine	4.0–5.5 g/L
Leucine	8.0–10.0 g/L
Lysine	6.0–8.0 g/L
Methionine	4.0–6.0 g/L
Phenylalanine	4.0–6.0 g/L
Threonine	4.0–6.0 g/L
Tryptophan	1.0–2.0 g/L
Valine	6.0–8.0 g/L
Arginine	10.0–12.0 g/L
Histidine	1.5–3.5 g/L
Alanine	9.0–12.0 g/L
Aminoacetic Acid (Glycine)	11.0–16.0 g/L
Asparagine	0–1.0 g/L
Aspartic Acid	5.5–8.0 g/L
Acetylcysteine	0–2.5 g/L
Glutamic Acid	6.0–10.0 g/L
Ornithine	0–1.0 g/L
Proline	4.0–6.0 g/L
Serine	1.0–3.0 g/L
Tyrosine	0.1–0.5 g/L
(as Acetyltyrosine)	0–2.0 g/L
Taurine	0–4.0 g/L

Aminohippurate Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Aminohippurate sodium	200.00	g
QS	mL	2	Sodium hydroxide for pH adjustment		
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 6.7 to 7.6 with item 2.

Aminophylline Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Aminophylline, USP, anhydrous	25.00	g
QS		2	Ethylenediamine, USP, for pH adjustment[a]	QS	
QS		3	Nitrogen gas, NF	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

[a] For pH adjustment to a maximum of 0.5 mg/mL.

Manufacturing Directions

1. The product must be manufactured in a glass-lined or stainless steel 316 or higher temper-grade tank.
2. Add item 4 to ca. 110% of the final volume into the tank.
3. Bring to boiling and keep it boiling for 10 minutes as a minimum. Begin bubbling item 3 through the solution.
4. Transfer ca. 20% of the final volume of item 4 from step 2 into another glass-lined or stainless steel tank under item 3 protection and cool to 75°C to 85°C.
5. To 90% of the final volume of item 4 at 75°C to 85°C, add and dissolve item 1 with mixing. Avoid vortex formation; maintain item 3 cover throughout.
6. Check and record pH. Add item 2 to solution with mixing to adjust pH to 8.6 to 9.0. Record pH and amount of item 2 used.
7. Bring to volume with boiled N_2-protected item 4 and mix until ingredients are dissolved and solution is uniform.
8. Check and record pH again and again adjust pH with item 2 to 8.6 to 9.0. Record amount used.
9. Cool solution to 20°C to 30°C.
10. Filter solution using an approved 0.45-μm or finer membrane filter with a prefilter into a glass-lined or stainless steel holding tank flushed and under N_2 protection.
11. Sample for testing and adjust batch composition accordingly.
12. Preflush the ampoules with item 3 prior to filling.
13. Fill nominal volume into each ampoule and N_2 flush the headspace.
14. Terminal sterilization: F_0 equal to 8.0 for the coolest container and the hottest container to not exceed an F_0 of 18.0; temperature of the sterilizer chamber to be 115°C during the process dwell period; water spray cooling until 45°C or lower.
15. Sample and test for final specifications.

Amiodarone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.80	mg	1	Amiodarone	1.80	g
0.02	mL	2	Lactic acid[a], 20%	20.00	mL
45.46	mg	3	Dextrose anhydrous, USP	45.46	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] Prepared by heat treatment of a dilute 90% lactic acid concentrate to hydrolyze lactic acid dimer.

Manufacturing Directions

1. In a suitable size jacketed tank, add 0.4 L of item 5.
2. Add to this item 2.
3. Heat the mixture to 55°C.
4. Add item 1 to the above solution, mix, and dissolve.
5. Add another 0.4 L of item 5, mix, and allow to cool to 30°C.
6. Add item 3. Mix with agitation to dissolve.
7. Check and adjust pH with item 4 to 3.5 (3.4–3.6).
8. Make up the volume with item 5.

Amiodarone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Amiodarone hydrochloride	50.00	g
20.20	mg	2	Benzyl alcohol	20.20	g
100.00	mg	3	Polysorbate 80	100.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Fill 3 mL per ampoule.

Amoxicillin Lyophilisate for Injection (250 mg)

Formulation

Amoxicillin sodium, 6.25 g; Kollidon 12 PF [1], 7.50 g; water for injections, add 100.00 mL.

Manufacturing Directions

Dissolve the active ingredient in the well-stirred solution of Kollidon 12 PF and after freeze-drying, fill 500-mg portions of the dry lyophilizate into ampoules. Prior to administration, the dry content of an ampoule is mixed with 1.9 mL of water to give a clear injection solution.

Amoxicillin–Clavulanic Acid Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
1.00	g	1	Amoxicillin as sterile amoxicillin sodium[a]	1.225	kg
200.00	mg	2	Clavulanic acid as sterile potassium clavulanate[b]	269.00	g

[a] Quantity of sterile amoxicillin sodium is calculated on the basis of assay 85% of amoxicillin ($C_{16}H_{19}N_3O_5S$) on the anhydrous basis and 4.0% for water compensation.
[b] Quantity of sterile potassium clavulanate is calculated on the basis of assay 75.5% of clavulanic acid ($C_8H_9NO_5$) on the anhydrous basis and 1.5% for water compensation.

Manufacturing Directions

1. Clean the vials and rubber closure in automatic machine.
2. Clean the filling accessories related to filling machine.
3. Sterilize and depyrogenize the clean, empty vials using sterilizer.
4. Sterilize the stopper and filling equipment.
5. Mix aseptically amoxicillin sodium sterile powder and clavulanate potassium sterile powder in a suitable mixer.
6. Aseptically fill the mixed powder into the vials automatically with purging of N_2 gas, to get labeled amount of active ingredient per vial.
7. Close the vials and cap with flip-off cap.

Amoxicillin Powder for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Amoxicillin as sodium amoxicillin equivalent[a] (276.88 ∞ 4), 3% excess	1107.53	g

[a] For 500 mg, use 553.76 g; for 1000 mg, use 1107.53 g. Actual weight (adjusted according to potency) = weight above $\times$ 930/potency.

Manufacturing Directions

Caution: Amoxicillin sodium is sensitive to moisture. This powder is sterile and must be handled aseptically in a dry, dust-free atmosphere. RH NMT 25% at 27°C.

1. Preparation. Wipe outer surface of each bottle with 3A alcohol and deliver immediately to sterile area.
2. Preparation of vials.
   a. Wash and dry type I 20- or 10-mL (for 500 and 250 mg, respectively) glass vials and load in appropriate containers for sterilization.
   b. Sterilize by dry heat at 200°C (–0, +50°C) bottle temperature, for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of the cycle (or an equivalent heat input).
   c. Deliver to the sterile filling area.
3. Preparation of stoppers.
   a. Wash west compound 888 stoppers by using rubber cycle (slow tumbling) with Triton X-100 detergent.
   b. Dry in dryer at 55°C. Rack, inspect, and wrap the stoppers for autoclaving.
   c. Sterilize in an autoclave for 1 hour at 121°C and vacuum dry with heat for a minimum of 4 hours at a temperature not exceeding 90°C.
   d. Deliver to sterile area for filling.
4. Filling.
   a. Sterile-fill required gram of powder (see formula in table) equivalent to labeled amount of amoxicillin into each clean, dry sterile vial. Check fill weight of vials at ca. 5-minute intervals.
   b. Insert sterile stopper and apply sterile overcap.
   c. Remove from sterile area and pack into bulk containers and label each container with product lot number.
   d. Sample for testing.
5. Finishing. Sample for testing.

Amphotericin B Cholesteryl Sulfate Complex for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Amphotericin B	50.00	g
26.40	mg	2	Sodium cholesteryl sulfate	26.40	g
5.64	mg	3	Tromethamine	5.64	g
0.372	mg	4	Disodium edetate dihydrate	0.372	g
950.00	mg	5	Lactose monohydrate	950.00	g
QS	mL	6	Hydrochloric acid for pH adjustment	QS	

Note: This is a 1:1 molar ratio complex of amphotericin B and cholesteryl sulfate. For 100-mg dose, use 52.8 mg of cholesteryl sulfate, lyophilized powder.

Amphotericin B Injection

Bill of Materials (Batch Size 15 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Amphotericin B, USP	150.00	g
8.20	mg	2	Sodium desoxycholate	123.00	g
4.04	mg	3	Monobasic sodium phosphate, USP (anhydrous)	60.60	g
QS		4	Sodium hydroxide, NF, as 4% solution for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 15.00	L

Manufacturing Directions

Caution: Do not inhale amphotericin. Avoid skin contact. Adjust amount of amphotericin on assay and sodium desoxycholate and monobasic sodium phosphate on moisture level.

1. Prepare a 4% sodium hydroxide solution by dissolving 20 g of sodium hydroxide, NF, in enough water for injection to make 500 mL; cool to less than 20°C before using.
2. Prepare a 2% (w/v) monobasic sodium phosphate solution by dissolving weighed amount (as calculated) in enough water for injection, USP, to make 3030 mL.
3. In a suitable compounding tank, collect ca. 10 L of cold (lower than 20°C) water for injection.
4. Add the sodium desoxycholate and mix to dissolve.
5. Add 4% sodium hydroxide solution and mix to adjust pH between 12.5 and 12.6. Cool solution to less than 20°C and maintain it at this temperature.
6. Add amphotericin B, USP, and mix to form a clear amber solution. Cover tank while mixing.
7. Check and record pH. Immediately after all drug has dissolved, slowly add 2% sodium phosphate monobasic solution in 100-mL portions to adjust pH to 7.6 (range 7.5–7.7). *Note*: pH must not drop less than 7.2. Add 3030 mL of sodium phosphate monobasic solution; use 4% sodium hydroxide to further adjust pH.
8. QS to 15 L with cold (lower than 20°C) water for injection and mix thoroughly for at least 10 minutes. Keep tank covered. Sample and keep solution cool until QC approval.
9. Aseptically filter the solution through a 0.22-mm filter system into a suitable sterile receiving vessel.
10. Aseptically fill and lyophilize.
11. Load the filled vials into lyophilizer. Place thermocouples as per current SOPs; turn freezer on. When at least four thermocouples reach –30°C or less, hold for at least 30 minutes. Turn condenser on. After condenser temperature reaches –40°C or less, turn vacuum on.
12. When the vacuum reading is less than 250 mm, adjust the shelf temperature to 0°C and dry the product with full vacuum.
13. When at least four product thermocouples reach −8°C (±5°C), raise the shelf temperature to +3°C or higher to maintain the product temperature at 25°C (± 5°C) and dry with full vacuum when at least four product temperature probes reach 25°C (±5°C) for at least 2 more hours.
14. Break the vacuum by bleeding N_2 and check the moisture of three representative samples. Close chamber and pull vacuum.
15. If the moisture content of any of the three samples is more than 6%, pull vacuum and dry for at least two more hours. Withdraw three more samples and repeat.
16. If the moisture is satisfactory, bleed the chamber with sterile N_2, stopper the vials with the door closed, and terminate cycle.
17. Finish. Sample.

Amphotericin B Lipid Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Amphotericin B	5.00	g
3.40	mg	2	L-(alpha)-dimyristoylphosphatidylcholine (DMPC)	3.40	g
1.50	mg	3	L-(alpha)-dimyristoylphosphatidylglycerol (DMPG)	1.50	g
9.00	mg	4	Sodium chloride	9.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: pH 5.0 to 7.0; fill 10 or 20 mL.

Amphotericin B Liposome for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
50.00	mg	1	Amphotericin B	50.00	g
213.00	mg	2	Hydrogenated soy phosphatidylcholine	213.00	g
84.00	mg	3	Distearoylphosphatidylglycerol	84.00	g
0.64	mg	4	Alpha-tocopherol	0.64	g
52.00	mg	5	Cholesterol	52.00	g
900.00	mg	6	Sucrose	900.00	g
27.00	mg	7	Disodium succinate hexahydrate	27.00	g
QS	mL	8[a]	Water for injection, USP	QS	

[a] For reconstitution; pH after reconstitution 5.0 to 6.0.

Antazoline Sulfate and Xylometazoline Hydrochloride Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/5 mL		Item	Material	Qty	UOM
5.00	mg	1	Antazoline sulfate	5.00	g
0.50	mg	2	Xylometazoline hydrochloride, USP	0.50	g
1.50	mg	3	Hydroxypropyl methylcellulose 2910, USP, 4000 cps	1.50	g
0.10	mg	4	Benzalkonium chloride 0.1 g, use benzalkonium chloride solution, USP, 17%, 7% excess or benzalkonium chloride solution (50% w/v), BP, 7% excess	0.637 0.214	mL mL
1.00	mg	5	Disodium edetate, USP/BP	1.00	g
8.43	mg	6	Sodium chloride, USP/BP	8.43	g
QS	mL	7	Water purified, USP	QS to 1.00	L

Manufacturing Directions

Equipment

Thoroughly clean and rinse equipment used before proceeding. Use steam-jacketed, glass-lined, or stainless steel (No. 304 or better). The tank must be equipped with an agitator (preferably with speed control) and a cover to prevent at all times during the manufacturing process except when ingredients are being added or samples being taken.

Foaming

Benzalkonium chloride markedly lowers the surface tension. During severe agitation or turbulent flow, substantial foaming will occur. This condition often exists in the processing equipment and in the overflow system of vacuum filling machines. This item tends to concentrate in the foam. If the foam is not dissipated quickly, and if allowed to accumulate, a substantial excess of it may result near the surface of the liquid after the foam condenses. It is therefore advisable to design the processing and filling systems in such a way as to minimize foaming and ensure rapid dissipation of any unavoidable foaming.

1. Preparation of bulk solution.
   a. Charge mixing tank to 90% of final volume with item 7.

b. Heat water to 90°C and while agitating, add and dissolve item 3 by slowly sprinkling onto the surface of the water. It must be dispersed evenly over a period of time to ensure complete wetting and dispersion. Adjust agitation rate to avoid excessive foaming. Allow 15 minutes for hydration before cooling.
c. Discontinue heating and cool solution to ca. 40°C.
d. While agitating, add and dissolve items 1, 2, 4, 5, and 6.
e. Continue cooling to 25°C.
f. Turn off agitator and QS to final volume. Mix well. Sample.

2. Prefiltration. *Note*: Methylcellulose solutions filter slowly.
   a. Recirculate the solution through filter assembly until clear.
   b. Transfer clean solution into a holding or sterilization tank.
3. Sterilization and filling.
   a. Use only recommended filters for sterile filtration.
   b. Prepare and steam-sterilize the recommended filter unit.
   c. Aseptically fill sterile solution into sterilized container and apply sterile closure component and sample.

Antipyrine, Phenylephrine, and Pyrilamine Maleate Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
		1	Water purified (distilled), USP	40.00	L
12.000	mg	2	Boric acid, NF	540.00	g
4.600	mg	3	Sodium citrate dihydrate, USP	207.00	g
0.548	mg	4	Sodium metabisulfite, NF	24.65	g
1.000	mg	5	Antipyrine, USP	45.00	g
1.320	mg	6	Phenylephrine hydrochloride, USP (10% overage)	59.40	g
1.100	mg	7	Pyrilamine maleate, USP (10% overage)	49.50	g
0.127	mg	8	Disodium edetate, USP	5.70	g
0.040	mL	9	Benzalkonium chloride, NF (use 10% solution)	18.00[a]	mL
QS	mL	10	Water purified (distilled), USP	QS to 45.00	L

[a] The amount of benzalkonium chloride, 10% solution, to be added must be calculated on the basis of the assay of the raw material lot used as per the following formula: 18.0 mL × 10.0% = mL of benzalkonium chloride, 10% solution, required.

Manufacturing Directions

1. Measure 40 L of item 1 into a suitable plastic mixing tank. Add items 2 to 9, in order, allowing each to dissolve before adding the next.
2. QS to 45 L with item 10 and mix well for 15 minutes. Sterile filtration.
3. Sterilize for 1 hour (range 45–60 minutes) at 121°C (–0, +5°C) in autoclave at 15 psi, the Sartorius mini cartridge, filter, and a stainless steel pressure vessel.
4. Mix the product for at least 10 minutes before filtration. Before sterile filtration to the 100-L pressure vessel, perform the bubble point test at NLT 46 psi.
5. After completion of product filtration, flush the sterilizing filter with at least 20 L of water purified (distilled). Sample.
6. Aseptically fill sterile solution through sintered glass into sterilized containers. Perform the bubble point test on a 0.22-μm inline gas filter before and after filtration at 18 psi.

Antipyrine, Phenylephrine, and Sodium Thiosulfate Ophthalmic Solution

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Water purified (distilled), USP, ca.	10.00	L
14.00	mg	2	Polyvinyl alcohol, 20–90	630.00	g
Part II					
		3	Water purified (distilled), USP, ca.	30.00	L
6.70[a]	mg	4	Sodium phosphate dibasic heptahydrate, USP[a]	301.50	g
3.45	mg	5	Sodium phosphate monobasic, USP	155.25	g
0.0127	mg	6	Disodium edetate, USP	0.57	g
7.35[b]	mg	7	Sodium acetate trihydrate USP[b]	330.75	g
1.00	mg	8	Antipyrine, USP	45.00	g
0.04	mg	9	Benzalkonium chloride, NF (use 10% solution)[c]	18.00[c]	mL
		10	1 N hydrochloric acid, NF	QS	mL
		11	1 N sodium hydroxide, NF	QS	mL
1.57	mg	12	Sodium thiosulfate, pentahydrate, USP	70.65	g
1.32	mg	13	Phenylephrine hydrochloride, USP (10% overage)	59.40	g
QS	mL	14	Water purified (distilled), USP	QS to 45.00	L

[a] Equivalent to 3.55 mg/mL sodium phosphate dibasic anhydrous.
[b] Equivalent to 4.43 mg/mL sodium acetate anhydrous.
[c] The amount of benzalkonium chloride, 10% solution, to be added must be calculated on the basis of the assay value of the raw material lot(s) used.
Assay value: (mL)
Formula: 18.0 mL × 10.0% = mL of benzalkonium chloride, 10% solution, required.
Assay value (%)
Calculation: 18.0 mL × 10.0% = mL of benzalkonium chloride, 10% solution, ____ (%) required.

Manufacturing Directions

Part I

1. Measure out ca. 10 L of item 1 into a stainless steel-jacketed pressure vessel. Begin mixing with a suitable mixer. Heat to 85°C to 90°C.
2. When the temperature reaches 85°C to 90°C, turn off the heat source. Add item 2 slowly to the vortex. Mix for at least 90 minutes until dissolved. Cool to room temperature, with force cooling.

Part II

1. Measure out ca. 30 L of item 3 into a mixing tank suitably calibrated for a final QS of 45 L.
2. Add items 4 to 9, in order, allowing each to dissolve before adding the next.
3. Check pH (range 6.7–6.9). If necessary, adjust the pH to 6.7 to 6.9 with item 10 or 11.
4. After pH is within the specified range, add item 12. Mix until dissolved.
5. Add item 13. Mix until dissolved.
6. Add part I to part II, while mixing part II. Use 2 to 3 L of item 14 to rinse the part I container, pump, and hoses. Add the rinsings to the batch. Allow any foam to dissipate.
7. QS to 45 L with item 14 and mix thoroughly for at least 15 minutes.

Sterile Filtration

1. Sterilize for 1 hour (range 45–60 minutes) at 121°C (–0, +5°C) in autoclave at 15 psi, the Sartorius mini cartridge, filter, and 100-L stainless steel pressure vessel. Transfer to solution preparation area.
2. Attach the cartridge mini prefilter/final filter and hosing sterilization chart.
3. Mix the product for at least 10 minutes before filtration.
4. Connect the sterilized Sartorius mini cartridge filter and sterile filter with the aid of N_2 pressure (15–30 lb). Discard initial 10 L of filtrate, attach sterilized hose to sterilized filter holder, and connect to sterilized 100-L stainless steel pressure vessel, aseptically. *Note*: Before sterile filtration to the 100-L pressure vessel, perform the bubble point test at NLT 46 psi.
5. After completing product filtration, disconnect the Sartorius mini cartridge filter from the pressure vessel, flush the sterilizing filter with at least 20 L of water purified (distilled) for the bubble point test (after filtration).
6. After filtration, decontaminate the outer surface of bulk holding pressure vessel and then transfer to filling cubicle. Sample (ca. 60 mL) for bulk assay.

Sterilization

Sterilize at 121°C (–0°, +2°C) and 5-psi pressure for 1 hour the filling unit, 20-L surge bottle, or manifold of filling unit and uniforms.

Sterile Filling

1. Transfer the presterilized bottles, plugs, and caps to the filling cubicle after swabbing their outer polyethylene

packing with filtered methylated spirit and keep under the laminar flow hood.
2. Transfer the sterilized assembly line to filling room and surgical gloves and uniforms to change room sterile side. Aseptically connect the sterilized filling tubing and N_2 line from the 100-L pressure vessel to surge bottle.
3. Aseptically fill 15.40 mL of sterile solution into sterilized container by the automatic filling, plugging, and sealing machine and apply sterile closure components (plugs and caps). *Note*: Discard 50 to 100 bottles initially during volume adjustment. While filtering, do not exceed to N_2 pressure 5 to 10 lb.
4. Perform the bubble point test on a 0.22-μm inline gas filter before and after filtration at 18 psi.

Antithymocyte Globulin (Rabbit) for Injection

Bill of Materials (Batch Size 5 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Antithymocyte globulin (rabbit)	25.00	g
50.00	mg	2	Glycine	50.00	g
50.00	mg	3	Mannitol	50.00	g
10.00	mg	4	Sodium chloride diluent vial	10.00	g
5.00	mL	5	Water for injection, USP	QS to 5.00	L

Note: Viral inactivation step (pasteurization, i.e., heat treatment of active ingredient at 60°C/10 h) is performed for each lot. After reconstitution pH is 6.6 to 7.4.

Aprotinin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10,000	KIU[a]	1	Aprotinin	1.40	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] Kallikrein inhibitor units; adjust pH to 4.5 to 6.5 with item 3 or 4.

Argatroban (Thrombin Inhibitor) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Argatroban	100.00	g
100.00	mg	2	D-Sorbitol	100.00	g
100.00	mg	3	Dehydrated alcohol	100.00	g

Note: Fill 2.5 mL into each single-use vial.

Arsenic Trioxide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Arsenic trioxide	1.00	g
QS	mL	2	Hydrochloric acid for pH adjustment	QS	
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 7.0 to 9.0 with item 2 or 3. Fill 10 mL into glass ampoules.

Ascorbic Acid and B Complex Vitamins (Two Vials)

Bill of Materials Vial 1 (Batch Size 561 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Ascorbic acid, USP, 50% excess	16.83	kg
660	IU	2	Vitamin A, use retinol in polysorbate 80, 50% excess, labeled 555.39 million U, factored for potency (e.g., 1.5 million U/g)	—	—
40	IU	3	Vitamin D, 25% excess, labeled for 40 million U, factored for potency such as 28 million U/g	—	—
0.67	mg	4	Thiamine hydrochloride, USP, 25% excess	469.84	g
0.97	mg	5	Pyridoxine hydrochloride, USP, 25% excess	680.21	g
7.94	mg	6	Niacinamide, USP, 10% excess	4899.77	g
2.81	mg	7	Dexpanthenol[a]	1970.51	g
2.00	mg	8	DL-alpha tocopheryl acetate, NF, 25% excess	1402.50	g
48.00	mg	9	Polysorbate-20[b]	26.928	kg
20.00	mg	10	Gentisic acid ethanolamide	11.22	kg
0.30	mL	11	Propylene glycol	169.30	L
QS	mL	12	Sodium hydroxide, 10% solution, for pH adjustment	12807.63	g
QS	—	13	Carbon dioxide	QS	—
QS	mL	14	Water for injection, USP	QS to 561.00	L
0.984	mg	15	Riboflavin, 25% excess	690.03	g

[a] Includes 2% excess.
[b] Adjust for contribution from vitamins A and D.

Manufacturing Directions

1. Place 153.10 L of item 11 and 117.95 L of item 14 into appropriate vessels, bubble item 13 through the solution for 15 minutes, and then blanket with item 13.
2. Dissolve item 7 in 13.3 L of hot item 14 (50–60°C). Allow to cool. Add to the vessel above.
3. Add, with constant stirring, items 1, 4, 5, 6, 10, and 15. Allow each ingredient to dissolve before proceeding.
4. Place item 9 in a suitable container on a hot plate with stirrer and heat to 40°C to 50°C (do not exceed 60°C) and cover with a blanket of item 13. Do not pass gas through solution.
5. With constant stirring, add items 2, 3, and 8 to item 9 and allow for 5 to 6 minutes to mix. Carefully watch temperature—the solution should become crystal clear. Turn off the heat.
6. Using 10 mL at a time, add 15.2 L of item 11 to the polysorbate fat-soluble vitamin mixture. Allow the liquids to mix completely after dilution.
7. With constant stirring, pour the polysorbate mixture as a thin stream into the aqueous vitamins. Work slowly. Transfer final drops with a rubber policeman.
8. Dissolve item 12 in 145.81 L of item 14 and cool it to room temperature.
9. Add 10% item 12 to a pH of 4.9±0.1. Allow mixture to cool.
10. Add 10% item 12 to a final pH of 5.1 to 5.15.
11. QS to final volume with item 14. Cover with aluminum foil. Flush with item 13.
12. Sample after 3 days. After approval, fill by filtering through a 0.22-μm filter into a reservoir covered with CO_2 for filling; pre- and postflush vials (amber) with CO_2 during filling.

Ascorbic Acid and B Complex Vitamins

Bill of Materials Vial 2 (Batch Size 561 L)					
Scale/mL		Item	Material	Qty	UOM
80.00	mg	1	Folic acid, USP, 25% excess	56.10[a]	g
1.00	mg	2	Cyanocobalamin, USP, 25% excess	701.25[b]	mg
12.00	mg	3	Biotin FCC, 25% excess	8.42	g
30%	mL	4	Propylene glycol	168.30	L
QS	mL	5	0.2 M Citric acid for buffer	QS	mL
QS	mL	6	0.2 M Sodium citrate for buffer	QS	mL
QS	mL	7	0.2 M Sodium hydroxide	QS	mL
QS	mL	8	Water for injection, USP	QS to 561.00	L

[a] Calculate on anhydrous basis.
[b] Calculate the raw material on the assay value.

Manufacturing Directions

1. Prepare a solution of item 6 by dissolving 20.58 kg in 350 L of item 8.
2. Weigh 5 times the amount of item 2 required for the batch and dissolve in 1 L of item 8.
3. Weigh item 1 and completely dissolve in approximately 280.50 L of item 6 solution prepared in step 1.
4. Add item 3 and dissolve completely.
5. Take 200 mL of item 2 solution prepared in step 2 and add to the compounding tank. Mix thoroughly. *Note*: Item 2 is hygroscopic and weighing small amounts may result in excessive variation. This step precludes this variation.
6. Add item 4 and mix until dissolved.
7. Adjust volume to ca. 540 L with item 8.
8. Check pH and adjust to 7.9 to 8.0, if necessary, with item 5 solution.
9. Check pH check and filter through a 0.22-μm filter and fill under N_2 in amber vials.

Stopper Sterilization

Dissolve 6.375 kg of disodium edetate in 255 kg of purified water. Rinse stoppers with water that has undergone reverse osmosis (RO). Cover the stoppers with disodium edetate solution and autoclave at 121°C for 1 hour. Rinse stoppers at least 3 times with RO water.

Ascorbic Acid and B Complex Vitamins Lyophilized in Covial

Bill of Materials Lower Chamber (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	μg	1	Folic acid, 25% excess	250.00	mg
2.50	μg	2	Cyanocobalamin, 25% excess	3.125	mg
30.00	μg	3	Biotin, 25% excess	37.50	mg
7.02	mg	4	Dexpanthenol, 20% excess	8.43	g
19.84	mg	5	Niacinamide, 20% excess	23.81	g
5.00	mg	6	Mannitol	5.00	g
2.43	mg	7	Pyridoxine hydrochloride, 20% excess	2.92	g
QS	mL	8	0.2 M Sodium hydroxide to buffer	QS	mL
QS	mL	9	0.2 M Potassium phosphate monobasic to buffer	QS	mL
QS	mL	10	Water for injection	QS to 1.00	L
QS	–	11	Nitrogen gas	QS	–

Note: The lower chamber is lyophilized and filled first, followed by the upper chamber (see manufacturing directions).

Manufacturing Directions

1. Heat 50 mL of item 10 to 60°C and completely dissolve item 4. Keep aside.
2. Prepare a 0.2 M item 8 solution by dissolving 4 g of item 8 in 500 mL of item 10.
3. Prepare a 0.2 M item 9 solution by dissolving 13.61 g of item 9 in 500 mL of item 10.
4. Weigh accurately 312.5 mg of item 2 and dissolve in 1 L of item 10. Keep aside.
5. Weight item 1 and dissolve in 234 mL of item 8 solution prepared in step 2. Check pH.
6. Immediately add 246 mL of item 9 solution prepared in step 3.
7. Mix and note pH.
8. Add item 3 and dissolve completely.
9. Add 10 mL of item 2 solution prepared in step 4.
10. Add all other ingredients one by one (including item 4 solution prepared in step 1) with the exception of item 7. Check pH.
11. Add item 7 to solution, stir to dissolve, and check pH again.
12. Adjust the pH between 8.0 and 10.0 with item 8 or 9 solution. QS to volume with item 10.
13. Flush item 11 for 10 minutes.
14. Filter through a sterile 0.22-μm filter into the sterile area and fill the vials.
15. Lyophilize as follows:
    a. Prepare shelves to –40°C or less.
    b. Transfer the filled vials in covered trays onto the shelves of the lyophilizer (or if the system is autoloading, following directions accordingly).
    c. Place thermocouples in appropriate vials.
    d. The product thermocouples should register –35°C for at least 3 hours.
    e. Start condenser. Let the condenser cool to –55°C or less.
    f. Start vacuum and let the chamber achieve a level of 100 μm or less.
    g. Set the temperature controller at –30°C and let the lyophilizer run for 24 hours.
    h. Raise the shelf temperature to 0°C and let run for additional 6 hours.
    i. Raise the shelf temperature to +20°C and run for additional 12 hours.
    j. Raise shelf temperature to +35°C and run additional 6 hours.
    k. Bleed chamber to atmospheric pressure with item 11.
    l. Open the lyophilizer chamber door, withdraw nine sample vials (three from each of the top, middle, and lower shelves representing the left, center, and right positions, respectively) for determination of moisture.
    m. Submit samples to QC for moisture test while keeping the chamber door shut and vacuum pulled.
    n. If samples pass the test, remove them. If the samples fail the test, prolong lyophilization cycle.
    o. For finished samples, place center seal, fill the upper chamber, and seal with top seal.
    p. Place aluminum ferrule around the top seal.
    q. Deice and clean lyophilizer.

Ascorbic Acid and B Complex Vitamins

Bill of Materials Upper Chamber (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Ascorbic acid, USP, 50% excess	75.00	g
2.46	mg	2	Riboflavin-5′-phosphate USP, 20% excess	2.95	g
1.68	mg	3	Thiamine hydrochloride, USP, 50% excess	2.52	g
0.20	mg	4	Gentisic acid ethanolamide	200.00	mg
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	10% Sodium hydroxide (w/v) for pH adjustment	QS	mL
QS	–	7	Carbon dioxide	QS	–

Manufacturing Directions

1. Prepare 150 mL of 10% item 6 solution in item 5 and let it cool to room temperature.
2. Place approximately 500 mL of item 5 into a clean compounding tank and bubble item 7 for 10 minutes. Keep a CO_2 blanket over the solution during the remainder of the compounding steps.
3. Add items 2, 1, 3, and 4, in order, to the tank and stir to a complete solution.
4. Bring to approximately 800 mL with item 5 and check pH.
5. Adjust the pH between 4.0 and 4.5 with 10% item 6 solution prepared in step 1.
6. QS to final volume with water for injection.
7. Filter through a sterile 0.22-μm filter into the sterile room. Keep the receiving jug under CO_2 blanket and protected from light.
8. Fill the upper chamber.

Ascorbic Acid and B Complex Vitamins Lyophilized with Diluent

Bill of Materials B-Complex Lyophilized (Batch Size 3.9 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Thiamine hydrochloride, USP, ampoule grade, 10% excess	195.00	g
5.00	mg	2	Riboflavin, USP, 14% excess	14.40	g
	–	3	Riboflavin-5′-phosphate (combined with above for scale)	8.00	g
10.00	mg	4	Pyridoxine HCl, USP, 10% excess	39.00	g
100.00	mg	5	Niacinamide, USP, 10% excess	390.00	g
0.22	mg	6	Propyl paraben USP	0.78	g
0.89	mg	7	Methyl paraben, USP	3.16	g
QS	mL	8	Water for injection,	QS to 3.90	L
QS	mL	9	Sodium bicarbonate, USP, for pH adjustment (4.3–4.5)	QS	mL

Note: All ingredient quantities are based on 100% assay amounts; adjust accordingly; entire preparation protection under N_2 and light.

Manufacturing Directions

1. Measure 3 L of item 8 into a 4-L beaker, heat to 95°C, and hold it at that temperature and agitate vigorously.
2. Add items 6 and 7. Then add item 5.
3. Add item 2. Once the ingredients are in solution, cool the solution to 50°C with agitation in a water bath; let it stand to room temperature.
4. Add items 4, 1, and 3, in order. Measure pH and adjust with item 9 to 4.3 to 4.5.
5. QS to 3.9 L with item 8.
6. Filter aseptically into a previously sterilized vessel by passing through filter.
7. Aseptically fill into 10-mL vials. Place stoppers.
8. Lyophilize as follows:
   a. Freeze to -40°C for not less than 3 hours.
   b. Turn vacuum on to less than 300 μm for a 20-hour cycle time.
   c. Raise the temperature to +15°C for at least 8 hours. Break vacuum with N_2 and open under aseptic conditions.
   d. Stopper and seal with aluminum three-piece caps.

Ascorbic Acid and B Complex Vitamins

Bill of Materials (Batch Size 45 L)					
Scale/10 mL		Item	Material	Qty	UOM
2000.00	mg	1	Ascorbic acid, USP, ampoule grade, 10% excess	9.90	kg
1.00	mg	2	Sequestrene disodium purified	4.50	g
QS	mL	3	Sodium bicarbonate, USP, for pH adjustment (5.8–6.0)	4.695 (ca.)	kg
10.00	mg	4	Sodium bisulfite, USP	45.00	g
QS	mL	5	Water for injection	QS to 45.00	L

Manufacturing Directions

1. Add 20 L item 5 to a glass-lined steam jacketed kettle and heat to 95°C with stirring.
2. Add item 2, begin continuous N_2 gas flush, and cool to 50°C with cold water in jacket.
3. Add items 1 and 3 slowly to avoid foaming and agitate well until pH is between 5.8 and 6.0. Fumes of CO_2 need to be vented out.
4. Add item 4. Filter aseptically into a previously sterilized bottle.
5. Store in cold room until filling. Fill aseptically into 10-mL vials with N_2 flush.
6. Autoclave sealed vials at 105°C and 5 psi for 10 minutes.
7. Remove from autoclave and cool rapidly by squelching into 21°C water.

Ascorbic Acid, B Complex Vitamin, with Beta-Carotene Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Beta-carotene	5.00	g
5.00	mg	2	Tocopherol acetate	5.00	g
10.00	mg	3	Sodium ascorbate	10.00	g
3.50	mg	4	Ascorbyl palmitate	3.50	g
1.00	mg	5	Riboflavin-5′-phosphate sodium	1.00	g
1.00	mg	6	Thiamine hydrochloride	1.00	g
3.00	mg	7	Nicotinamide	3.00	g
1.00	mg	8	Pyridoxine hydrochloride	1.00	g
14.00	mg	9	Glycerol	14.00	g
35.00	mg	10	Lutrol F-68®	35.00	g
QS	mL	11	Sodium hydroxide for pH adjustment	QS	
QS	mL	12	Water for injection, USP	QS to 1.00	L
66.50	mg	13	Coconut oil fractionated (Miglyol 812)	66.50	g

Manufacturing Directions

1. To item 9, add item 10 and items 4 to 8.
2. Add 0.6 L of item 12, mix, and heat to 60°C; mix again.
3. Adjust pH to 7.4 with 1 M item 11.
4. Heat the mixture of items 13 and 3 to 180°C.
5. Add item 1 to step 4 with N_2 protection.
6. Emulsify the oily solution into the aqueous solution of the vitamins by using an Ultra-Tur-rax® at 3000 rpm. Further emulsification to a fine-particle emulsion takes place by two passages through a homogenizer under 1000 bars.
7. Subsequently, cool the emulsion to room temperature and dispense into vials. The particle size is 200 nm. The beta-carotene concentration is 5% of the weight of the oil phase.

Ascorbic Acid Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Ascorbic acid, USP, 20% excess	3000.00	g
1.00	mg	2	Parachlorometa cresol	1.00	g
145.80	mg	3	Sodium bicarbonate, NF	145.80	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS		7	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Boil approximately 110% of item 4 in a separate vessel and allow to cool to room temperature.
2. In another vessel, take approximately 0.60 L of item 4 and dissolve in it item 1 slowly with continuous mixing in an open vessel. Item 1 will not completely dissolve at this stage.
3. Provide continuous mixing of item 7 throughout manufacturing.
4. Add item 3 with vigorous mixing gradually and allowing effervescence to subside as more item 3 is added. Keep mixing until both items 1 and 3 are completely dissolved.
5. Add item 2 and dissolve completely.
6. Make up the volume with item 4.
7. Sample. Take pH (5.5, range 5.5–6.4). Adjust pH with item 5 or 6.
8. Filter through a presterilized filtration assembly using a 0.22-μm filter and a 0.45-μm prefilter.
9. Fill ca. 2.15 mL into amber type I glass ampoules.
10. Autoclave at 121°C for 30 minutes.
11. Sample for clarity and final check.

Ascorbic Acid, USP, Injection With Disodium Edetate

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Ascorbic acid as sodium ascorbate 300 mg	250.00	g
0.025	%	2	Disodium edetate	0.025	%
QS	mL	3	Water for injection	QS to 1.00	L
QS	mL	4	Hydrochloric acid for pH adjustment	QS	mL
QS	mL	5	Sodium hydroxide for pH adjustment	QS	mL

Ascorbic Acid, USP (250 mg/mL Injection)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Ascorbic acid as sodium ascorbate	300.00	g
1.00	mg	2	Sodium bisulfite, USP	1.00	g
1.50	%	3	Benzyl alcohol, NF	1.50	%
QS	mL	4	Water for injection, USP	QS to 1.00	L

Asparaginase for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
10,000	IU	1	Asparaginase	10MM	IU
80.00	mg	2	Mannitol	80.00	g
QS		3	Water for injection	1.00	L

Note: Lyophilized powder.

Manufacturing Directions

Dissolve items 1 and 2 in item 3 and lyophilize.

Atropine, Chlorpheniramine Maleate, and Phenylpropanolamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.20	mg	1	Atropine sulfate, USP	0.20	g
12.50	mg	2	Phenylpropanolamine HCl, NF	12.50	g
5.00	mg	3	Chlorpheniramine maleate, USP	5.00	g
5.00	mg	4	Chlorobutanol anhydrous, USP	5.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Atropine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	mg	1	Atropine sulfate, USP, 5% excess	0.525	g
0.0003	mL	2	Acetic acid	0.30	mL
1.20	mg	3	Sodium acetate	1.20	g
6.50	mg	4	Sodium chloride, NF	6.50	g
1.00	mg	5	Sodium metabisulfite, NF	1.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	Cy	7	Nitrogen gas, NF	QS	cy

Manufacturing Directions

Note: This solution must be prepared in a clean Pyrex bottle. This product needs N_2 protection during all steps of production. Avoid contact; wear gloves, glasses, and mask. Definitely avoid eye and skin contact; if exposed wash promptly with water.

1. Bring to boil item 6 in a suitable vessel; allow to cool to room temperature.
2. Add items 1 through 5, one by one, and by applying vigorous mixing.
3. Measure pH 4.0 to 6.0; do not adjust pH.
4. Filter solution through a 0.22-μm filter assembly.
5. Fill 1.1 mL into a flint type I glass ampoule.
6. Terminally sterilize at 116°C for 30 minutes.
7. Sample for final testing, clarity, and sterility.

Atropine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Atropine sulfate, USP	1.00	g
8.50	mg	2	Sodium chloride, USP	8.50	g
QS	mL	3	Sulfuric acid, reagent grade	QS	mL
QS	cy	4	Nitrogen gas, NF	QS	cy
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

See precautions above.

1. Collect ca. 0.9 L of item 5 in a suitable Pyrex bottle and 0.1 L of item 5 in another bottle.
2. Check pH range 5.5 to 6.5.
3. Bubble N_2 through step 1 preparation and continue bubbling throughout.
4. While bubbling N_2 gas, add and dissolve items 1 and 2. Mix well.
5. Check and record pH; adjust downward to 5.0 (range 4.8–5.2) by 0.1 N sulfuric acid. (Prepare a fresh solution by taking 0.3 mL of concentrated sulfuric acid and adding to it 99.7 mL freshly distilled water.)
6. QS to 1 L by item 5 previously saturated with N_2 gas.
7. Prepare a 0.2-μm filter and sterilize in autoclave at 121°C for 30 to 35 minutes.
8. Sterilize all Pyrex bottle fittings and filling parts in autoclave at 121°C for 30 to 35 minutes.
9. Sterilize sufficient number of Pyrex bottles with dry heat (270–280°C) for 2 hours and 50 minutes (range 2 hours and 45 minutes to 3 hours). Use bottles within 72 hours.
10. Perform the pressure test on the filter unit.
11. Filter the solution through the sterile filter unit into sterile Pyrex bottles. The process should not go beyond 24 hours.
12. Perform the bubble point test at the end of filtration.
13. Wash 1-mL ampoules and sterilize at 270°C to 280°C for 2 hours and 50 minutes to 3 hours. Use them within 24 hours.
14. Aseptically fill 1.15 mL (1.10–1.18 mL). Flush each ampoule with sterile-filtered N_2 gas. Seal.
15. Autoclave at 122°C (121–124°C) for 12 minutes (10–14 minutes).
16. Sample for complete testing.

Aztreonam for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
1.00	g	1	Aztreonam	1.00	kg
0.78	g	2	Arginine	0.78	kg

Note: After reconstitution, pH is 4.5 to 7.5.

Basiliximab for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
20.00	mg	1	Basiliximab	20.00	g
7.21	mg	2	Potassium phosphate monobasic	7.21	g
0.99	mg	3	Disodium hydrogen phosphate anhydrous	0.99	g
1.61	mg	4	Sodium chloride	1.61	g
20.00	mg	5	Sucrose	20.00	g
80.00	mg	6	Mannitol	80.00	g
40.00	mg	7	Glycine	40.00	g
5.00	mL	8	Water for injection for reconstitution		

Benzylpenicillin + Dihydrostreptomycin Injectable Suspension (200,000 U + 200 mg/mL)

Formulation

I. Procaine benzylpenicillin, 20.0 g; dihydrostreptomycin sulfate, 20.0 g.

II. Kollidon 12 PF [1], 0.5 g; carboxymethyl cellulose sodium, 0.5 g; sodium citrate, 0.6 g; paraben, QS; water for injectables, add 100 mL.

Manufacturing Directions

Prepare solution II, add the components I to the well-stirred solution II, and pass through a colloid mill.

B Complex Injection: Niacinamide, Pyridoxine, Riboflavin, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Thiamine hydrochloride, 25% excess	12.50	g
0.50	mg	2	Riboflavin, use sodium phosphate, 12.5% excess	0.80	g
1.00	mg	3	Pyridoxine, use HCl, 15% excess	1.20	g
20.00	mg	4	Niacinamide, 12.5% excess	22.50	g
0.50	%	5	Liquefied phenol, NF	5.00	mL
0.012	mL	6	Benzyl alcohol, NF	12.00	mL
1.00	mg	7	Disodium edetate, NF	1.00	g
1.00	mg	8	Thiourea	1.00	g
0.02	mL	9	Polysorbate 80 (Tween)	20.00	mL
0.10	mL	10	Propylene glycol	100.00	mL
QS	mL	11	Sodium hydroxide for pH adjustment	QS	
QS	mL	12	Hydrochloric acid for pH adjustment	QS	
QS	mL	13	Water for injection, USP	QS to 1.00	L
QS		14	Nitrogen gas, NF	QS	
0.0175	mL	15	Concentrated hydrochloric acid (10%)	17.50	mL

Manufacturing Directions

1. Use freshly distilled item 13; autoclave at 121°C for 30 minutes, cooled and bubbled with item 14 for 20 minutes.
2. Dissolve items 4 and 2 in sufficient item 13 in a suitable container.
3. Dissolve items 1, 3, and 7.
4. Add item 15 to step 3 and then one by one add items 10, 6, and 5. Mix well.
5. Add item 9 slowly with vigorous mixing.
6. Check pH to 3.8 to 4.2 and adjust with items 11 or 12, as necessary.
7. Let the solution age in a covered vessel flushed with item 14 for 7 days.
8. Filter through a presterilized assembly using a 0.45-μm prefilter and a 0.22-μm membrane filter into a sterilized staging vessel.
9. Fill aseptically into type I 10-mL amber vials (sterilized at 200°C for 4 hours) and using butyl coated with Teflon® rubber stoppers sterilized at 115°C for 30 minutes after washing. Provide pre- and postflush with item 14.
10. Sample for complete testing.

B Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine hydrochloride, 10% excess	110.00	g
2.00	mg	2	Riboflavin-5′-phosphate, 10% excess	2.20	g
2.00	mg	3	Pyridoxine hydrochloride, 10% excess	2.20	g
100.00	mg	4	Niacinamide, 10% excess	110.00	g
20.00	mg	5	Benzyl alcohol	20.00	g
QS	mL	6	0.1 N sodium hydroxide for pH adjustment	QS	
QS	mL	7	3 N hydrochloric acid for pH adjustment	QS	
QS	mL	8	Water for injection	QS to 1.00	L

Manufacturing Directions

1. Measure ca. 0.5 L of water for injection in appropriate clean vessel. Heat to between 50°C and 60°C. Cool to room temperature.
2. Add thiamine, riboflavin, pyridoxine, niacinamide, and benzyl alcohol with constant stirring.
3. Bring to final volume of 30 L with water for injection. Check pH and adjust to between 4.5 and 7.0 if necessary.
4. Sample for pH.
5. Filter through a sterile 0.45- and 0.22-μm membrane filter. Check for integrity.
6. Autoclave vials at 121°C for 20 minutes.
7. Sample for assay, sterility, pyrogen/LAL, and stability.

B Complex Injection: Niacinamide, Pantothenate, Pyridoxine, Riboflavin, Thiamine Injection

This product is made up of two solutions prepared separately and mixed at the time of administration.

Solution 1

Bill of Materials for Solution 1 (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
160.00	mg	1	Thiamine hydrochloride, USP, 5% excess	168.00	g
8.00	mg	2	Pyridoxine hydrochloride, USP, 0.5% excess	8.04	g
0.90	%	3	Benzyl alcohol, NF (0.9%)	9.075	g
0.38	mg	4	Sodium formaldehyde sulfoxylate	379.82	g
QS	—	5	Carbon dioxide gas, technical	QS	—
QS	mL	6	Water for injection, USP	QS to 1.00	L

Solution 2

Bill of Materials for Solution 2 (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Niacinamide, USP, powder 3% excess	206.00	mg
0.10	mg	2	Sodium sulfide (nonahydrate) crystals[a]	103.00	mg
1.00	%	3	Charcoal activated, USP[b]	2.06	mg
5.30	mg	4	Riboflavin, use riboflavin-5′-phosphate sodium, USP[c]	7.26	g
0.90	%	5	Benzyl alcohol, NF (0.9%)	9.00	g
13.25	mg	6	Sodium pantothenate dextro, 10% excess	14.57	g
QS	—	7	Carbon dioxide gas, technical	QS	—
QS	mL	8	Acid hydrochloric, reagent-grade bottles[d]	QS	mL
QS	mL	9	Water for injection, USP	QS to 1.00	L

Note: The 3% excess of niacinamide is allowed for possible loss in charcoal-sodium sulfide treatment.
[a] Sodium sulfide calculated at 0.05% w/w niacinamide.
[b] Charcoal activated is calculated at 1% w/w niacinamide.
[c] Riboflavin-5′-phosphate sodium is calculated at 73% of riboflavin.
[d] Used for pH adjustment only.

Manufacturing Directions

Note: Protect solution from light and oxidation. Use CO_2 gas at all times to protect solution. Sodium formaldehyde sulfoxylate precipitates out metallic impurities and also acts as an antioxidant. Use glass equipment wherever possible. Avoid inhaling hydrogen sulfide fumes given off during the sodium sulfate purification treatment of niacinamide.

Solution 1

1. Preparation.
   a. Dissolve items 1, 2, and 3 in 370 mL of item 6. Saturate with CO_2 gas.
   b. Dissolve item 4 in 14 mL of item 6 and add to the solution in step 1a.
   c. Age for 2 days under CO_2 protection.
   d. QS with item 6 to 1 L and age another 2 days under CO_2 gas protection.
   e. Check pH (range 2.5–3.5). Sample.
   f. Transfer solution to a portable glass-lined tank for filling. Seal tank under CO_2 gas protection.
   g. Prepare for sterilization a 0.22-μm membrane and approved prefilter.
2. Preparation of containers. Wash, dry, stack, and then sterilize ampoules in an electric oven for 2 hours at 200°C. Deliver to sterile filling area.
3. Filtration. *Precaution*: Sterile solution; handle aseptically. Protect from light and oxidation.
   a. Protect surge bottle headspace with sterile CO_2 gas.
   b. Connect tank, the sterile filtration setup, which has been previously prepared, and a sterile surge bottle with aseptic technique.
   c. Apply 5 to 10 lb (do not use more than 10-lb pressure) of CO_2 pressure to the tank and filter enough solution to half-fill surge bottle. Use aseptic technique.
   d. Transfer filter delivery tube to filling siphon in an empty, sterile surge bottle. Siphon should be attached to filling machine.
   e. Filter enough solution to fill surge bottle and start filling.
   f. Sterile-fill the appropriate amount of solution into each clean, dry sterile container. Displace remaining air with sterile-filtered CO_2 gas and seal the ampoules. Sample.

Solution 2

1. Preparation.
   a. Boil 550 mL of item 9 and dissolve items 1, 2, and 3.
   b. Filter solution through a carbon precoated filter by using approved pads and papers. Recirculate until solution is clear.
   c. Reheat solution from step 1b to 75°C to 85°C, then add and dissolve item 4. When solution is complete, cool to 25°C under CO_2 protection.
   d. Add and dissolve items 5 and 6. Circulate solution through bottom tank valve to ensure complete solution.
   e. QS with item 9 to 1 L. Keep solution protected with CO_2 gas.
   f. Check pH. Adjust to 5.6 to 5.9 with concentrated hydrochloric acid. Sample.
   g. Transfer solution to a portable glass-lined tank for filling. Seal tank under CO_2 gas protection.
   h. Prepare for sterilization a 0.22-μm membrane and approved prefilter.
   i. Sterilize ampoules in an electric oven for 2 hours at 200°C.
   j. Transfer filter delivery tube to filling siphon in an empty, sterile surge bottle. Siphon should be attached to filling machine.
   k. Filter enough solution to fill surge bottle and start filling. Adjust flow through the filter to equal that of filling so that there is no surge on the filter.
   l. Sterile-fill the appropriate amount of solution into each clean, dry sterile container. Displace remaining air with sterile-filtered CO_2 gas and seal the ampoules. Sample.

B Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Thiamine hydrochloride, 50% excess	15.00	g
2.00	mg	2	Riboflavin, use sodium phosphate, 20% excess	3.30	g
2.00	mg	3	Pyridoxine, use HCl, 20% excess	2.40	g
100.00	mg	4	Niacinamide, injectable grade, 15% excess	115.00	g
0.50	%	5	Liquefied phenol, NF	5.00	mL
0.012	mL	6	Benzyl alcohol, NF	12.00	mL
1.00	mg	7	Disodium edetate, NF	1.00	g
1.00	mg	8	Thiourea	1.00	g
0.020	mL	9	Polysorbate 80 (Tween)	20.00	mL
0.10	mL	10	Propylene glycol	100.00	mL
QS	mL	11	Sodium hydroxide for pH adjustment	QS	
QS	mL	12	Hydrochloric acid for pH adjustment	QS	
QS	mL	13	Water for injection, USP	QS to 1.00	L
QS		14	Nitrogen gas, NF	QS	
0.0175	mL	15	Concentrated hydrochloric acid (10%)	17.50	mL
5.00	mg	16	D-Panthenol, 20% excess	6.00	g

Manufacturing Directions

1. Use freshly distilled item 13. Autoclave at 121°C for 30 minutes, cooled and bubbled with item 14 for 20 minutes.
2. Dissolve items 4 and 2 in sufficient item 13 in a suitable container.
3. Dissolve items 1, 3, and 7.
4. Add item 16 to solution in step 3 and dissolve.
5. Add item 15 to solution in step 3 and then one by one add items 10, 6, and 5. Mix well.
6. Add item 9 slowly with vigorous mixing.
7. Check pH to 3.8 to 4.2 and adjust using items 11 or 12, as necessary.
8. Let the solution age in a covered vessel flushed with item 14 for 7 days.
9. Filter through a presterilized assembly using a 0.45-μm prefilter and a 0.22-μm membrane filter into a sterilized staging vessel.
10. Fill aseptically into 10-mL amber type I vials (sterilized at 200°C for 4 hours) and using butyl coated with Teflon or latex rubber stoppers sterilized at 115°C for 30 minutes after washing. Provide pre- and postflush with item 14.
11. Sample for complete testing.

B Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Thiamine hydrochloride, 50% excess	15.00	g
3.00	mg	2	Riboflavin-5′-phosphate, 20% excess	3.30	g
5.00	mg	3	Pyridoxine, use HCl, 20% excess	2.40	g
60.00	mg	4	Niacinamide, injectable grade, 15% excess	115.00	g
0.50	%	5	Chlorbutol	5.00	mL
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Hydrochloric acid for pH adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L
QS		9	Nitrogen gas, NF	QS	
5.00	mg	10	D-Panthenol, 20% excess	6.00	g

Manufacturing Directions

1. Use freshly distilled item 8. Autoclave at 121°C for 30 minutes, cooled and bubbled with item 14 for 20 minutes.
2. Dissolve items 2 and 4 in 0.4 L of item 8 in a suitable container.
3. Dissolve items 1 and 3 in 0.4 L of item 8 in another vessel.
4. Dissolve item 10 in 0.15 L of item 8 and add this solution to step 3.
5. Add this solution to the solution in step 2.
6. Make up volume with item 8 and add item 5. Stir to dissolve completely.
7. Check and adjust pH with item 6 or 7 to 5.0 to 5.5 (do not adjust if within this range).
8. Keep the preparation at 10°C for 7 days and then at room temperature for another 7 days.
9. Filter through a presterilized assembly using a 0.45-μm prefilter and a 0.22-μm membrane filter into a sterilized staging vessel.
10. Fill aseptically into 10-mL amber type I vials (sterilized at 200°C for 4 h) and using butyl coated with Teflon or latex rubber stoppers sterilized at 115°C for 30 minutes after washing. Provide pre- and postflush with item 9 (purified by passing through 1% phenol solution).
11. Sample for complete testing.

B Complex, Vitamin D, Vitamin E Lyophilized Injection

This product comprises two solutions, which are mixed together before injecting.

Solution 1

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.02	mg	1	Sodium formaldehyde sufoxylate, NF	0.02	g
10.20	mg	2	Thiamine HCl ampoule powder 200 mesh, 10% excess	11.22	g
2.55	mg	3	Pyridoxine HCl, USP	2.55	g
38.25	mg	4	Niacinamide, USP, powder for ampoules	38.25	g
0.02	mg	5	Sodium sulfide (nonahydrate) crystals	0.02	g
		6	Charcoal activated, USP	1.00	g
2.55	mg	7	Riboflavin-5′-phosphate sodium USP, 10% excess	3.842	g
51.00	mg	8	Ascorbic acid, USP, 15% excess	58.65	g
39.02	mg	9	Polysorbate 80 NF	39.02	g
510	U	10	Vitamin D, use Vitamin D_3 in arachis oil with 20% excess	0.612	g
4080	U	11	Vitamin A, use vitamin A palmitate 1.7 million IU/g with 31.25% excess; use only potency 1375–1500/g	3.15	g
1.02	IU	12	Vitamin E USP, use D-alpha-tocopheryl acid succinate USP	0.843	g
QS	mL	13	Carbon dioxide gas, technical	QS	
QS	mL	14	Water for injection, USP	QS	

Note: Solution 1 contains a 2% manufacturing excess of all vitamins to satisfy label claim when between 10.0 and 10.3 mL of lyophilized solution is reconstituted to 10.2 mL. The scale column includes this 2% manufacturing excess. Figures in the Standard Qty column include both the manufacturing excesses and any stability excesses indicated in bill of materials.

Manufacturing Directions

Note: Protect solution from light. Use CO_2 gas at all times during manufacturing process to protect solution. Sodium formaldehyde sulfoxylate precipitates out metallic impurities and also acts as an antioxidant. Use glass equipment wherever possible.

1. Preparation.
   Part I
   a. Heat 16% of final volume of water for injection to boiling.
   b. Cool to room temperature while bubbling through CO_2 gas.
   c. Add sodium formaldehyde sulfoxylate, thiamine HCl, and pyridoxine HCl.
   d. Seal under CO_2 gas protection and age 2 or more days.
   e. If a precipitate forms, remove by filtering through paper.
   Part II
   a. Heat 300 mL water for injection to boiling.
   b. Add and dissolve niacinamide and sodium sulfide.
   c. Add charcoal and stir for 1 hour under a hood. Cut off heat supply to allow cooling.
   d. Filter off the charcoal.
   e. Add and dissolve riboflavin-5′-phosphate sodium and cool to 25°C under CO_2 gas protection.
   f. After aging part I combine with part II.
   g. Add and dissolve ascorbic acid. Add ascorbic acid slowly while constantly stirring and bubbling CO_2 gas through solution.
   h. Saturate polysorbate 80 with CO_2 gas and add vitamin D_3 in arachis oil, vitamin A palmitate, and vitamin E. Mix well.
   i. Add polysorbate–vitamin mixture (step h) to main batch and mix thoroughly while bubbling CO_2 gas through solution.
   j. Add water for injection to a QS of 1000 mL. Check pH (range 3.0–4.0).
   k. Sample for testing.
   l. Transfer solution to a portable glass-lined tank for filling. Seal tank under CO_2 gas protection.
   Caution: Do not hold solution more than 4 days without reassay of vitamins before filling. Seal under CO_2 gas protection.
   m. Prepare a sterile 0.22-μm membrane filter, using an approved prefilter.
   Note: Protect solution from light and oxidation. Handle aseptically.
2. Filtration.
   a. Connect tank, sterile filter, and sterile surge bottle with aseptic technique.
   b. Apply 5 to 10 lb CO_2 pressure to tank (do not use more than 10 lb) and filter to fill surge bottle. When full, remove filling tube and replace with sterile venting filter by using aseptic technique.
   c. Transfer full surge bottles to filling area.
3. Preparation of vials.
   a. Wash and dry vials and load in appropriate containers for sterilization.

   b. Sterilize using dry heat at 200°C (–0, +50°C) glass temperature for 225 minutes (–0, +360 minutes).
      Note: This cycle or an equivalent cycle that ensures sterile, pyrogen-free vials may be used.
   c. Deliver vials to the sterile filling area.
4. Preparation of stoppers.
   a. Leach stoppers by boiling for 10 minutes in deionized water.
   b. Wash stoppers using rubber cycle (slow tumbling) with Triton X-100.
   c. Dry in a fast dryer at 55°C.
   d. Store in suitable containers until ready for use.
   e. Tray, inspect, and rinse thoroughly. Wrap tray and identify.
   f. Sterilize in a steam autoclave at 121°C for 60 minutes.
5. Filling. Sterile 25-mL vial or sterile 2-mL vial.
   a. Under aseptic conditions, fill the appropriate amount of solution 1 into each sterile vial.
      1. Fill 10.1 mL (range 10.0–10.3 mL) for the 10-mL final reconstituted product.
      2. Alternatively, fill 1.13 mL (range 1.05–1.18 mL) for the 1-mL final reconstituted product.
   b. Sample for testing.
   c. Place each filled vial into a sterile tray. Immediately cover the vial with a rubber stopper. Label trays.
   d. Place each tray in a freezer at -40°C and freeze overnight.
   e. Transfer to lyophilizer (at -40°C) and lyophilize to less than 2% moisture. Do not allow temperature to go more than 45°C.
   f. At end of lyophilization cycle, bring chamber to 5-in vacuum with sterile CO_2 gas. Ram stoppers home into vials and then bring chamber to atmospheric pressure with sterile CO_2 gas.
   g. Apply aluminum caps.
   h. Sample for testing.

Solution 2
B Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.73	mg	1	Sodium pantothenate dextro, 20% stability excess	6.12	g
10.31	mg	2	Benzyl alcohol, NF	9.176	g
2.29	μg	3	Cyanocobalamin (B_{12}), USP, 25% stability excess	2.548	mg
114.60	mg	4	Polyethylene glycol 400, NF low color	101.98	g
QS	mL	5	Hydrochloric acid, reagent grade, for pH adjustment[a]		
QS	mL	6	Nitrogen gas, NF[b]	QS	
QS	mL	7	Water for injection, USP	QS to 890.00	mL

Note: Solution 2 contains a 14.6% manufacturing excess of vitamins and benzyl alcohol to insure label claim when 8.9 mL of solution is reconstituted to 10.2 mL. Figures in the Scale column include this 14.6% manufacturing excess. Figures in the Standard Qty column include both the manufacturing excess and any stability excesses indicated in the bill of materials. Alternatively, solution 2 contains a 14.6% manufacturing excess of vitamins and benzyl alcohol to ensure label claim when 1.0 mL of solution is reconstituted to 1.15 mL. Figures in the Scale column include this 14.6% manufacturing excess. Figures in the Standard Qty column include both the manufacturing excess and any stability excess indicated in the bill of materials.

[a] Used only for pH adjustment if necessary.

[b] Bulk container should be flushed with N_2 and resealed after weighing.

Manufacturing Directions

1. Preparation.
   a. Dissolve sodium pantothenate and benzyl alcohol in 560 mL of water for injection.
   b. Add vitamin B_{12} and polyethylene glycol 400.
   c. Add water for injection and QS to 890 mL. Check pH. If pH is more than 8, adjust down to 6 to 8 with 0.1 N hydrochloric acid.
   d. Allow solution to stand overnight. Check pH (range 6–8).
   e. Sample for testing.
   f. Prepare a sterile 0.22-μm membrane filter by using an approved prefilter.
2. Filtration
   C*aution*: Handle solution aseptically to preserve sterility.
   a. Connect tank, sterile filter, and sterile surge bottle with aseptic technique.
   b. Apply 5 to 10 lb of N_2 gas pressure to tank (do not use more than 10 lb) and filter enough solution to half-fill surge bottle. If pH does not have pressure head, connect pump between tank and filter.
   c. Transfer filter delivery tube to filling siphon in an empty, sterile surge bottle. Siphon should be aseptically attached to filling equipment.
   d. Filter sufficient solution to fill surge bottle. Check quality of filtrate and start filling. Adjust flow through the filter to equal that of filling.
3. Preparation of ampoules.
   a. Wash and dry ampoules and load in appropriate containers for sterilization.
   b. Sterilize by using dry heat at 200°C (–0, +50°C) glass temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (+10°C) for the duration of the cycle.
      Note: This cycle or an equivalent cycle that ensures sterile, pyrogen-free ampoules may be used.
   c. Deliver to the sterile filling area.
4. Filling. Sterile 10- or 1-mL ampoule.
   a. Aseptically fill the appropriate amount of solution 2 into each sterile ampoule and seal.
      1. Fill 9.2 mL (range 9.1–9.3 mL) for the 10-mL final reconstituted product.
      2. Alternatively, fill 1.1 mL (range 1.05–1.15 mL) for the 1-mL final reconstituted product.
   b. Sample for testing.

1. Finishing.
   a. Label each vial of freeze-dried solution 1 and each ampoule of solution 2. Pack one of each into product carton.
   b. Sample for testing.

B Complex Vitamin Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Pyridoxine HCl, USP, as riboflavin-5′-phosphate sodium	10.00	g
15.00	mg	2	D-Panthenol	15.00	g
150.00	μg	3	Cyanocobalamin USP	150.00	mg
10.00	mg	4	Choline chloride	10.00	g
0.70	mg	5	Cobalt gluconate	0.70	g
0.20	mg	6	Copper gluconate	0.20	g
15.00	mg	7	Ferric ammonium citrate	15.00	g
2.00	%	8	Benzyl alcohol, NF	2.00	%
100.00	mg	9	Niacinamide, USP	100.00	g
5.00	mg	10	Chlorobutanol anhydrous, USP	5.00	g
10.00	mg	11	Inositol	10.00	g
10.00	μg	12	Biotin	10.00	mg
20.00	mg	13	Methionine, NF	20.00	g
20.00	mg	14	*dl*-Lysine	20.00	g
20.00	mg	15	Glycine	20.00	g
QS	mL	16	Water for injection, USP	QS to 1.00	L

B Complex Vitamin Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150.00	mg	1	Thiamine HCl, USP	150.00	g
150.00	mg	2	Niacinamide, USP	150.00	g
2.00	mg	3	Riboflavin as riboflavin-5′-phosphate sodium	2.00	g
10.00	mg	4	D-Panthenol	10.00	g
10.00	mg	5	Pyridoxine HCl, USP	10.00	g
20.00	mg	6	Choline chloride	20.00	g
20.00	mg	7	Inositol	20.00	g
100.00	μg	8	Cyanocobalamin, USP	100.00	mg
2.00	%	9	Benzyl alcohol, NF	2.00	%
QS	mL	10	Water for injection, USP	QS to 1.00	L

B Complex Vitamin Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
125.000	mg	1	Niacinamide, USP	125.000	g
100.000	mg	2	Ascorbic acid as sodium ascorbate, USP	100.000	g
5.000	mg	3	Riboflavin-5′-phosphate sodium	5.000	g
5.000	mg	4	Pyridoxine HCl, USP	5.000	g
50.000	mg	5	D-Panthenol	50.000	g
1.169	mg	6	Methyl paraben, USP	1.169	g
0.134	mg	7	Propyl paraben, USP	0.134	g
QS	mL	8	Water for injection	QS to 1.00	L
QS	mL	9	Hydrochloric acid for pH adjustment	QS	mL

B Complex Vitamin Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Choline chloride	100.00	g
50.00	mg	2	Inositol	50.00	g
50.00	mg	3	Methionine, NF	50.00	g
2.00	%	4	Benzyl alcohol, NF	2.00	%
QS	mL	5	Water for injection	QS to 1.00	L
QS	mL	6	Hydrochloric acid for pH adjustment	QS	mL

B Complex with Minerals Injection (Veterinary)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Thiamine HCl, USP	10.00	g
1.00	mg	2	Pyridoxine HCl, USP	1.00	g
1.50	mg	3	Riboflavin-5′-phosphate sodium	1.50	g
7.00	mg	4	D-Panthenol	7.00	g
50.00	μg	5	Cyanocobalamin, USP	50.00	mg
8.00	μg	6	Sodium chloride, USP	8.00	mg
0.10	mg	7	Copper gluconate	0.10	g
1.00	mg	8	Cobalt gluconate	1.00	g
8.00	mg	9	Ferric ammonium citrate (16–18% elemental iron)	8.00	g
100.00	mg	10	Niacinamide, USP	100.00	g
1.50	%	11	Benzyl alcohol, NF	1.50	%
QS	mL	12	Water for injection, USP	QS to 1.00	L

B Complex Vitamins with Hormones

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Testosterone, NF	10.00	g
0.50	mg	2	Estrone, NF	0.50	g
100.00	μg	3	Cyanocobalamin, USP	100.00	mg
50.00	mg	4	Thiamine HCl, USP	50.00	g
1.00	mg	5	Pyridoxine HCl, USP	1.00	g
5.00	mg	6	D-Panthenol	5.00	g
100.00	mg	7	Niacinamide, USP	100.00	g
20.00	mg	8	Lidocaine HCl, USP	20.00	g
0.20	%	9	Carboxymethylcellulose sodium, USP	0.20	%
0.20	%	10	Sodium phosphate, USP	0.20	%
4.00	%	11	Benzyl alcohol, NF	4.00	%
QS	mL	12	Water for injection, USP	QS to 1.00	L

B Complex Vitamins with Liver Extract Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Thiamine HCl, USP	10.00	g
5.00	mg	2	Riboflavin-5′-phosphate sodium	5.00	g
50.00	mg	3	Niacinamide, USP	50.00	g
3.00	mg	4	D-Panthenol	3.00	g
5.00	mg	5	Pyridoxine HCl, USP	5.00	g
30.00	μg	6	Cyanocobalamin, USP	30.00	mg
0.25	mL	7	Liver injection (20 μg/mL concentrate, supplies 5 μg B132 activity)	0.25	L
0.01	%	8	Edetate sodium	0.01	%
2.00	%	9	Benzyl alcohol, NF	2.00	%
QS	mL	10	Water for injection, USP	QS to 1.00	L

Benzodiazepine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
15.00	mg	1	Benzodiazepine[a]	15.00	g
0.18	mL	2	Polyethylene glycol (MW 300)	180.00	mL
0.75	mL	3	Propylene glycol (~QS volume)	750.00	mL
0.020	mL	4	Benzyl alcohol	20.00	mL

[a] 7-Chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2H-1,4-benzodiazepine-2-one.

Manufacturing Directions

1. To item 2 in a suitable container, mix items 3 and 4.
2. Add item 1 and dissolve.
3. Make up solution with item 3.
4. Filter and sterilize.

Benztropine Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Benztropine mesylate	1.00	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Beta-Carotene Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
32.00	mg	1	Beta-carotene (30% dispersed in coconut oil; Miglyol 810)	32.00	g
40.00	mg	2	Poloxamer 188 (Pluronic F-68®)	40.00	g
10.00	mg	3	Glycerol	10.00	g
1.00	mg	4	Thimerosal	1.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 418 mL of item 5 and mix in it item 2 in a suitable jacketed vessel.
2. Add 10 g of item 3 and heat to 45°C.
3. Add item 1 in a separate container and heat to 180°C to dissolve. Cool to 45°C.
4. Add to aqueous solution above with stirring to yield an emulsion.
5. The emulsification takes place at 45°C. Use an emulsifier such as an Ultraturrax® (7000–8000 rpm) for 8 minutes. Homogenize the emulsion at 1000 bar. The finished emulsion has an item 1 content of 1.6% and an average particle size of 210 nm.
6. Add item 4 and mix.
7. Fill 10 mL into vials aseptically.

Betamethasone Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.00	mg	1	Betamethasone as betamethasone sodium phosphate	3.00	g
3.00	mg	2	Betamethasone acetate	3.00	g
7.10	mg	3	Sodium phosphate dibasic	7.10	g
3.40	mg	4	Sodium phosphate monobasic	3.40	g
0.10	mg	5	Disodium edetate	0.10	g
0.20	mg	6	Benzalkonium chloride	0.20	g
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Fill 5 mL into multidose vials; pH 6.8 to 7.2.

Bethanechol Chloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Bethanechol chloride	5.15	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Note: May be autoclaved at 120°C for 20 minutes without loss of potency.

Biotin Injection

Bill of Materials (Batch Size 1.5 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	μg	1	Biotin FCC	150.00	mg
QS	mL	2	Water for injection	1.50	L
QS	mL	3	Sodium hydroxide, NF, 1% for pH adjustment	QS	mL
QS	—	4	Nitrogen gas, NF	QS	—

Manufacturing Directions

1. Put approximately 1.2 L of item 2 into a suitable mixing tank and dissolve item 1.
2. Add 1 N item 3 in drops until item 1 is dissolved and pH is around 7.0.
3. Carefully adjust the pH between 7 and 7.5 with 1 N item 3.
4. QS to volume with item 2. Check pH.
5. Filter using a 0.22-μm filter and fill under item 4 into sterilized vials (220°C for at least 240 minutes). Autoclave stoppers at 121°C for 60 minutes in 2% disodium edetate solution (final rinse stopper with RO water 3 times).

Biperiden Lactate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Biperiden lactate	5.00	g
14.00	mg	2	Sodium lactate	14.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Bisantrene Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.52	mg	1	Bisantrene base (96.15%)	0.52	g
100.00	mg	2	Sorbitan triisostearate	100.00	g
20.00	mg	3	Benzyl alcohol	20.00	g
30.00	mg	4	Sesame oil refined	30.00	g
7.50	mg	5	Pluronic C-68®	7.50	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Mix and stir item 1 at room temperature with items 2 to 5 until complete solution is obtained.
2. Make up the volume with item 6. Shake and sonicate for 20 seconds using a Branson Sonifier driver at a DC setting of 6 to 7 A to yield an emulsion wherein 95% of the particles are from 2 to 5 μm in size.

Bisantrene Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.52	mg	1	Bisantrene base (96.15%)	0.52	g
100.00	mg	2	Triglycerol pentaoleate	100.00	g
20.00	mg	3	Benzyl alcohol	20.00	g
8.00	mg	4	Soy lecithin, 95% PC	8.00	g
22.50	mg	5	Glycerin, USP	22.50	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Borax Sodium Lubricating Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.70	mg	1	Borax sodium borate, NF, powder/borax EP	5.70	g
2.50	mg	2	Sorbic acid, NF/BP	2.50	g
1.00	mg	3	Disodium edetate, USP/BP	1.00	g
5.15	mg	4	Boric acid, NF, granular/EP	5.15	g
5.00	mg	5	Glycerin, USP (96%)/Glycerol, BP	5.00	g
1.00	mg	6	Sodium chloride, USP	1.00	g
4.50	mg	7	Hydroxypropyl methylcellulose 2906, USP, 4000 cps	4.50	g
QS	mg	8	Sodium hydroxide, reagent-grade pellets	QS	mL
QS	mL	9	Hydrochloric acid, reagent-grade bottles	QS	mL
QS	mL	10	Water purified	QS to 1.00	L

Manufacturing Directions

Note: Use thoroughly clean glass-lined or 304 or better-grade stainless steel steam-jacketed tank equipped with a speed-control agitator and cover. Keep cover closed.

1. Preparation of bulk solution.
   a. Charge 750 mL of item 10 into the mixing tank and begin mixing. Begin heating item 10 to 72°C to 82°C.
   b. While heating, slowly add items 1 to 6 with mixing, allowing each to disperse prior to addition of next in-
   e. Discontinue heating and continue mixing for at least 20 minutes after last addition of item 7.
   f. With mixing, continue to cool batch to less than 40°C and make up to 1 L with water, taking care to avoid foaming. Make the final adjustment with the stirrer turned off. Continue mixing for at least 20 minutes while batch is cooling to less than 40°C. Check pH (range 6.7–6.9). Adjust, if necessary, with 1 N item 8 or 1 N item 9. Mix for 15 minutes. Sample.
2. Sterilization and filling. Initiate sterilization within 48 hours of completion of bulk solution.

gredient. Rinse the inside tank walls and agitator shaft with 15 mL of item 10.

   c. Continue mixing the solution for at least 20 minutes. Stop agitation and visually verify dissolution. With continued agitation, verify that the solution temperature is in the range of 72°C to 82°C.
   d. With mixing, slowly add and disperse item 7 by slowly sprinkling on the surface of solution. Allow each addition to be dispersed before adding more powder. Adjust agitation rate so as to avoid excessive foaming.
   a. Sterilize bulk solution at 121°C to 123°C for 30 to 35 minutes. As the tank temperature reaches 121°C to 123°C, carefully bleed air from tank.
   b. After sterilization, as the batch is cooling, pressurize tank to approx 10 psig with sterile-filtered compressed air. With mixing, cool batch to less than 30°C. Stop mixing and store in tank at ambient temperature until ready to fill. Maintain a positive pressure in the tank until filling is complete.
   c. Set up a previously sterilized product filter and transfer line. Aseptically fill sterile solution into sterilized containers and apply sterile closure components. Sample.

Botulinum Toxin: Type A Purified Neurotoxin Complex

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
100.00	U	1	Clostridium botulinum type A neurotoxin complex	100,000	U
0.50	mg	2	Albumin (human)	0.50	g
0.90	mg	3	Sodium chloride	0.90	g

Note: Vacuum-dried.

Botulinum Toxin (Type B Injectable Solution)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1428	U	1	Clostridium botulinum type B neurotoxin complex	1428,000	U
0.50	mg	2	Human serum albumin	0.50	g
0.01	M	3	Sodium succinate	0.01	M
0.10	M	4	Sodium chloride	0.10	M
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Fill 3.5 mL for 5000 IU; adjust pH to 5.6 with item 5 or 6.

Bretylium Tosylate in Dextrose Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Dextrose anhydrous, USP	50.00	g
4.00	mg	2	Bretylium tosylate	4.00	g
QS	mL	3	Sodium hydroxide for pH adjustment		
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP		

Note: This is the formula for 4.0 mg/mL; for other strengths, 2.0 or 8.0 mg/mL, use appropriate amounts of bretylium tosylate.

Manufacturing Directions

1. Add item 6 to ca. 95% of the final volume into tank.
2. Add and dissolve item 1 with mixing.
3. Add and dissolve item 2 with mixing.
4. Check pH, adjust if necessary to between 5.5 and 6.5 with item 4 or 5.
5. QS to final volume with item 6; mix to a uniform solution.
6. Check pH and adjust again as in step 4.
7. Filter solution through an appropriate filtration setup using an approved 0.45-μm or finer filter membrane with approved prefilter.
8. Autoclave using appropriate cycle with F_0 ranging from 8.0 to 18.0.
9. When filled in flexible plastic container, perform sterilization by circulated hot water spray and steam sterilization.

Buflomedil Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Buflomedil hydrochloride, injectable grade	10.00	g
42.00	mg	2	Dextrose hydrous, USP (use 38.18 g if anhydrous)	42.00	g
8.00	mg	3	Sodium chloride, USP	8.00	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Carbon dioxide, technical grade	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: Prepare the solution in a glass-lined or a 316 or higher temper-grade stainless steel tank cleaned according to approved plant SOPs. In place of item 6, N_2 gas, NF, can be used.

1. Preparation.
   a. Add water for injection to tank to ca. 90% of the final volume and bubble in CO_2 gas. Continue CO_2 protection throughout processing.
   b. With agitation, add and dissolve the buflomedil hydrochloride and dextrose. Mix until completely dissolved and solution is formed.
   c. QS to final volume with water for injection and mix well.
   d. Check and record pH (range 3.9–4.5). Adjust if necessary to pH 4.2 with 10% sodium hydroxide solution or dilute hydrochloric acid solution.
   e. Filter solution through a previously rinsed filtration setup by using an approved 0.45-μm or finer membrane and an approved prefilter. Filter into clean glass-lined or 316 stainless steel tank and protect with CO_2 gas.
   f. Sample for testing.
   g. Prepare an in-line 0.22-μm membrane filter for the filling line.
2. Filling. Use type I 5-mL glass ampoules.
   a. Using the inline filter, fill 5.3 mL into each clean, dry ampoule.
   b. Flush headspace with filtered CO_2 gas and seal.
   c. Sterilize in a steam autoclave at 120°C for 20 minutes.
   d. Sample for testing.

Bupivacaine Hydrochloride Injection 1: 0.75% in Dextrose 8.25% Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
7.50	mg	1	Bupivacaine hydrochloride (anhydrous), use bupivacaine HCl, USP, monohydrate	7.50	g
82.50	mg	2	Dextrose, powder, anhydrous, USP[a]	82.50	g
QS	mL	3	Hydrochloric acid[b]	QS	mL
QS	mL	4	Sodium hydroxide[b]	QS	mL
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] For tonicity adjustment.
[b] For pH adjustment.

Manufacturing Directions

1. Prepare the solution in a glass-lined or 316 stainless steel tank.
2. Mix and dissolve items 1 and 2.
3. Check pH (range 5.8–6.2). If necessary, adjust pH with item 3 or 4 solution.

Bupivacaine Hydrochloride Injection (0.25%)

1. QS with item 5 to final volume and mix.
2. Check the pH (range 5.8–6.2). If necessary, adjust pH with item 3 or 4 solution. Sample.
3. Prior to filling, filter the solution through a 0.22-μm membrane with an approved prefilter, if needed.
4. Fill appropriate volume into ampoules. Sample.

Bupivacaine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Bupivacaine hydrochloride, use bupivacaine HCl, USP, monohydrate	2.64	g
1.00	mg	2	Methyl paraben NF (Aseptoform M) powder	1.00	g
8.55	mg	3	Sodium chloride, USP	8.55	g
QS	mg	4	Sodium hydroxide, reagent-grade pellets[a]	QS	mg
QS	mL	5	Acid hydrochloric, reagent-grade bottles[a]	QS	mL
QS	mL	6	Water for injection	QS to 1.00	L

[a] Used for pH adjustment only.

Manufacturing Directions

Note: The solution must be prepared in a glass-lined or a 316 or more resistant-grade stainless steel tank cleaned according to approved plant basic operating procedure.

1. Preparation.
   a. Add item 6 to ca. 90% of the final volume into the tank and heat to NLT 90°C.
   b. Add item 2 and mix until dissolved.
   c. Cool to 25°C (range 25–30°C). Add and dissolve item 1. *Note*: Item 1 goes into solution slowly. Do not proceed until all drug is completely in solution.
   d. Add and dissolve item 3 with mixing. Mix solution for at least 10 minutes.
   e. Check pH. Adjust to 5.6 (range 5.6–5.8) with diluted item 4 (1%) or 5 (1%). Allow solution to mix for 10 minutes and recheck adjusted pH. *Note*: Make dilute item 4, 1.0% w/v, by dissolving 1.0 g of item 4 in sufficient water for injection to make 100 mL. Make diluted item 5 solution, 1.0% v/v, by dissolving 1.0 g of item 5 in sufficient water for injection to make 100 mL.
   f. QS solution to final volume with item 6. Mix for 10 minutes.
   g. Check pH (range 5.4–5.8). Readjust, if necessary, to pH 5.6 with dilute item 4 or 5.
   h. Filter solution through a previously rinsed filtration setup, using an approved 0.45-μm or finer membrane with an approved prefilter into a glass-lined or a 316 stainless steel tank.
2. Filling. Bottle: Type II glass.
   a. Fill specified amount into each clean, dry bottle. Apply stopper and overseal.
   b. Sterilize in a steam autoclave at 115°C for an F_0 of 8 to 18. Use terminal air overpressure and water spray cooling. Sample.

Bupivacaine Hydrochloride Injection: Bupivacaine with Epinephrine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Bupivacaine hydrochloride, use bupivacaine HCl, USP, monohydrate	2.64	g
0.005	mg	2	Epinephrine as epinephrine bitartrate	0.005	g
0.50	mg	3	Sodium metabisulfite	0.20	g
0.20	mg	4	Citric acid anhydrous	0.20	g
1.00	mg	5	Methyl paraben, NF (Aseptoform M) powder[a]	1.00	g
QS	ft^3	6	Nitrogen gas	QS	
8.00	mg	7	Sodium chloride	8.00	g
QS	mg	8	Sodium hydroxide, reagent-grade pellets[a]	QS	mg
QS	mL	9	Hydrochloric acid, reagent-grade bottles[a]	QS	mL
QS	mL	10	Water for injection	QS to 1.00	L

[a] Add only in multiple-dose vials. Adjust pH to 3.3 to 5.5 with item 4 or 5. Fill under N_2.

Buprenorphine Hydrochloride Injectable

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.30	mg	1	Buprenorphine as buprenorphine hydrochloride	0.324	g
50.00	mg	2	Dextrose anhydrous, USP	50.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Hydrochloric acid for pH adjustment		

Note: Adjust pH using item 4.

Caffeine Citrate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Caffeine anhydrous	10.00	g
5.00	mg	2	Citric acid monohydrate	5.00	g
8.30	mg	3	Sodium citrate dihydrate	8.30	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium hydroxide for pH adjustment		

Note: Caffeine citrate (20 mg) is formed by addition of caffeine as above; adjust pH to 4.7.

Calcitonin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	IU	1	Calcitonin, Eel	5000.00	IU
2.00	mg	2	Albumin, human	2.00	g
0.414	mg	3	Sodium phosphate monobasic monohydrate	0.414	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: For 100 IU dose per vial, increase the label quantity to 10.00 mg/mL.

Calcitonin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200	IU	1	Calcitonin-salmon synthetic[a]	200,000	IU
2.25	mg	2	Acetic acid	2.25	g
5.00	mg	3	Phenol	5.00	g
2.00	mg	4	Sodium acetate trihydrate	2.00	g
7.50	mg	5	Sodium chloride	7.50	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] Calcitonin–salmon synthetic is a synthetic polypeptide of 32 amino acids in the same linear sequence found in calcitonin of salmon origin.

Manufacturing Directions

1. Dissolve item 3 in a suitable quantity of item 4.
2. Add and dissolve, with slow agitation, item 2 to prevent frothing.
3. Add item 1 and dissolve.
4. Filter and fill 10 mL into each vial; stopper loosely.
5. Lyophilize [each vial contains 50 IU of calcitonin (SerGln GluLeuHisLysLeuGlnThr-TyrProArgThrAspValGlyAla GlyThrProNH_2)].

Calcitriol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00[a]	mg	1	Calcitriol in polysorbate 20 concentrate, 575 mg/g	2.00	g
2.00	mg	2	Polysorbate 20 (Tween 20), NF	2.00	g
1.50	mg	3	Sodium chloride, USP	1.50	g
10.00	mg	4	Sodium ascorbate microcrystalline, USP	10.00	g
7.60	mg	5	Sodium phosphate dibasic, USP, anhydrous	7.60	g
1.84	mg	6	Sodium phosphate, monobasic, USP, monohydrate	1.84	g
1.11	mg	7	Disodium edetate (dihydrate), USP	1.11	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

[a] Consists of 1.0 mg of calcitriol and 2.00 mg polysorbate 20.

Manufacturing Directions

1. Prepare solution in a pressurizable glass-lined tank.
2. Add item 8 to ca. 110% of final volume into a suitable tank and commence bubbling of N_2 gas.
3. Heat item 8 to a temperature of NLT 85°C and hold at that temperature for 10 minutes. Vapor generated must be vented from the tank.
4. Continue to bubble N_2 gas into the water and begin to cool. Before the water reaches 30°C (range 30–45°C) transfer all but 90% of the final volume to a separate covered tank that has been pregassed with N_2 and maintain this water under an N_2 sparge as it continues to cool. This water is to be used for QS. Continue bubbling N_2 gas into the mixing tank.
5. When the water in the mixing tank has cooled to 20°C to 30°C, begin drug addition. *Note*: For all drug additions, minimize excessive agitation of solution with mixer (to avoid introducing oxygen into solution).
6. Add and dissolve items 3 to 7 with mixing.
7. Mix until all ingredients are dissolved and solution is uniform. Switch to an N_2 gas blanket.
8. Check pH (range 7.0–7.6). If the pH falls outside of the specific pH range, discard the solution and prepare another aqueous solution.
9. Add item 2 with mixing. Maintain an N_2 gas blanket, exercising caution to avoid excessive foaming.
10. Add an accurately weighed factored amount of item 1 to the aqueous solution with gentle mixing.
11. QS to final volume with item 8 that has been previously boiled and cooled under N_2 gas protection. Mix gently until solution is uniform. Sample.
12. Filter the solution through an approved 0.45-μm or finer membrane connected in series to a prefilter, if needed, into a glass-lined holding tank.
13. Prior to filling, aseptically filter solution through a filtration setup by using an approved 0.22-μm or finer membrane.
14. Aseptically fill appropriate quantity into sterile ampoules. Maintain N_2 gas protection.

Calcitriol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00[a]	mg	1	Calcitriol in polysorbate 20 concentrate, 575 mg/g	2.00	g
1.50	mg	2	Sodium chloride, USP	1.50	g
10.00	mg	3	Sodium ascorbate microcrystalline, USP	10.00	g
7.60	mg	4	Sodium phosphate dibasic, USP, anhydrous	7.60	g
1.84	mg	5	Sodium phosphate monobasic, USP, monohydrate	1.84	g
1.11	mg	6	Disodium edetate (dihydrate), USP	1.11	g
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a] Consists of 2.0 mg of calcitriol and 4.00 mg polysorbate 20.

Manufacturing Directions

1. Prepare solution in a pressurizable glass-lined tank.
2. Add item 7 to ca. 110% of final volume into a suitable tank and commence bubbling of N_2 gas.
3. Heat item 7 to a temperature of NLT 85°C and hold at that temperature for 10 minutes. Vapor generated must be vented from the tank.
4. Continue to bubble N_2 gas into the water and begin to cool. Before the water reaches 30°C (range 30–45°C) transfer all but 90% of the final volume to a separate covered tank that has been pregassed with N_2 and maintain this water under an N_2 sparge as it continues to cool. This water is to be used for QS. Continue bubbling N_2 gas into the mixing tank.
5. When the water in the mixing tank has cooled to 20°C to 30°C, begin drug addition. *Note*: For all drug additions, minimize excessive agitation of solution with mixer (to avoid introducing oxygen into solution).
6. Add and dissolve items 2 to 6 with mixing.
7. Mix until all ingredients are dissolved and solution is uniform. Switch to an N_2 gas blanket.
8. Check pH (range 7.0–7.6). If the pH falls outside the specific pH range, discard the solution and prepare another aqueous solution.
9. Add an accurately weighed factored amount of item 1 to the aqueous solution with gentle mixing.
10. QS to final volume with item 7 that has been previously boiled and cooled under N_2 gas protection. Mix gently until solution is uniform. Sample.
11. Filter the solution through an approved 0.45-μm or finer membrane connected in series to a prefilter, if needed, into a glass-lined holding tank.
12. Prior to filling, aseptically filter solution through a filtration setup by using an approved 0.22-μm or finer membrane.
13. Aseptically fill appropriate quantity into sterile ampoules. Maintain N_2 gas protection.

Calcium Glycerophosphate Injection with Lactate

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Calcium glycerophosphate	5.00	g
5.00	mg	2	Calcium lactate pentahydrate	5.00	g
0.25	%	3	Liquefied phenol, USP	2.50	g
5.00	mg	4	Sodium chloride, USP	5.00	g
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Hydrochloric acid for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	mL	8	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Preboil the total volume of item 7, maintain N_2 flush, and blanket throughout production.
2. In three separate suitable containers, dissolve item 1 in 40% of item 7, item 2 in 30% of item 7, and item 4 in 20% of item 7.
3. Let the calcium glycerophosphate and calcium lactate stand for at least 60 minutes and then combine in a suitable container. Add the liquefied phenol (item 3) and mix.
4. Add item 4 solution and mix to homogeneity.
5. Record pH and adjust to 7.0 to 7.5 with items 5 and 6.
6. Bring to volume with N_2-saturated item 7 and mix.
7. Sample for testing. Test for tonicity.

Calcium Glycerophosphate Injection: Calcium Glycerophosphate Injection (Human and Veterinary)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Calcium glycerophosphate	10.00	g
15.00	mg	2	Calcium levulinate	15.00	g
5.00	mg	3	Chlorobutanol anhydrous, USP	5.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Calcium Gluconate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
94.00	mg	1	Calcium gluconate, USP	94.00	g
5.00	mg	2	Calcium-*d*-saccharate. $4H_2O$	5.00	g
QS		3	1 N sodium hydroxide for pH adjustment	QS	
QS		4	Nitrogen gas, NF	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: Complete step 3 at least 90 hours prior to start of filling.

1. Boil 0.8 L of water for injection, bubble filtered N_2 for 10 to 15 minutes, and maintain an N_2 blanket throughout the following operation.
2. Add calcium gluconate to the water for injection and stir until the solution is clear.
3. Add calcium-*d*-saccharate and mix to a clear solution.
4. Transfer to another tank. After 24 hours, take into account the solution temperature and check pH and adjust to between 7.0 and 7.5, using 1 N sodium hydroxide solution.
5. Allow the above solution to come to room temperature and bring to final volume with water for injection. Do not reheat even if a few crystals come out of solution.
6. After cooling and pH adjustment, filter the solution once every 24 hours through a 0.45-μm prefilter and a sterilized 0.22-μm filter into a clean stainless steel tank. Repeat this for 3 days (see note).
7. After third filtration, sample and submit to QC; after QC approval pass again through a 0.45-μm prefilter and a 0.22-μm sterilized filter and fill under N_2 (postflush).
8. Heat the filled vials in autoclave at 105°C±5°C for 10 minutes. Carefully monitor for slow exhaust and temperature. Autoclave stoppers in 2% disodium edetate solution after rinsing with RO water and final rinsing again with RO water.
9. Finish. Sample.

Calcium Glycerophosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Calcium glycerophosphate	10.00	g
15.00	mg	2	Calcium levulinate	15.00	g
5.00	mg	3	Chlorobutanol anhydrous, USP	5.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
12.00	mg	5	Lactic acid, USP	12.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Sodium hydroxide for pH adjustment	QS	

Camphor Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Camphor	200.00	g
20.00	mg	2	Benzyl alcohol	20.00	g
QS	mg	3	Sesame oil	QS to 1.00	L

Camptothecin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.40	%	1	Camptothecin[a]	0.40	%
30.00	%	2	Alcohol absolute, USP	QS to 30.00	%
4.60	%	3	Benzyl alcohol	4.60	%
10.00	%	4	Citric acid	10.00	%
50.00	%	5	Polyethylene glycol 400	55.00	%
5.00	%	6	Polysorbate 80 (Tween®)	5.00	%

[a] Highly lipophilic derivative or 7-ethyl-10-hydroxy or 10,11-methylenedioxy or 10-bromo compounds of camptothecin-labeled quantity to be adjusted according to the derivative used.

Manufacturing Directions

1. Add item 1 to item 2 and mix well.
2. Add item 5 and mix well.
3. Add and dissolve item 6.
4. Add item 4 and mix well.
5. Add item 1 and mix thoroughly in a homogenizer.

Carboplatin for Infusion

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
50.00	mg	1	Carboplatin	50.00	g
50.00	mg	2	Mannitol	50.00	g

Note: Lyophilized powder 50, 150, or 450 mg per vial with equal parts by weight of mannitol.

Carboplatin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Carboplatin	10.00	g
QS	ft^3	2	Nitrogen gas, NF	QS	cy
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add ca. 75% of item 3 to a clean mixing vessel. Manufacturing should be done at temperature of 30°C or less.
2. Bubble N_2 through step 1 for at least 15 minutes prior to adding item 1.
3. Add item 1 by first making a slurry in small amount of item 3 and then adding this slurry to step 1 with mixing to achieve complete solution.
4. Check pH (4.0–7.0); do not adjust pH.
5. Make up volume.
6. Check pH again (4.0–7.0); do not adjust.
7. Filter through 0.2-μm sterile filter and transfer via silicon tubing into a sterile receiving vessel vented by a sterile bacteria-retaining filter. Fill volume 15.4 to 15.6 mL. Filter integrity checked before and after filling. Use West Type 1888 S63 stoppers, type I 20-mL glass vial with flip-off aluminum metal cap, and medical-grade silicone tubing.
8. Sterilized closures are aseptically inserted into vials.

Carprofen Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
88.50	mg	1	Glycocholic acid	88.50	g
0.019	mL	2	Sodium hydroxide, NF, 40%	19.00	mL
169.00	mg	3	Lecithin, fine	169.00	g
30.00	mg	4	L-Arginine	30.00	g
50.00	mg	5	Carprofen	50.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Hydrochloric acid 2 N		
QS	ft^3	8	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Put 0.5 L of item 6 into a suitable vessel and pass item 8 into it for 20 minutes.
2. Add item 2 to it and mix.
3. Add item 1, mix, and dissolve.
4. Add item 3 and dissolve with strong stirring.
5. Heat the solution to between 50°C and 60°C. This is a micelle solution.
6. Add item 4 to 150 mL of item 6 (purged with item 8) at 40°C in a separate vessel.
7. Add item 5 in the mixed micelle solution heated to 50°C to 60°C.
8. Add the preparation in step 6 to it slowly with mixing maintaining the temperature of 50°C to 60°C.
9. Check and adjust pH to 5.8 to 6.2 with item 7.
10. Filter solution through a 0.45-μm membrane filter and fill into type I glass ampoule under aseptic conditions with pre- and postflush of item 8.
11. Sterilize by autoclaving 121°C for 20 minutes.

Cefamandole Nafate for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
1.00	g	1	Cefamandole as cefamandole nafate equivalent	1.00	kg
63.00	mg	2	Sodium carbonate	63.00	g

Note: On reconstitution, the pH is 6.0 to 8.5; cefamandole nafate rapidly hydrolyzes to cefamandole, which is also active.

Cefazolin Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/50 mL		Item	Material	Qty	UOM
1.00	g	1	Cefazolin	20.00	g
2.00	g	2	Dextrose hydrous, USP	40.00	g
QS	mL	3	Water for injection,	QS to 1.00	L

Note: For a 500-mg dose, the amount of item 2 is 2.40 g/vial; fill 50 mL per container and keep it frozen. Also available as 0.5 or 1.0 g lyophilized powder. The pH of reconstituted solution is between 4.5 and 6.0.

Cefepime Hydrochloride for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	g	1	Cefepime hydrochloride	1.00	kg
725.00	mg	2	L-Arginine to control pH	725.00	g

Note: Dry mixture for reconstitution; pH of reconstituted solution is 4 to 6.

Cefotaxime Injection

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Qty	UOM
1.00	g	1	Cefotaxime	20.00	g
1.70	g	2	Dextrose hydrous, USP	34.00	g
QS	mg	3	Sodium citrate hydrous for buffering	QS	
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: The 2.0-g dose uses 0.7 g of item 2 (for tonicity).

Cefotetan Injection

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Qty	UOM
1.00	g	1	Cefotetan	20.00	g
1.90	g	2	Dextrose hydrous, USP	38.00	g
QS	mg	3	Sodium bicarbonate for pH adjustment	QS	
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Sodium bicarbonate also added to convert cefotetan free acid to the sodium salt. The pH is adjusted to 4.0 to 6.5 with item 3 or 4. Frozen until used. Cefotetan disodium powder is supplied as 80 mg/vial for reconstitution.

Cefoxitin Injection Premixed IV Solution

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Qty	UOM
1.00	g	1	Cefoxitin	20.00	g
2.00	g	2	Dextrose hydrous, USP	44.00	g
QS	mg	3	Sodium bicarbonate for pH adjustment	QS	
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: For a 2.0-g dose, the quantity of item 2 is 1.1 g. The pH is ca. 6.5. After thawing, the solution is intended for IV use only.

Ceftazidime for Injection: L-Arginine Formulation

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
1.00	g	1	Ceftazidime pentahydrate eq.	1.00	kg
349.00	mg	2	L-Arginine[a]	349.00	g

[a] Quantity calculated on the basis of ceftazidime activity 1:0.349 ratio. The pH of freshly constituted solution ranges from 5 to 7.5. Other strengths include 2 and 10 g/vial.

Ceftazidime Injection Dry Powder

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
1.00	g	1	Ceftazidime pentahydrate eq.	1.00	kg
118.00	mg	2	Sodium bicarbonate	118.00	g

Note: Other strengths include 2 and 6 g; pH of reconstituted solution is 5 to 8.

Ceftazidime Injection Premix

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Qty	UOM
1.00	g	1	Ceftazidime pentahydrate eq.	20.00	g
2.20	g	2	Dextrose hydrous, USP	44.00	g
QS	mL	3	Sodium hydroxide for pH adjustment		
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5 to 7.5 with item 3 or 4; item 3 also used to convert acid to salt.

Ceftriaxone Injection: 500-mg Injection (IM and IV)

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
596.60	mg	1	Ceftriaxone, use ceftriaxone disodium (3.5 H_2O), 8% excess	645.00	g
QS	mL	2	Water for injection, USP	QS to 1.75	L

Manufacturing Directions

1. Solution. Suspend item 1 under N_2 gas flushing, using freshly distilled water, and stir to dissolve.
2. Filter through a 0.22-μm filter.
3. Fill aseptically into vials, freeze, and lyophilize.
4. After drying, close the vials under N_2 protection, apply rubber stopper and an aluminum cap with a rim, and check them visually. Avoid microbial contamination during processing.

Water for reconstitution is filtered, germ-free distilled water sterilized in an autoclave after filling aseptically in ampoules.

Ceftriaxone Injection (250-mg Injection, IM and IV)

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
298.30	mg	1	Ceftriaxone, use ceftriaxone disodium (3.5 H_2O), 8% excess	322.50	g
QS	mL	2	Water for injection, USP	QS to 1.75	L

Manufacturing Directions

1. Solution. Suspend item 1 under N_2 gas flushing, using freshly distilled water, and stir to dissolve.
2. Filter through a 0.22-μm filter.
3. Fill aseptically into vials, freeze, and lyophilize.
4. After drying, close the vials under N_2 protection, apply rubber stopper and an aluminum cap with a rim, and check them visually. Avoid microbial contamination during processing.

Water for reconstitution is filtered, germ-free distilled water sterilized in an autoclave after filling aseptically in ampoules.

Ceftriaxone Injection Premix

Bill of Materials (Batch Size 1 L)					
Scale/50 mL		Item	Material	Qty	UOM
1.00	g	1	Ceftriaxone sodium	20.00	g
2.00	g	2	Dextrose hydrous, USP	40.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: For a 2-g strength, use 1.2 g of item 2.

Cefuroxime for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.75	g	1	Cefuroxime sodium	15.00	g
1.40	g	2	Dextrose hydrous, USP	28.00	g
300.00	mg	3	Sodium citrate hydrous	300.00	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5 to 7.50. For a 1.5-g strength, the quantity of item 3 is 600 mg.

Cetrorelix Acetate for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
0.25	mg	1	Cetrorelix as cetrorelix acetate	0.27	g
54.80	mg	2	Mannitol	54.80	g

Note: For a 3.0-mg dose, use 164.40 mg of item 2. The pH of reconstituted solution is 5 to 8.

Chloramphenicol and Phenylmercuric Nitrate Ophthalmic Drops

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
0.1327	mL	1	Polyethylene glycol 300	5.972	L
70.00	mg	2	Polyoxyl 40 stearate, NF	3.15	kg
6.20	mg	3	Chloramphenicol, USP (24% overage)	279.00	g
Part II					
		4	Water Purified (distilled), USP	25.00	L
0.127	mg	5	Disodium edetate, USP	5.72	g
0.04	mg	6	Phenylmercuric nitrate	1.80	g
QS	mL	7	5 N Hydrochloric acid, NF[a]	QS	mL
QS	mL	8	1 N Sodium hydroxide, NF[a]	QS	mL
QS	mL	9	Water purified (distilled), USP	QS to 45.00	L

[a] Use only for pH adjustment.

Manufacturing Directions

Note: Weigh out the chloramphenicol in the antibiotic weigh room. Be careful to prevent any cross contamination of the antibiotic during weighing and handling. The temperature of part I is critical and must be precisely controlled or precipitation may result. Mixing must be continuous while adding part II to part I or precipitation may result.

Part I

1. Add items 1 and 2 to a suitable water-jacketed heating kettle of at least 45-L capacity. Begin mixing with a suitable mixer.
2. Heat to 85°C to 90°C while mixing. Do not allow the temperature to rise more than 90°C. Mix until all of item 2 has melted.
3. When all of the item 2 has melted, turn off the heat source and allow the mixture to cool to 53°C to 55°C by circulating cold water through the kettle jacket.
4. When the temperature of part I reaches 53°C to 55°C, add item 3. Mix thoroughly for at least 15 minutes.
5. Maintain the temperature of part I at 53°C to 55°C and immediately add part II at 50°C to 52°C according to the instructions that follow.

Part II

1. Measure out ca. 25 L of item 4 into a suitable water-jacketed heating kettle. Begin mixing.
2. Add items 5 and blended item 6, in order, allowing the first to dissolve completely before adding the next. Rinse out the blender cup with item 9 and add the rinsings to the kettle.
3. Heat part II to 50°C to 52°C.
4. With part I at 53°C to 55°C and part II at 50°C to 52°C, add part II to part I, while mixing parts I and II.
5. Use 4 to 5 L of item 9 to rinse the part II kettle, pump, and hoses.
6. Add the rinsings to combined parts I and II. Continue mixing and allow the batch to cool to 30°C or less.
7. When the temperature is at 30°C or less, transfer the batch into a suitable mixing tank for a final QS of 45 L.
8. Use 2 to 3 L of item 9 to rinse out the kettle, pump, and hoses. Add the rinsings to the calibrated mixing tank. Mix well for at least 15 minutes.
9. Check pH (range 5.4–5.8). If necessary, adjust the pH to 5.4 to 5.8 with item 7 or 8.
10. Allow any foam to dissipate and QS the batch to 45 L with item 9. Mix thoroughly for at least 15 minutes.

Sterile Filtration

1. Sterilize for 1 hour (range 45–60 minutes) at 121°C (–0, +5°C) in an autoclave at 15 psi and then filter to a 100-L stainless steel pressure vessel. Transfer to solution preparation area.
2. Mix the product for at least 10 minutes before filtration.
3. Connect the sterilized filter and sterile-filter with the aid of N_2 pressure (15–30 lb). Discard initial 10 L of filtrate, attach sterilized hose to sterilized filter holder, and connect to the sterilized 100-L stainless steel pressure vessel aseptically. *Note*: Before sterile filtration to 100-L pressure vessel, perform the bubble point test at NLT 40 psi and on 0.22-μm inline gas filter at 18 psi.
4. After completion of product filtration, disconnect filter from pressure vessel and flush the sterilizing filter with at least 10 L of water purified (distilled) for the bubble point test (after filtration).
5. After filtration, decontaminate the outer surface of bulk holding pressure vessel and then transfer to filling cubicle. Sample.

Sterilization

1. Filling unit, 20-L surge bottle, manifold of filling unit, and uniforms.
2. Sterilize at 121°C (–0°, +2°C) pressure 15 psi for 1 hour.

Sterile Filling

1. Aseptically connect the sterilized filling tubing and N_2 line from 100-L pressure vessel to surge bottle.
2. Aseptically fill sterile solution into sterilized container.
3. Perform the bubble point test on a 0.22-μm in-line gas filter before and after filtration at 18 psi. Sample.

Chloramphenicol Ophthalmic Solution (3%)

Formulation

Chloramphenicol, 3 g; Kollidon 25 [1], 15 g; preservative, QS; water, add 100 g.

Manufacturing Directions

Dissolve the preservative in hot water, cool, dissolve Kollidon 25, add chloramphenicol, and stir until a clear solution is obtained.

Chloramphenicol for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/Vial		Item	Material	Qty	UOM
1.44	g	1	Chloramphenicol hemisuccinate	1.92	kg
136.55	mg	2	Sodium hydroxide	136.55	g
QS	mL	3	Sodium hydroxide for pH adjustment		
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Measure ca. 0.3 L of water for injection in a clean, identified Pyrex bottle and dissolve sodium hydroxide. Cool the solution to between 10°C and 15°C.
2. Measure ca. 0.4 L of water for injection in a clean, identified mixing tank.
3. Add chloramphenicol hemisuccinate into the mixing tank with constant agitation to suspend the material.
4. Add sodium hydroxide solution slowly to the chloramphenicol hemisuccinate suspension in a steady stream to pH 6.6 to 6.8.
5. Bring to final volume and check pH.
6. Prefilter through a 1-mm prefilter cartridge and through a Millipore® prefilter #CW03 012 02 Milligard cartridge.
7. QC sample for pH, UV scan, and specific gravity.
8. Sterile-filter through a 0.22-mm filter and fill as required and lyophilize.
9. Cool the shelves in the lyophilizer to approximately −40°C. Load the product and place thermocouples.
10. The product thermocouples should register −30°C or less for at least 4 hours before starting the cycle.
11. Cool condenser until it attains −45°C or less. Start vacuum pump to achieve a vacuum level of 300 μm or less in the chamber.
12. Set to low heat and set temperature control to +30°C. Let the product temperature rise by itself. When it reaches +30°C, hold at this temperature ±3°C for at least 4 hours.
13. Set temperature controller to +45°C, hold at this temperature for at least 12 hours, stop the vacuum, bleed the chamber with sterile dry air, and take out one vial from each shelf. Send these samples (stoppered) for moisture check. Immediately close the lyophilizer chamber and start vacuum to as low as it will go. Continue to dry for at least 12 hours.
14. Bleed chamber slowly to approximately 5 in Hg vacuum with sterile dry air.
15. Stopper vials by using the internal stoppering mechanism and bleed chamber to atmosphere pressure.
16. Withdraw the product from the lyophilizer. Seal the stoppered vials.

Chloramphenicol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
123.00	mg	1	Chloramphenicol, USP	125.00	g
5.14	mg	2	Lidocaine HCl, USP	5.14	g
4.05	mg	3	Lidocaine base, USP	4.05	g
10.00	mg	4	Chlorocresol	10.00	g
0.12	mL	5	Water for injection, USP	0.12	L
QS	mL	6	Propylene glycol, NF	QS to 1.00	L
QS		7	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Take approximately 0.75 L of item 6 and heat in a steam-jacketed kettle for 30 minutes.
2. Add item 1 to above kettle at 80°C, stir, and dissolve. Allow to cool.
3. In a separate vessel, take freshly boiled item 5 and dissolve in it items 4 and 2 to complete solution.
4. Cool the solution in step 3 and make up volume with step 2.
5. Flush with item 7 and keep covered.
6. Check pH (6.5–6.8); do not adjust.
7. Filter through a 0.22-μm presterilized assembly with a 0.45-μm prefilter.
8. Flush amber type I glass vials presterilized with item 7 and fill 10.5 mL. Stopper and seal.
9. This is the aseptic filling process; no terminal heating allowed.
10. Sample for sterility, particles.

Chloramphenicol Sodium Succinate for Injection

Bill of Materials (Batch Size 118 L)					
Scale/Vial		Item	Material	Qty	UOM
1.44	mg	1	Chloramphenicol hemisuccinate	22.656	kg
136.55	mg	2	Sodium hydroxide, USP	2.1483	kg
QS	mg	3	10% Sodium hydroxide, USP, for pH adjustment	QS	mL
QS	mL	4	Water for injection, USP	QS to 118.00	L

Manufacturing Directions

1. Measure ca. 40 L of item 4 in a clean, identified Pyrex bottle and dissolve item 2. Cool the solution to between 10°C and 15°C.
2. Measure ca. 50 L of item 4 in a clean, identified mixing tank.
3. Add item 1 into the mixing tank with constant agitation to suspend the material.
4. Add item 2 solution from step 1 slowly to item 1suspension in a steady stream to pH 6.6 to 6.8.
5. Bring to final volume and check pH.
6. Prefilter through a 1-μm prefilter cartridge and through a Millipore® prefilter #CW03 01202 Milligard cartridge. Sample.
7. Sterile filter through a 0.22-μm filter and fill as required and lyophilize.
8. Cool the shelves in the lyophilizer to approximately −40°C, load the product, place thermocouples.
9. The product thermocouples should register −30°C or less for at least 4 hours before starting the cycle.
10. Cool condenser until it attains −45°C or less. Start vacuum pump to achieve a vacuum level of 300 μm or less in the chamber.
11. Set to low heat and set temperature control to +30°C. Let the product temperature rise by itself. When it reaches +30°C, hold at this temperature ±3°C for at least 4 hours.
12. Set temperature controller to +45°C, hold at this temperature for at least 12 hours, stop the vacuum, and bleed the chamber with sterile dry air. Sample. Immediately close the lyophilizer chamber and start vacuum to as low as it will go. Continue to dry for at least 12 hours.
13. Bleed chamber slowly to approximately 5 in Hg vacuum with sterile dry air.
14. Stopper vials by using the internal stoppering mechanism and bleed chamber to atmosphere pressure. Withdraw the product from the lyophilizer. Seal the stoppered vials.

Chlordiazepoxide Hydrochloride Injection

Bill of Materials (Batch Size 2 L for Diluent)					
Scale/mL		Item	Material	Qty	UOM
Powder Vial					
100.00	mg	1	Chlordiazepoxide hydrochloride	100.00	g
Diluent Vial					
15.00	mg	1	Benzyl alcohol	15.00	g
40.00	mg	2	Polysorbate 80	40.00	g
200.00	mg	3	Propylene glycol	200.00	g
16.00	mg	4	Maleic acid	16.00	g
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 2.00	L

Note: Adjust pH to ca. 3.0.

Chloroprocaine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Chloroprocaine hydrochloride	10.00	g
6.70	mg	2	Sodium chloride	6.70	g
0.111	mg	3	Disodium edetate dihydrate	0.111	g
1.00	mg	4	Methyl paraben	1.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: For infiltration and nerve block. Also available without items 3 and 4 at 20- and 30-mg concentrations; the quantity of item 2 is 4.7 mg/mL for 20-mg and 3.3 mg/mL for 30-mg concentration.

Chloroquine Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Chloroquine base, use chloroquine phosphate	64.50	g
5.00	mg	2	Chlorbutol	5.00	g
0.01	mL	3	benzyl alcohol, NF	10.00	mL
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take ca. 0.75 L of item 4 freshly boiled and cooled to room temperature and dissolve item 1 into it.
2. Dissolve item 2 in item 3 and add this solution to step 1 gradually to ensure good dispersion and dissolution.
3. When the solution is clear, make up the volume with item 4.
4. Sample and check final product to pH 3.5 to 4.5; do not adjust.
5. Filter through 0.45-μm and 0.22-μm filters.
6. Fill 30.5 to 31.0 mL into presterilized vials under aseptic conditions.
7. Sample for clarity, sterility.

Chlorothiazide Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	g	1	Chlorothiazide sodium equivalent to chlorothiazide	0.50	kg
0.25	g	2	Mannitol	0.25	kg
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Lyophilize for reconstitution.

Chlorpheniramine Maleate Injection (25 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Chlorpheniramine maleate, USP	25.00	g
2.50	mg	2	Liquefied phenol, NF	2.50	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Hydrochloric acid for pH adjustment	QS	

Manufacturing Directions

1. Dissolve item 1 in 0.6 L of item 3.
2. In a separate vessel, dissolve item 2 in 0.2 L of item 3 and add to step 1.
3. Bring to volume with item 3.
4. Mix well and sample for pH to 4.3 (range 4.3–4.5). Adjust with item 4 or 5, if necessary.
5. Filter through a 0.22-μm presterilized filter to a sterilized vessel.
6. Fill 2.1 mL into presterilized ampoules.
7. Sterilize in an autoclave at 121°C for 30 minutes.
8. Sample for clarity, sterility.

Chlorpheniramine Maleate Injection (10 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Chlorpheniramine maleate	10.00	g
5.00	mg	2	Chlorobutanol anhydrous	5.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Chlorpromazine Hydrochloride Injection (10 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Chlorpromazine HCl, USP	10.00	g
2.00	mg	2	Ascorbic acid, USP	2.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS		6	Nitrogen gas, NF	QS	

Manufacturing Directions

Caution: Avoid exposure to product. Solutions should be colorless to faint yellow; discard if turns pink.

1. Dissolve item 1 in 0.90 L of item 3, which has been freshly boiled and allowed to cool.
2. Dissolve item 2 and make up volume with item 3.
3. Begin and maintain cover of item 6 throughout.
4. Measure pH to 5.5 (5.0–6.0). Adjust with 10% item 4 or 4% item 5 if necessary.
5. Filter through 0.22- and 0.45-μm prefilters.
6. Flush presterilized ampoules with item 6 and fill under cover of item 6.
7. Fill 5.2 mL into flint type I glass ampoules.
8. Autoclave at 116°C for 30 minutes.

Chlorpromazine Hydrochloride Injection (25 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Chlorpromazine hydrochloride, USP	25.00	g
2.00	mg	2	Ascorbic acid (as sodium ascorbate), USP	2.00	g
1.00	mg	3	Sodium metabisulfite, NF	1.00	g
1.00	mg	4	Sodium chloride, USP	1.00	g
20.00	mg	5	Benzyl alcohol, NF	20.00	g
QS	mL	6	Water for injection	QS to 1.00	L
QS	mL	7	Hydrochloric acid for pH adjustment	QS	mL

Choriogonadotropin-Alpha (Recombinant) for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
285.00	mg	1	Recombinant human chorionic gonadotropin	285.00	g
30.00	mg	2	Sucrose	30.00	g
0.98	mg	3	Phosphoric acid	0.98	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 6.5 to 7.5; lyophilize. Can be given to newborns.

Chorionic Gonadotropin for Injection (20,000 U/10 mL Covial)

Bill of Materials (Batch Size 24- and 75-L Diluent)					
Scale/m		Item	Material	Qty	UOM
5000	U	1	Chorionic gonadotropin, USP (potency U/mg)	120,000,000	U
50.00	mg	2	Mannitol USP, 10% overage	1.32	kg
1.50	mg	3	Sodium phosphate monobasic (85–95%)	40.00	g
6.50	mg	4	Sodium phosphate Dibasic	156.00	g
QS	mL	5	Water for injection, USP	QS to 24.00	L
0.90	%	6	Benzyl alcohol, 20% excess	810.00	mL
QS	mL	7	Water for injection, USP	QS to 75.00	L
QS	mL	8	Hydrochloric acid for pH adjustment	QS	mL

Manufacturing Directions

1. Measure 69 L of item 7 into a tank. Add item 6 to the tank with agitation until a clear solution results. Bring to ca. 73 L (item 7) and check pH and adjust to 5 to 7 and recheck with item 8.
2. Bring the final volume with item 7 and then pass through a 0.22-μm filter into a sterile reservoir for filling. Check first vials for reconstitution pressure, which should be less than 5 kg.
3. Dry mix item 1 with ca. 2 times its weight, using item 2 in an appropriate container.
4. Measure 15 L of item 5 in a container. Add the dry-mixed items 1 and 2 from step 5 to the mixing tank with slow agitation to avoid vortex and foaming.
5. Dry rinse all utensils needed for items 1 and 2 with the balance of item 2 and add to the mixing tank. Dissolve items 3 and 4 in ca. 1 L of item 5 which has been heated to ca. 35°C.
6. Add items 3 and 4 solution from step 5 to the mixing tank with slow agitation. Bring to final volume and check pH; do not adjust pH. Expect pH to be around 7.2 to 7.4. Sample.
7. Pass the solution through a 0.22-μm filter into a sterile reservoir for filling. Lyophilize.
8. Load the product into the lyophilizer keeping the covials covered during the transfer.
9. Set temperature for −40°C; product thermocouple should register –30°C or less for at least 2 hours before starting the cycle.
10. Start condenser and start vacuum only when condenser is less than –40°C; start vacuum to chamber to at least 300 μm.

11. Bring up temperature controller to +25°C. Set to low heat and switch on heat. Hold at +25°C for at least 36 hours.
12. Bring up temperature controller to 45°C. Hold at 45°C for 8 hours.
13. Shut off the lyophilizer and bleed chamber slowly with dry sterile air to atmosphere pressure. Remove product sample. Repeat if not dried to specifications.

Chorionic Gonadotropin for Injection (10000 U//10 mL)

Bill of Materials (Batch Size 1 L)					
Scale/Vial		Item	Material	Qty	UOM
10,000	U	1	Chorionic gonadotropin	10 MM	U
5.00	mg	2	Sodium phosphate monobasic	5.00	g
4.40	mg	3	Sodium phosphate dibasic	4.40	g
5.60	mg	4	Sodium chloride	5.60	g
9.00	mg	5	Benzyl alcohol	9.00	g
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Phosphoric acid for pH adjustment		
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: This composition is after reconstitution with 10 mL of water for injection.
Not for use in newborns.

Chromium Chloride Additive Injection (5-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
102.50	mg	1	Chromium chloride hexahydrate	102.50	mg
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Chromium Chloride Additive Injection (10-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.50	mg	1	Chromium chloride hexahydrate	20.50	mg
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Chromium Chloride Additive Injection (30-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.50	mg	1	Chromium chloride hexahydrate	20.50	mg
0.90	%	2	Benzyl alcohol, NF	0.90	%
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Sulfuric acid for pH adjustment	QS	

pH 3.0 to 6.0
Assay by colorimeter 85% to 115%
Packaging commodity: type I glass vial, West Co.1888 gray stopper, West Co.
flip-off aluminum seals.

Cidofovir Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
75.00	mg	1	Cidofovir	75.00	g
QS	mL	2	Sodium hydroxide for pH adjustment	QS	
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: Fill 5 mL per vial; adjust pH to 7.4 with item 2.

Cimetidine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Cimetidine	100.00	g
QS	mL	2	Hydrochloric acid, reagent-grade bottles[a]	QS	mL
QS	mL	3	Water for injection, BP	QS to 1.00	L

[a] Sufficient to protonate 95 to 97.5% of cimetidine. Fill 2 mL.

Manufacturing Directions

1. Item 1 is only slightly soluble in item 3 but yields a highly soluble protonated ion.
2. Adjust pH to 5.1 to 6.2. The solution should be clear, colorless, and particle free, with no noticeable odor but a mercaptan-like color.
3. Sterilize the ampoule at 121°C for 30 minutes.
4. Determine item 1 content by HPLC method.
5. Determine cimetidine impurities TLC: corresponds to raw material plus moderate spot Compound II and traces spot Compound I and spot at *Rf* 0.09. TLC loaded at 1000 mg to trace small impurities. Trace spots.

Cimetidine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150.00	mg	1	Cimetidine hydrochloride equivalent to cimetidine	150.00	g
10.00	mg	2	Phenol	10.00	g
QS	mL	3	Sodium hydroxide for pH adjustment		
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.8 to 6.0 with item 3. Fill 50 mL for premixed in plastic container.

Ciprofloxacin Hydrochloride Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.00	mg	1	Ciprofloxacin base as ciprofloxacin hydrochloride	3.50	g
0.06	mg	2	Benzalkonium chloride	0.06	g
QS	mg	3	Sodium acetate	QS	
QS	mg	4	Acetic acid	QS	
46.00	mg	5	Mannitol	46.00	g
0.50	mg	6	Disodium edetate	0.50	g
QS	mL	7	Sodium hydroxide for pH adjustment	QS	
QS	mL	8	Hydrochloric acid for pH adjustment	QS	
QS	mL	9	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 4.5; ointment contains 3.3 mg of ciprofloxacin hydrochloride in mineral oil/white petrolatum.

Ciprofloxacin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Ciprofloxacin	10.00	g
1.00	M	2	Lactic acid	1.00	M
50.00	mg	3	Dextrose anhydrous, USP	50.00	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.3 to 3.9 with item 4 in vials and 3.5 to 4.6 in infusion solutions.

Cisplatin Diaminedichloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.33	mg	1	Cisplatin (II) diaminedichloride	1.33	g
6.00	mg	2	Sodium chloride, USP	6.00	g
QS	mL	3	Hydrochloric acid (1 N) for pH adjustment	QS	
0.00214	mL	4	Isopropyl alcohol	214.00	mL
1.40	mg	5	Mannitol, USP	1.40	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: For higher label amount of active, substitute appropriate amounts (25 or 50 mg).

Manufacturing Directions

1. In 90% of item 6, deaerated by bubbling in of N_2, dissolve item 2 under agitation.
2. Heat the resulting solution to 40°C to 45°C and dissolve item 1 under bubbling N_2 gas and vigorous agitation. Perform this operation protected from light. In the subsequent processing, also keep the solution protected from light.
3. Slowly cool the solution to 28°C to 30°C and dissolve item 5.
4. Check and adjust the pH of the solution to 3.5 with item 3.
5. Under agitation, add item 4 and make up to the final volume.
6. Aseptically filter the solution through a membrane filter of pore size 0.22 mm.
7. Aseptically dispense the solution into colorless, sterile glass filters, type I, capacity 20 mL, to a volume of 7.5 mL/vial.
8. Freeze the vials at -45°C.
9. Proceed to freeze-drying, heating the shelves of the freeze-dryer system to 4°C. Limit the time employed for the final drying of the product at 25°C to 30°C (preferably 30°C) to 3 to 6 hours, and preferably 4 hours.
10. Stopper the freeze-dried vials with sterile stoppers made of elastomeric material, preferably halobutylic rubbery material (a mixture in chlorobutyl rubber type PH 21/50, manufactured by Pharmagummi), and seal with sterile aluminum caps. The freeze-drying time (excluding freezing time) should be 18 hours.

Cisplatin with 2,2′-Dithio-*bis*-Ethane Sulfonate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.90	mg	1	Cisplatin	0.90	g
14.30	mg	2	2,2′-Dithio-*bis*-ethane sulfonate	14.30	g
0.90	%	3	Sodium chloride, USP	0.90	%
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable container, dissolve item 3 in item 5 to yield a 0.9% solution.
2. Check and adjust pH to 2.0 to 6.0 with item 4.
3. Add and dissolve item 3 with fast agitation (1500–2500 rpm) at room temperature for 60 to 90 minutes.
4. Add portion by portion of item 2, agitating to dissolve completely.
5. Check and adjust pH as in step 2.
6. Filter through a 0.22-μm membrane filter aseptically into type I glass vials.

Cladribine Injection Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Cladribine	1.00	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mg	3	Phosphoric acid for pH adjustment	QS	
QS	mg	4	Sodium phosphate dibasic for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL into flint single-use vials; adjust pH to 5.5 to 8.0 with item 3 or 4.

Clarithromycin Injection

Bill of Materials (Batch Size 10.4 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Clarithromycin (approved excess range 0–3%)	520.00	g
QS	mL	2	Water for injection	QS to 10.40	L
QS	—	3	Nitrogen gas, NF	QS	—
QS	mL	4	Lactobionic acid 12% w/v solution[a]	QS	L
QS	mL	5	Sodium hydroxide 1 N solution	QS	mL

[a] Preparation shown in the next table.

Lactobionic Acid (12% w/v Solution)

Bill of Materials (Batch Size 430 L)					
Scale/mL		Item	Material	Qty	UOM
120.00	mg	6	Lactobionic acid	51.660	kg
QS	mL	7	Water for injection	QS to 430.00	L

Manufacturing Directions

1. Sterilization of vials and stoppers. Sterilize the empty vials by dry heat by using a standard nominal cycle of 225°C for 270 minutes. Sterilize the lyophilization stoppers in an autoclave at 121°C for 60 minutes, followed by vacuum drying for 90 minutes.
2. Preparation of lactobionic acid solution.
   a. Transfer an appropriate volume of item 7 into a clean stainless steel tank.
   b. Add item 6 and mix to give a clear solution. Bring to volume with item 7.
   c. Filter through a 0.22-μm filter into sterilized vessels. Sample.
   d. Store solution between 2°C and 8°C. Use within 90 days.
3. Preparation of process solution.
   a. Transfer appropriate volume of item 2 into a clean stainless steel tank. Cool to 0°C to 10°C.
   b. Mix item 1, stirring slowly for 15 minutes.
   c. Add item 4 solution cautiously so the pH does not fall to less than 4.8 at any time during the addition. Stir until the solution is clear.
   d. Check pH and adjust to 5.3 (range 5.0–5.6) with either item 4 or 5. Add item 2 to volume.
   e. Filter the clarithromycin solution through a 0.22-μm or smaller pore-size filter into a clean storage container. Sample.
   f. Maintain solution at (2–15°C) until ready for filling.
4. Sterile filtration and filling.
   a. Connect storage container to sterilized 0.22-μm or smaller pore-size filter. Test filter integrity.
   b. Fill surge bottle with sterile-filtered solution and start filling. If the assay of the solution is outside action limits, calculate the fill volume to be delivered into each vial.
   c. Perform final filter integrity test.
   d. Apply lyophilization stoppers to filled vials and place on lyophilizer trays.
5. Lyophilization.
   a. Transfer trays to lyophilizer.
   b. Freeze product to -25°C or lower.
   c. Cool condenser to -40°C or lower.
   d. Reduce chamber pressure to 200 to 600 mm Hg.
   e. Raise shelf to 15°C to 25°C.
   f. After sublimation of ice, raise shelf to 40°C to 50°C and reduce chamber pressure to minimum.
   g. When lyophilization cycle is complete, release vacuum with filtered N_2.
   h. Collapse the shelves to stopper the vials.
   i. Apply over seals. Sample.

Clindamycin Injection in 5% Dextrose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
300.00	mg	1	Clindamycin phosphate equivalent	300.00	g
50.00	mg	2	Dextrose anhydrous, USP	50.00	g
0.04	mg	3	Disodium edetate	0.04	g
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Use 600 or 900 mg of item 1 for other concentrations.

Clindamycin Phosphate Injection 150 mg/mL (4 mL in 5-mL Vial, 600 mg; 6-mL in 10-mL vial, 900 mg)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150.00	mg	1	Clindamycin base, use clindamycin phosphate, USP, 5% excess	157.50[a]	g
0.50	mg	2	Disodium edetate anhydrous, use disodium edetate, USP (dihydrate)	0.554	g
9.45	mg	3	Benzyl alcohol, NF	9.45	g
QS	mg	4	Sodium hydroxide, reagent-grade pellets[b]	QS	mL
QS	mL	5	Hydrochloric acid, reagent-grade bottles[b]	QS	mL
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] This value is multiplied by an appropriate lot-specific factor, which accounts for the phosphate moiety and bulk drug potency.
[b] Used for pH adjustment.

Manufacturing Directions

Note: The solution must be prepared in glass-lined or a 316 or higher temper-grade stainless steel tank.

Allow adequate time for ingredient's dissolution between each drug or excipient step.

1. Preparation.
   a. Collect ca. 45% of the batch size of item 6 in a stainless steel tank.
   b. With mixing, add item 3 and mix until solution is uniform.
   c. Add and dissolve item 2. Mix until ingredient is dissolved and solution is uniform.
   d. Slowly add ca. 20% of the total item 1 to the solution with continued mixing. Mix for not less than 15 minutes. Maintain a minimal vortex.
   e. Slowly add one-half of the sodium hydroxide slurry to the solution. *Note*: Prepare sodium hydroxide slurry by dissolving 11 g of item 4 per liter of total batch size in a volume of item 6 equal to 5% of the total batch size.
   f. Add slowly ca. 25% of the remaining total item 1 to the solution with mixing. Mix for not less than 10 minutes before proceeding.
   g. Slowly add the remaining volume of the sodium hydroxide slurry from step 1e to the solution.
   h. Slowly add the remaining item 1 to the solution with mixing. Mix for not less than 30 minutes and until all ingredients are dissolved and solution is uniform. Make sure any ingredients that have accumulated on the sides of the tank and mixing shaft are dissolved into the solution.
   i. Check pH. Adjust pH to 6.4 (range 6.2–6.6) with a 10% sodium hydroxide solution or 1:10 hydrochloric acid (see note). Mix thoroughly between pH samplings. *Note*: A 10% sodium hydroxide solution is made mixing 100 g of item 4 with sufficient item 6 to make 1 L. A 1:10 hydrochloric acid solution is prepared by mixing 100 mL of item 5 with sufficient item 6 to make 1 L.
   j. QS to final volume with item 6.
   k. Check pH. If necessary, readjust to 6.4 (range 6.2–6.6) with 10% sodium hydroxide solution or 1:10 hydrochloric acid solution, both from step 1.
   l. Filter the solution through a previously rinsed filtration setup, using an approved 0.45-μm or finer membrane filter with an approved prefilter into a stainless steel tank. Sample.
   m. Prepare for sterilization, a 0.22-μm or finer membrane filtration setup with a prefilter if needed.
2. Preparation of vials and stoppers. Use type I glass, treated, 13-mm 5-mL vials.
   a. Wash and dry vials and load in appropriate containers for sterilization.
   b. Sterilize by using dry heat to 200°C (–0°C, +50°C) glass temperature for 225 minutes (–0, +360 minutes).
   c. Leach stoppers by boiling for 10 minutes in deionized water. Wash stoppers by using rubber cycle. Dry in a fast dryer at 55°C. Sterilize in a steam autoclave at 121°C for 60 minutes.
   d. Fill. Sample.

Clonidine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.10	mg	1	Clonidine hydrochloride	0.10	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP,	QS to 1.00	L

Note: Adjust pH to 5 to 7 with item 3 or 4. Fill 10 mL; other concentrations include 1.0 mg or 5.0 mg of item 1.

Closantel Veterinary Injectable Solution (12–20 g/100 mL)

Formulation

I. Closantel, 12.0–20.0 g.
II. Kollidon 12 PF or Kollidon 17 PF [1], 9.0–12.0 g; sodium hydroxide, 50% in water, 2.5–3.0 g; propylene glycol [1], ca. 60 g.
III. Sodium bisulfite, 0.01–0.04 g; water for injectables, ca. 20 g.

Manufacturing Directions

Dissolve Closantel in solution II and add solution III. The sterilization can be done by heating (120°C, 20 minutes)

The function of Kollidon 12 PF or Kollidon 17 PF is to reduce strongly the local side effects (e.g., formation of edemas) and to increase the retention time in the tissue.

Coagulation Factor VIIa (Recombinant) for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
1.20[a]	mg	1	rFVIIa	1.20	g
5.84	mg	2	Sodium chloride	5.84	g
2.94	mg	3	Calcium chloride dihydrate	2.94	g
2.64	mg	4	Glycine	2.64	g
0.14	mg	5	Polysorbate 80	0.14	g
60.00	mg	6	Mannitol	60.00	g

[a] 60 KIU; reconstitute with water for injection.

Coagulation Factor IX (Recombinant) for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
500	IU	1	Coagulation factor IX	500,000	IU
10.00	mM	2	L-Histidine	10.00	mM
1.00	%	3	Sucrose	1.00	%
260.00	mM	4	Glycine	260.00	mM
0.005	%	5	Polysorbate 80	0.005	%
QS	mL		Water for injection, USP,	QS to 1.00	L

Note: Lyophilized product. After reconstitution gives above concentration.

Colistin Sulfate, Neomycin Sulfate, Thonzonium Bromide, and Hydrocortisone Acetate Otic Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.00	mg	1	Colistin base, use colistin sulfate equivalent	3.00	g
3.30	mg	2	Neomycin activity as sulfate	3.30	g
0.50	mg	3	Thonzonium bromide	0.50	g
10.00	mg	4	Hydrocortisone acetate	10.00	g
0.50	mg	5	Polysorbate 80	0.50	g
QS	mg	6	Sodium acetate for buffering	QS	
QS	mg	7	Acetic acid for buffering	QS	
0.02	mg	8	Thimerosal	0.02	g
QS	mL	9	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL into dropper bottle.

Conjugated Estrogens for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
Lyophilized Vial					
25.00	mg	1	Conjugated estrogens	25.00	g
200.00	mg	2	Lactose	200.00	g
0.20	mg	3	Simethicone	0.20	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
Reconstitution Solution (5 mL)					
20.00	mg	1	Benzyl alcohol	20.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Copper Sulfate Additive Injection (5-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
7.85	mg	1	Copper sulfate pentahydrate	7.85	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Copper Sulfate Additive Injection (10-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.57	mg	1	Copper sulfate pentahydrate	1.57	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Copper Sulfate Additive Injection (30-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.57	mg	1	Copper sulfate pentahydrate	1.57	g
0.90	%	2	Benzyl alcohol, NF	0.90	%
QS	mL	3	Water for injection, USP	QS to1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Sulfuric acid for pH adjustment	QS	

pH: 1.5 to 2.5
Assay by atomic absorption (85–115%) Packaging Commodity: type I glass vials, West Co. 1888 gray stoppers, West Co. flip-off aluminum seals.

Corticorelin Ovine Triflutate for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
0.10	mg	1	Corticorelin ovine (as the trifluoroacetate)	0.10	g
10.00	mg	2	Lactose	10.00	g
26.00	mg	3	Cysteine hydrochloride monohydrate	26.00	g

Cortisone Acetate Injectable Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Cortisone acetate	50.00	g
9.00	mg	2	Sodium chloride	9.00	g
4.00	mg	3	Polysorbate 80	4.00	g
5.00	mg	4	Carboxymethylcellulose 2910	5.00	g
9.00	mg	5	Benzyl alcohol	9.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill into 10-mL vials.

Cosyntropin for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
Lyophilized Vial					
0.25	mg	1	Cosyntropin	0.25	g
Reconstitution Solution					
9.00	mg	1	Sodium chloride	9.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Cromolyn Sodium Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Cromolyn sodium	4.00	g
1.00	mg	2	Disodium edetate	1.00	g
0.10	mg	3	Benzalkonium chloride	0.10	g
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 4.0 to 7.0 with item 4 or 5. Fill into 10-mL dropper bottles.

Crude Liver Extract Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Crude liver extract (concentrate 20 mg/mL) to give B12 activity of 2 mg (limit 1.8–4.0 mg/mL)	2.00	mg
5.00	mg	2	Phenol, USP, as preservative	5.00	g
QS	mL	3	Water for injection	QS to 1.00	L

Cyanocobalamin and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine HCl, USP	100.00	g
1.00	mg	2	Cyanocobalamin, USP	1.00	g
15.00	mg	3	Benzyl alcohol, NF	15.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Sodium hydroxide for pH adjustment	QS	

Cyanocobalamin, Choline, and Niacinamide Injection

Bill of Materials (Batch Size L)					
Scale/mL		Item	Material	Qty	UOM
300.00	mg	1	Cyanocobalamin, USP	300.00	mg
100.00	mg	2	Choline chloride	100.00	mg
50.00	mg	3	Niacinamide, USP	50.00	g
15.00	mg	4	Benzyl alcohol, NF	15.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Glacial acetic acid for buffering	QS	
QS	mL	7	Sodium acetate for buffering; see item 6	QS	

Cyanocobalamin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Cyanocobalamin, USP, 20% excess	1.00	g
0.010	mL	2	Benzyl alcohol, NF	10.00	mL
7.50	mg	3	Sodium chloride, NF	7.50	g
3.00	mg	4	Sodium dihydrogen phosphate	3.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS		6	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Use freshly boiled and cooled item 5, bubble item 6, and provide cover all the time.
2. Take 0.9 L of item 5 and dissolve items 1 to 4 in it, one at a time, and allowing complete dissolution.
3. Check pH 4.0 to 5.5; do not adjust pH.
4. Filter through a 0.45-μm prefilter and a 0.22-μm filter into a sterilized staging assembly.
5. Fill 10.0 mL into 10-mL amber type I vials presterilized (200°C for 4 h); use butyl or latex rubber stoppers previously disinfected and sterilized. Sterile-fill; do not autoclave.
6. Sample for complete testing.

Cyanocobalamin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.6294	mg	1	Glacial acetic acid, USP	629.40	g
QS	–	2	Nitrogen gas, NF	QS	–
2.25	mg	3	Sodium acetate trihydrate, USP	2.25	g
8.00	mg	4	Sodium chloride, USP	8.00	g
QS	mg	5	Sodium hydroxide, reagent-grade pellets	QS	mg
0.115	mg	6	Vitamin B_{12} cyanocobalamin, USP, 15% excess	115.00	mg
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: The product requires N_2 gas and light protection during solution preparation.

1. Preparation.
   a. Add item 7 to ca. 75% of the final volume into glass-lined light-protected tank. Bubble-filter N_2 into item 7 for 10 minutes.
   b. Add and dissolve items 4, 3, and 1 with mixing. Dissolve item 6 in approximately 25 mL of item 7 and add to other ingredients.
   c. Check and adjust pH to 5 (range 4.5–5) with 0.1 N acetic acid solution or 0.1 N sodium hydroxide solution.
   d. QS with item 7 to final volume. Sample.
   e. Sterilize a 0.2- or 0.22-μm membrane filter with an approved prefilter.
   f. Filter the solution through the sterilized filter unit into a sterile glass-lined holding container.
2. Preparation of ampoules. Wash and dry type 1, 1-mL sulfur-treated ampoules and sterilize by using dry heat at 245°C for at least 3 hours and 25 minutes to assure sterile, pyrogen-free bottles.
3. Filling.
   a. Connect bulk solution container with an aseptic technique to the filling machine.
   b. Aseptically fill solution into each clean, sterile ampoule.
   c. Flush headspace of each ampoule with sterile-filtered N_2 and immediately seal.

Cyanocobalamin Injection for Veterinary Use

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00[a]	μg	1	Cyanocobalamin, USP	100.00[a]	mg
9.00	mg	2	Sodium chloride, USP	9.00	g
1.50	%	3	Benzyl alcohol, NF	1.50	%
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Acetic acid for buffering	QS	mL
QS	mL	6	Sodium acetate for buffering	QS	mL

[a] Adjust according to required strength; 1000, 3000, and 5000 μg for veterinary use.

Cyanocobalamin Repository Injection (1000 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1000.00	μg	1	Cyanocobalamin, USP	1000.00	mg
9.00	mg	2	Sodium chloride, USP	9.00	g
1.50	%	3	Benzyl alcohol, NF	1.50	%
4.00	%	4	Gelatin, USP	4.00	%
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Acetic acid for buffering	QS	mL
QS	mL	7	Sodium acetate for buffering; see item 6	QS	mL

Cyanocobalamin, Pyridoxine, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
33.33	mg	1	Thiamine HCl, 20% excess[a]	40.00	g
33.33	mg	2	Pyridoxine HCl, 20% excess[b]	40.00	g
0.33	mg	3	Cyanocobalamin crystalline,[c] 40% excess	0.47	g
10.00	mg	4	Benzyl alcohol	10.00	g
QS	mg	5	Sodium hydroxide[d]	QS	mg
QS	mL	6	Hydrochloric acid, 1 N	QS	mL
QS	mL	7	Water for injection,	QS to 1.00	L
QS	–	8	Nitrogen gas	QS	–

[a] Quantity of thiamine HCl $= 40 \times \frac{(100)}{100-\%\ \text{moisture}} \times \frac{(100)}{\%\ \text{Assay on dry basis}}\text{g}$

[b] Quantity of pyridoxine HCl $= 40 \times \frac{(100)}{100-\%\ \text{moisture}} \times \frac{(100)}{\%\ \text{Assay on dry basis}}\text{g}$

[c] Quantity of cyanocobalamin $= 0.47 \times \frac{(100)}{100-\%\ \text{moisture}} \times \frac{(100)}{\%\ \text{Assay on dry basis}}\text{g}$

[d] For pH adjustment, make 10% sodium hydroxide solution.

Manufacturing Directions

1. Check item 7 to be used for solution preparation and verify that it meets conductivity (NMT 1.0 mS/cm) and pH (5.0–7.0).
2. Put 900 mL of item 7 into the preparation vessel and bubble N_2 gas to expel dissolved oxygen (O_2% Limit = NMT 1).
3. Add and dissolve item 4 into step 2 preparation vessel. Mix well with stirring to make clear solution. Then dissolve items 1 and 2 and make clear solution.
4. Put 9 mL of item 7 into flask, slowly add item 3, and make slurry of item 3.
5. Transfer item 3 slurry from step 4 to the solution, rinse the flask 2 or 3 times with item 7, and transfer to the above solution. Mix well till it becomes clear solution.
6. Check pH (range 3.5–4.0). Adjust pH if necessary with 10% NaOH solution or 1 N HCl solution.
7. After adjustment of the pH, make up volume to 1 L by adding item 7 and mix while bubbling N_2 gas until O_2% is less than 1. Check final pH (range 3.5–4.0). Sample.
8. Clean and sterilize filtration assembly before starting the primary filtration. Check the integrity of filter cartridge by the bubble point test.
9. Transfer the solution from the preparation vessel to mobile vessel through filtration assembly containing 0.45-μm filter cartridge.
10. Sterilize the ampoules by dry heat.
11. Before starting the final filtration, check the integrity of filter cartridge by the bubble point test.
12. Aseptically connect the N_2 line through sterile N_2 filter to the inlet of mobile vessel. Check the validity of N_2 filter.
13. Aseptically connect one end of previously sterilized filtration assembly with 0.22-μm pore-size filtration cartridge to the outlet of mobile vessel and other end to buffer holding tank on the ampoules filling machine parts. Filter the solution.
14. Fill solution from the bulk into each sterile dry clean ampoule and seal it. Perform the leak test.

Cyanocobalamin, Pyridoxine, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine HCl, USP	100.00	g
100.00	mg	2	Pyridoxine HCl, USP	100.00	g
1000.00	mg	3	Cyanocobalamin, USP	1000.00	mg
15.00	mg	4	Benzyl alcohol, NF	15.00	mg
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	

Cyanocobalamin, Pyridoxine, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
33.00	mg	1	Thiamine hydrochloride, USP (B_1), 15% excess	38.00	g
33.00	mg	2	Pyridoxine (B_6), 12% excess	36.97	g
0.333	mg	3	Cyanocobalamin (B_{12}), 45% excess	0.45	g
1.80	mg	4	Methyl paraben sodium	1.80	g
0.20	mg	5	Propyl paraben sodium	0.20	g
4.80	mg	6	Disodium hydrogen phosphate	4.80	g
1.00	mg	7	Disodium edetate	1.00	g
0.015	mL	8	Thioglycerol	1.50	mL
0.10	mg	9	Ferric chloride	0.10	g
QS	mL	10	Water for injection, USP	QS to 1.00	L
QS		11	Nitrogen gas, NF	QS	
QS	mL	12	Hydrochloric acid for pH adjustment	QS	
QS	mL	13	Sodium hydroxide for pH adjustment	QS	

Manufacturing Directions

1. Vitamin formulations are highly prone to degradation and are affected by exposure to light and air. As a general rule, these must be manufactured protecting them from light and providing continuous N_2 (or in some cases CO_2) cover.
2. Use freshly distilled and freshly autoclaved (121°C for 30 minutes) item 10; bubble item 11 for 20 minutes.
3. Add and dissolve items 4 and 5 in item 10 at 70°C; allow to cool.
4. Add items 6, 7, and 8 and stir to dissolve.
5. Add 1, 2, 3 to step 4, one at a time, and with complete solution stirring.
6. Check pH to 3.8 to 4.0; adjust pH with item 12 or 13.
7. Filter aseptically through a 0.45-μm prefilter and a 0.22-μm membrane filter into a staging sterilized vessel.
8. Fill into sterilized (200°C for 4 hours) amber type I glass ampoule using pre- and post-item 11 flushing.
9. Sample for complete testing.

Cyanocobalamin, Pyridoxine, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
33.30	mg	1	Thiamine HCl, USP, ampoule grade, 20% excess	40.00	g
33.30	mg	2	Pyridoxine HCl, 20% excess	40.00	g
0.16	mg	3	Sodium formaldehyde sulfoxylate, NF	0.16	g
0.333	mg	4	Vitamin B_{12} (cyanocobalamin, USP), 40% excess	0.467	g
QS		5	Nitrogen gas, NF	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: The solution must be prepared in glass-lined or 316 stainless steel tank cleaned according to approved plant BOPs. Use N_2 protection throughout.

1. Preparation of solution.
   a. Heat 800 mL water for injection to boiling.
   b. Add and dissolve thiamine HCl, pyridoxine HCl, and sodium formaldehyde sulfoxylate.
   c. Boil solution slowly for 15 minutes.
   d. Dissolve vitamin B_{12} in a small quantity of N_2-saturated water for injection and add to the thiamine–pyridoxine solution from step d.
   e. Make up to 1 L with N_2-saturated water for injection.
   f. Adjust pH to 3.8 to 4.2 with freshly prepared 10 N sodium hydroxide solution.
   g. Filter solution through a previously rinsed filter using an approved 0.45-μm membrane and an approved prefilter.
   h. Sample for testing.
   i. Prepare a sterile 0.22-μm membrane filtration setup for the filling line.
2. Preparation of ampoules. Use type I 3-mL glass ampoules.
   a. Wash and dry ampoules and load into appropriate containers for sterilization.
   b. Sterilize using dry heat at 200°C glass temperature for 225 minutes or equivalent cycle.
3. Filling. *Caution*: Careful protection with N_2 is essential for stability.
   a. Aseptically connect tank and sterile-filter setup. Fill specified amount into each clean, dry sterile ampoule.
   b. Flush with sterile-filtered N_2 and seal.
   c. Inspect. Sample for testing.

Cyclosporine Ampoules for Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Cyclosporine, USP	10.00	g
130.00	mg	2	Polyoxyethylated castor oil (Cremophor® EL)	130.00	g
32.90	%	3	Alcohol, USP (by volume)	32.90	%
QS		4	Nitrogen gas, NF	QS	

***Note*: This solution can be further diluted with 0.9% sodium chloride, USP, or 5% dextrose injection, USP.**

Manufacturing Directions

1. Dissolve item 1 in item 2 in a suitable vessel. Provide item 4 cover throughout the process.
2. Add item 2 gradually and mix thoroughly.
3. Bring to volume with item 3; note that this is by volume preparation.
4. Filter through a prefilter of 0.45- and a 0.22-μm filter.
5. Fill 5 mL into each ampoule and sterilize.

Cytarabine Liposome Injection for Intrathecal Use (50 mg/5 mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Cytarabine	10.00	g
4.10	mg	2	Cholesterol	4.10	g
1.20	mg	3	Triolein	1.20	g
5.70	mg	4	Dioleoyphosphatidylcholine (DOPC)	5.70	g
1.00	mg	5	Dipalmitophosphatidylglycerol (DPPG)	1.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
0.90	%	7	Sodium chloride, USP	90.00	g
QS	mL	8	Hydrochloric acid for pH adjustment	QS	
QS	mL	9	Sodium hydroxide for pH adjustment	QS	
QS	ft^3	10	Nitrogen gas, NF		

Manufacturing Directions

1. This is a liposomal preparation, a suspension of cytabarine in normal saline. Do all manufacturing under item 10 cover.
2. Add and mix items 2 to 5 in a suitable vessel under item 10 cover. Add sufficient item 6 to make a fine dispersion.
3. Add fine cytarabine to step 2 and homogenize into liposomal structure.
4. Add item 7 and mix well.
5. Check and adjust pH (5.5–8.5).
6. Aseptically fill into 5-mL vial (for intrathecal use only).

Cytomegalovirus Immune Globulin IV (Human)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Immunoglobulin (IgG, traces of IgA and IgM)	40–60	g
50.00	mg	2	Sucrose, NF	50.00	g
10.00	mg	3	Albumin, NF	10.00	g
0.02–0.30	mEq	4	Sodium chloride	20–30	mEq
QS		5	Nitrogen gas, NF	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Item 1 is treated by a solvent–detergent inactivation process to remove viral load.

Manufacturing Directions

1. Place adequate quantity of item 6 into a suitable vessel purged with item 5 for at least 20 minutes.
2. Add item 2 and mix well. Add item 4 and mix well (calculate equivalent amounts)
3. While stirring, add item 1 slowly to avoid foaming. Keep covered with item 5.
4. Filter through appropriate filter system and fill 10 or 50 mL into each vial aseptically.

Dacarbazine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Dacarbazine	100.00	g
6.00	mg	2	Citric acid anhydrous	6.00	g
5.00	mg	3	Mannitol	5.00	g
QS		4	Nitrogen gas, NF	QS	
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: This is a light-sensitive product. Protect from light and provide N_2 cover throughout. The lyophilized powder is administered intravenously after reconstitution.

1. Add and dissolve items 2 and 3 in item 7 with item 4 cover.
2. Check and adjust pH to 3 to 4.
3. Add item 1 and dissolve.
4. Filter and fill either 1 or 2 mL and lyophilize.

Daclizumab for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Daclizumab	5.00	g
3.60	mg	2	Sodium phosphate monobasic monohydrate	3.60	g
11.00	mg	3	Sodium phosphate dibasic heptahydrate	11.00	g
4.60	mg	4	Sodium chloride, USP	4.60	g
0.20	mg	5	Polysorbate 80 (Tween®)	0.20	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Sodium hydroxide for pH adjustment	QS	
QS	mL	8	Hydrochloric acid for pH adjustment	QS	
QS	ft^3	9	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Put approximately 0.8 L of item 6 into a suitable vessel; purge with item 9 for 20 minutes.
2. Add and dissolve items 2 and 3.
3. Add item 4 and dissolve to complete solution.
4. Add item 5 slowly to avoid frothing and mix well; do not overstir.
5. Add item 1 and stir to dissolve.
6. Check and adjust pH 6.9 (6.7–7.0)
7. Filter product and fill vials aseptically.

Dactinomycin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	mg	1	Dactinomycin	0.50	g
20.00	mg	2	Mannitol	20.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: To be used after reconstitution for IV or regional perfusion.

Manufacturing Directions

1. Place a suitable quantity of item 3 into a suitable vessel.
2. Add and dissolve item 2.
3. Add item 1 and dissolve.
4. Filter product and fill vials.
5. Lyophilize.

Dalteparin Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
64.00	mg	1	Dalteparin sodium (10000 antifactor Xa IU/mL)	64.00	g
0.90	%	2	Sodium chloride, NF	90.00[a]	mg
14.00	mL	3	Benzyl alcohol, NF[b]	14.00	g
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] Adjust for content of sodium to isotonic. Dalteparin sodium is produced through controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosa followed by a chromatographic purification process. It is composed of strongly acidic sulfated polysaccharide chains (oligosaccharide, containing 2,5-anhydro-D-mannitol residues as end groups) with an average molecular weight of 5000 and approximately 90% of the material within the range 2000 to 9000. It is a low-molecular-weight heparin. It is available in two presentations: prefilled syringe and multiple-dose vial.
[b] Added only in multiple-dose vials.

Manufacturing Directions

1. Take appropriate quantity of item 6 and dissolve item 2 (calculate amount) and item 1 in it. (Optionally, add item 3 for multiple-dose vials.)
2. Check and adjust pH to 5.0 to 7.5 with item 4 or 5.
3. Bring to volume.
4. Filter and fill 0.1 mL (2500 IU) or 0.2 mL (5000 IU) into syringes or 9.5 mL into vial (95000 IU) aseptically.

Danaparoid Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1,250	U	1	Danaparoid sodium (anti-Xa units)	1250,000	U
0.15	%	2	Sodium sulfite	0.15	%
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	ft^3	6	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Place appropriate amount of item 5 into a stainless steel vessel and purge with item 6.
2. Add and dissolve item 2 under cover of item 6.
3. Add item 1 and dissolve completely.
4. Check and adjust pH to 7.0 (range 6.9–7.1).
5. Filter and fill aseptically into syringes (0.6 mL) or ampoule (0.6 mL); each unit containing 750 anti-Xa units.

Dantrolene Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.281	mg	1	Dantrolene sodium	0.281	g
42.85	mg	2	Mannitol	42.85	g
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	ft^3	4	Nitrogen gas, NF	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add sufficient quantity of item 5 to a stainless steel tank. Purge with item 4 for not less than 20 minutes.
2. Add and dissolve item 2.
3. Add item 1 and stir to dissolve.
4. Check and adjust pH with item 3 to 9.5 (range 9.4–9.6).
5. Filter and fill 70 mL (to give 20 mg of dantrolene sodium and 3000 g of mannitol) into each vial and lyophilize.

Dapiprazole Hydrochloride Ophthalmic Solution (0.5%)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Dapiprazole hydrochloride	5.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add item 1 to item 2 and dissolve.
2. Fill 5 mL into 10-mL vials and lyophilize.
3. Dispense with 5-mL diluent (water for injection) and a dropper for dispensing.

Daunorubicin HCl Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Daunorubicin, use daunorubicin hydrochloride	5.35	g
25.00	mg	2	Mannitol, USP	25.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	ft^3	4	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Add and dissolve item 2 to appropriate quantity of item 3 under cover of item 4.
2. Add and dissolve item 1.
3. Filter and fill 4 mL into 5-mL vials (equivalent to 20 mg of daunorubicin and 100 mg of mannitol) and lyophilize.
4. Dispense with water for injection for reconstitution (4 mL) to give activity of 5 mg daunorubicin/mL.

Daunorubicin Citrate Liposome Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Daunorubicin base, use daunorubicin citrate	2.72	g
28.16	mg	2	Distearoylphosphatidylcholine	28.16	g
6.72	mg	3	Cholesterol	6.72	g
85.00	mg	4	Sucrose, NF	85.00	g
18.80	mg	5	Glycine	18.80	g
0.28	mg	6	Calcium chloride dihydrate	0.28	g
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	mL	8	Sodium hydroxide for pH adjustment	QS	
QS	mL	9	Hydrochloric acid for pH adjustment	QS	
QS	ft^3	10	Nitrogen gas, NF	QS	

Manufacturing Directions

1. To 0.9 L of item 7 in a suitable stainless steel vessel, purge item 10 for 20 minutes.
2. Add items 4, 5, and 6; stir to dissolve.
3. Check and adjust pH with item 8 or 9 to between 4.9 and 6.0.
4. In a separate container, add items 2 and 3 and mix rapidly.
5. Add item 1 and homogenize.
6. Add the lipid solution to the aqueous phase with rapid mixing.
7. Check and adjust pH again to 4.9 to 6.0.
8. Filter and fill 25 mL in each vial.

The lipid to drug weight ratio is 18.7:1 (total lipid:base), equivalent to a 10:5:1 molar ratio of distearoylphosphatidylcholine:cholesterol:daunorubicin. Each vial (25 mL) contains daunorubicin citrate equivalent to 50 mg of daunorubicin base, encapsulated in liposomes consisting of 704 mg distearoylphosphatidylcholine and 168 mg cholesterol. The liposomes encapsulating daunorubicin are dispersed in an aqueous medium containing 2125 mg sucrose, 94 mg glycine, and 7 mg calcium chloride dihydrate in a total volume of 25 mL.

Desmopressin Acetate Injection (Intranasal)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00	μg	1	Desmopressin acetate	4.00	mg
9.00	mg	2	Sodium chloride	9.00	mg
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: For multidose vial (10-mL fill) or for intranasal drops, use, additionally, chlorobutanol 5.0 mg/mL. Adjust pH to 4.0 with item 3.

Dexamethasone Acetate Suspension Injection: Dexamethasone Acetate (8 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
8.00	mg	1	Dexamethasone acetate equivalent to dexamethasone	8.00	g
1.00	mg	2	Sodium bisulfite, USP	1.00	g
0.75	mg	3	Sodium chloride, USP	0.75	g
5.00	mg	4	Carboxymethylcellulose sodium, USP	5.00	g
5.00	mg	5	Creatinine	5.00	g
0.50	mg	6	Disodium edetate	0.50	g
0.90	%	7	Benzyl alcohol, NF	0.90	%
QS	mL	8	Water for injection	QS to 1.00	L

Dexamethasone Acetate/Sodium Phosphate Suspension (8/2 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
8.00	mg	1	Dexamethasone acetate	8.00	g
2.00	mg	2	Dexamethasone sodium phosphate, USP	2.00	g
0.75	mg	3	Polysorbate 80, USP	0.75	g
6.67	mg	4	Sodium chloride, USP	6.67	g
5.00	mg	5	Carboxymethylcellulose sodium, USP	5.00	g
0.50	mg	6	Disodium edetate	0.50	g
1.00	mg	7	Sodium bisulfite, USP	1.00	g
5.00	mg	8	Creatinine	5.00	g
0.90	%	9	Benzyl alcohol, NF	0.90	%
QS	mL	10	Water for injection, USP	QS to 1.00	L
QS	mL	11	Acetic acid for buffering	QS	mL
QS	mL	12	Sodium acetate for buffering	QS	mL

Dexamethasone Sodium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
24.00	mg	1	Dexamethasone sodium phosphate, USP, equivalent to dexamethasone phosphate	24.00	g
10.00	mg	2	Sodium citrate, USP	10.00	g
1.00	mg	3	Sodium bisulfite, USP	1.00	
1.50	mg	4	Methyl paraben, USP	1.50	g
0.20	mg	5	Propyl paraben, USP	0.20	g
8.00	mg	6	Creatinine	8.00	g
0.50	mg	7	Disodium edetate	0.50	g
QS	mL	8	Water for injection, USP	QS to 1.00	L
QS	mL	9	Sodium hydroxide for pH adjustment	QS	mL

Dexamethasone Sodium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	Dexamethasone phosphate, use dexamethasone sodium phosphate, USP	4.40	g
8.00	mg	2	Creatinine	8.00	g
10.00	mg	3	Sodium citrate, USP, dihydrate powder	10.00	g
1.00	mg	4	Sodium metabisulfite, NF	1.00	g
1.50	mg	5	Methyl paraben, NF (Aseptoform M) powder	1.50	g
0.20	mg	6	Propyl paraben, NF (Aseptoform P) powder	0.20	g
QS	mg	7	Sodium hydroxide[a]	QS	mg
QS	mL	8	Water for injection, USP	QS to 1.00	L
QS		9	Nitrogen gas, NF	QS	—

[a] Use for pH adjustment only.

Manufacturing Directions

1. Preparation of solution. *Note*: Use N_2 protection throughout process.
   a. Heat 80% of final volume of item 8 to boiling.
   b. Dissolve items 5 and 6 in step a with N_2 flushing.
   c. Discontinue heating and allow solution to cool to room temperature slowly while bubbling N_2 through solution.
   d. Add and dissolve items 1 to 4 in step c with continuous N_2 flushing.
   e. Check pH (range 7.0–8.5). Adjust pH to 8.0 if necessary, using freshly prepared 10% sodium hydroxide solution. Sample.
   f. QS to final volume with N_2-saturated item 8.
   g. Filter solution through a previously rinsed filtration setup, using a 0.45-μm or finer membrane and a prefilter.
   h. Prepare for the filling line a sterile 0.22-μm membrane filtration setup.
2. Preparation of ampoules. Use type I 1-mL glass ampoules. Wash and dry ampoules and sterilize by using dry heat at 200°C (–0, +50°C) glass temperature, for 225 minutes (–0, +360 minutes). This cycle or another cycle providing equivalent heat input may be used.
3. Filling. *Note*: Careful protection with N_2 is essential for stability.
   a. Aseptically connect tank and sterile filter setup.
   b. Fill specified amount into each clean, dry sterile ampoule. Sample.
   c. Flush with sterile-filtered N_2 and seal. Sample.

Dexamethasone Injection, Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Dexamethasone, USP	2.00	g
1.80	mg	2	Methyl paraben, USP	1.80	g
0.20	mg	3	Propyl paraben, USP	0.20	g
0.18	mg	4	Benzyl alcohol, NF	0.18	g
0.05	mL	5	Ethyl alcohol, USP	0.05	g
50.00	%	6	Polyethylene glycol 400, USP	50.00	%
QS	mL	7	Water for injection	QS to 1.00	L

Dexamethasone Sodium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	Dexamethasone, as dexamethasone sodium phosphate	5.20	g
8.00	mg	2	Creatinine	8.00	g
10.00	mg	3	Sodium metabisulfite	10.00	g
1.00	mg	4	Disodium edetate	1.00	g
10.00	mg	5	Sodium citrate	10.00	g
0.18	%	6	Methyl paraben sodium	1.80	g
0.02	%	7	Propyl paraben sodium	0.20	g
0.02	mL	8	Propylene glycol	20.00	mL
QS	mL	9	Water for injection, USP	QS to 1.00	L
0.030	g	10	Sodium hydroxide, NF, for pH adjustment	3.00	g
QS		11	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Autoclave item 9 at 121°C for 30 minutes and use this throughout manufacture.
2. Heat 0.2 L of item 9 to 80°C and dissolve items 6 and 7 in it.
3. In a separate vessel, dissolve item 5 in 0.1 L of item 9.
4. In a separate vessel, dissolve items 3 and 4 in 0.1 L of item 9.
5. Add contents of steps 2 and 3 into step 1, mix thoroughly, and then add item 8 with mixing.
6. Add and dissolve item 10 in 0.4 L of item 9 and add to step 5.
7. Make up the volume to 0.99 L.
8. Filter the solution in step 6, using a presterilized assembly and a 0.45-μm prefilter and a 0.22-μm filter into a sterile vessel.
9. Autoclave solution in step 7 at 121°C for 20 minutes.
10. On cooling to room temperature, add items 1 and 2 to step 8 and mix.
11. Check pH and adjust to between 7.5 and 8.5 with 4 N presterilized sodium hydroxide solution.
12. Make up the volume to 1 L with item 9.
13. Filter through presterilized assembly, using a 0.45-μm prefilter and a 0.22-μm filter into a staging sterilized vessel.
14. Fill 2.1 mL into presterilized type I flint vials with pre- and postflush with item 11. Use neoprene rubber stoppers sterilized by autoclaving at 121°C for 20 minutes.
15. Fill under aseptic conditions.

Dexpanthenol, Niacinamide, Pyridoxine, Riboflavin, and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine hydrochloride, USP, ampoule powder 200 mesh, 45% excess	145.50	g
5.00	mg	2	Pyridoxine hydrochloride, USP, 5% excess	5.25	g
9.00	mg	3	Benzyl alcohol, NF, 5% manufacturing excess	9.45	g
0.875	mg	4	Sodium formaldehyde sulfoxylate, NF[a]	875.00	mg
75.00	mg	5	Niacinamide, USP, powder for ampoule, 20% excess	90.00	g
1.00	%	6	Charcoal activated, USP[b]	900.00	mg
2.00 2.740	mg mg	7	Riboflavin, use riboflavin-5'-phosphate sodium, USP, 15% excess[c]	3.15	g
5.00	mg	8	D-Pantothenyl alcohol (dexpanthenol, FCC), 10% excess	5.50	g
QS	—	9	Carbon dioxide gas, technical	QS	—
QS	mg	10	Hydrochloric acid, reagent-grade bottles[d]	QS	mL
QS	mL	11	Water for injection, USP	QS to 1.00	L

[a] Sodium formaldehyde sulfoxylate is calculated to be ca. 0.0092% concentration in volume during first aging.
[b] Charcoal is calculated at 1% w/w of niacinamide.
[c] Riboflavin-5′-phosphate sodium is calculated at 73% riboflavin.
[d] Used for pH adjustment only.

Manufacturing Directions

Note: Protect solution from light and oxidation. Sodium formaldehyde sulfoxylate precipitates out metallic impurities and also acts as an antioxidant.

1. Take a sample from the water for injection and verify that it has NMT 3.0 (iS conductivity) and pH 5.0 to 7.0.
2. Boil 1.5 L of item 11 for 5 minutes in a jacketed pressure vessel. Cool to ambient temperature with continuous bubbling of CO_2 gas, and continue purging the headspace with CO_2 until the water has been used in manufacture.
3. Transfer 250 mL of the CO_2-saturated water to a suitable glass or stainless steel vessel. Purge vessel with CO_2 for the remainder of the process.
4. To the water from step 3, add and dissolve items 1, 2, and 3.
5. Dissolve item 4 in 20 mL of CO_2-saturated item 11 and add to the solution in step 4.
6. Dissolve item 5 in 200 mL of CO_2-saturated water and add to step 5.
7. Dissolve item 7 in 125 mL of CO_2-saturated water and add to step 6. Rinse the container with two 10-mL portions of the CO_2-saturated water and add to the solution.
8. Dissolve item 8 in 25 mL of CO_2-saturated water, warmed to 30°C to 40°C, cool and add to step 7. Rinse the container with two 10-mL portions of the CO_2-saturated water and add to the solution.
9. Add item 6 and mix under CO_2 gas protection using a stirrer for 1 hour.
10. Filter solution through a previously rinsed prefilter assembly and recirculate for at least 30 minutes until solution is clear of charcoal. Filter into another glass-lined or 316 stainless steel tank.
11. Make up to a volume of 950 mL with CO_2-saturated water.
12. Check pH (range 3.3–3.7). Adjust the pH to 3.5, if necessary, with concentrated hydrochloric acid. Age for 2 days under CO_2 gas protection.
13. Check pH (range 3.3–3.7). Adjust the pH to 3.5, if necessary, with concentrated hydrochloric acid or 10 M sodium hydroxide solution.
14. Make up to 1 L with CO_2-saturated water. Sample.
15. Filter solution through a previously rinsed filtration setup using an approved 0.45-μm or finer membrane and an approved prefilter into a glass-lined or 316 stainless steel holding tank and seal under CO_2 protection. Perform the bubble point test on the membrane before and after filtration.
16. Prepare for sterilization an approved 0.22-μm membrane and prefilter.
17. Preparation of containers. Use type I 1-mL glass ampoules, washed and dried, if not sealed type, and sterilized using dry heat at 200°C (–0, +50°C). Maintain oven temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for duration of the cycle.
18. Connect tank, sterile filtration setup, and a sterile surge bottle by using aseptic technique.
19. Aseptically fill solution into each clean, dry sterile ampoule. Displace headspace air with sterile-filtered CO_2 gas and seal the ampoules. Sample.

Dexrazoxane for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Dexrazoxane	10.00	g
0.167	M	2	Sodium lactate	0.167	M
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable quantity of item 4, add and mix item 2.
2. Add and dissolve item 1.
3. Bring volume up to 0.98 L.
4. Check and adjust pH to 3.5 to 5.5 with item 3.
5. Make up volume.
6. Filter through 0.22-μm membrane filter and fill into vials (25 mL for a 250-mg dose and 50 mL for a 500-mg dose) to lyophilize.

Dextrose 25% Injection (Flexible Container)

Bill of Materials (Batch Size 102 L)					
Scale/mL		Item	Material	Qty	UOM
245.00 269.31 269.31	mg mg mg	1	Dextrose anhydrous, USP, or dextrose, USP, powder hydrous or dextrose monohydrate, BP, for parenteral use	25.00 27.47 27.47	kg kg kg
QS	mg	2	Carbon activated (Darco Powder G-60) or charcoal activated, USP	QS	g
QS	mL	3	Water for injection, BP	QS to 102.00	L

Note: Water is added to 102 L to allow for losses during storage. Use of carbon is optional.

Manufacturing Directions

1. Check that item 3 meets conductivity (NMT 3 μS) and pH (5–7) requirements. Note temperature. Add item 3 to tank to ca. 70% of final volume, dissolve item 1 with mixing, and add item 3 to make up final volume. Check pH (4.0–6.5). Sample.
2. Filter through carbon precoated Sparkler or Niagara prefilter or equivalent until clear; filter through 0.45-μm or finer filter. Test filters by the bubble point test.
3. Fill into clean containers. Sample.
4. Sterilize. Sample.

Dextrose Injection (5% and 10% LVP)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Dextrose anhydrous, USP, 5% excess	52.50	g
0.15	mg	2	Activated charcoal, NF	0.15	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: For 10% strength, increase the quantity of item 1 accordingly; other items remain the same.

Manufacturing Directions

1. Use freshly prepared item 3 stored for NMT 24 hours at 80°C. Add item 1 to item 3 at 60°C and mix for 15 minutes.
2. Add item 2 and mix vigorously for 15 minutes.
3. Filter the mixture in step 2 through a presterilized filter assembled suitable for retaining charcoal and to yield a clean solution.
4. Filter by using at least a 0.45-μm filter before final filtration with 0.22-μm filter and fill into 540 mL type I glass bottles.
5. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers prewashed and sterilized at 116°C for 30 minutes. Use triple aluminum seals and suitable plastic hangers.
6. Sterilize filled bottle by autoclaving at 121°C for 20 minutes. Do not exceed temperature by 3°C or time by 2 minutes either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.
7. Check pH of solution (4.0–4.3); before autoclaving, pH is 5.5 to 6.5.

Dextrose with Sodium Chloride Injection LVP

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Dextrose anhydrous, USP, 10% excess	55.00	g
9.00	mg	2	Sodium chloride, USP, 4% excess	9.33	g
0.50	mg	3	Activated charcoal, NF	500	mg
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Use freshly prepared item 3 stored NMT 24 hours at 80°C. Add item 1 to item 3 at 60°C and mix for 15 minutes.
2. Add items 2 and 3 and mix vigorously for 15 minutes.
3. Filter the mixture in step 2 through a presterilized filter assembled suitable for retaining charcoal and to yield a clean solution.
4. Filter using at least through a 0.45-μm filter before final filtration with 0.22-μm filter and fill into 540-mL type I glass bottles.
5. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers prewashed and sterilized at 116°C for 30 minutes; use triple aluminum seals and suitable plastic hangers.
6. Sterilize filled bottle by autoclaving at 121°C for 20 minutes; do not exceed temperature by 3°C or time by 2 minutes either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.
7. Check pH of solution (4.0–4.3); before autoclaving, pH is 5.5 to 6.5.

Diazepam Injectable Solution (2.5 mg/mL)

Formulation

1. Diazepam, 0.25 g; Solutol HS 15 [1], 4.00 g; lecithin, 4.00 g.
2. Water for injectables, add 100 mL; Preservative, QS.

Manufacturing

Heat mixture I to 60°C to 70°C, stir well, and add very slowly the hot solution II.

Diazepam Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Diazepam	5.00	g
100.00	mg	2	Ethyl ester, animal/vegetable fat	100.00	g
12.00	mg	3	Phospholipid from eggs	12.00	g
22.50	mg	4	Glycerol	22.50	g
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve item 1 in item 2.
2. Add item 3 to solution in step 1 and mix well.
3. In sufficient quantity of item 6, dissolve item 4.
4. Check and adjust pH of solution in step 3 to 7.0 to 10.5 with item 5.
5. Add solution of Step 4 into step 3 and mix rapidly. Pass through homogenizer to make emulsion.
6. Fill vials and sterilize by autoclaving at 120°C for 17 minutes.

Diazepam Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Diazepam	5.00	g
120.00	mg	2	Egg lecithin	120.00	g
80.00	mg	3	Sodium glycolate	80.00	g
30.00	mL	4	Alcohol, USP (evaporated in processing)	30.00	L
QS	ft^3	5	Nitrogen gas, NF	QS	
QS	mL	6	Phosphate buffer solution (pH 7) 1/15	QS to 1.00	L
12.00	mg	7	Sodium ascorbate	12.00	g

Manufacturing Directions

1. Dissolve items 1, 2, and 3 in item 4 in a flask.
2. Evaporate item 4 in rotary evaporator under vacuum at 35°C. This yields a lipid film in the flask.
3. Make up the volume with item 6, which had been purged with item 5 for 20 minutes in a separate vessel. The micelles are formed spontaneously at room temperature.
4. Add item 7 and dissolve.
5. Filter the solution aseptically into ampoules.

Diazepam Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Diazepam, USP	5.00	g
1.00	mg	2	Benzoic acid	1.00	g
100.00	mg	3	Alcohol absolute, USP	100.00	g
400.00	mg	4	Propylene glycol	400.00	g
49.00	mg	5	Sodium benzoate	49.00	g
15.00	mg	6	Benzyl alcohol	15.00	g
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	cy	8	Nitrogen gas, NF	QS	cy
QS	mL	9	Sodium hydroxide for pH adjustment	QS	mL
QS	mL	10	Hydrochloric acid for pH adjustment	QS	mL

Manufacturing Directions

Note: The following operations must be carried out under aseptic conditions. All containers and filters must be sterilized. The equipment that cannot be sterilized must be washed with 3% solution of benzyl alcohol and rinsed with sterilized water. Protect the solution from light. If directions are not followed strictly, diazepam may crystallize out.

1. Add item 2 and item 1 to item 3 previously heated to 30°C to 35°C and stir to complete solution.
2. Separately dissolve item 4 in item 6.
3. Separately dissolve item 5 in the first portion of item 7. Let item 8 bubble through the solution for 30 minutes and then filter.
4. Pool together solutions of steps 1 and 2. Cautiously add solution in step 3 with stirring.
5. Bring to volume with item 7. Mix and let item 8 bubble through the solution for 30 minutes.
6. Check and adjust pH to 6.5 to 7.2 with item 9 or 10.
7. Filter the solution through a 0.15-μm Sartorius filter and collect filtrate in a glass container.
8. Fill into ampoules under N_2 atmosphere through a 0.22-μm filter.

Diazepam Rectal Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	Diazepam, USP	4.00	g
1.00	mg	2	Benzoic acid	1.00	g
100.00	mg	3	Alcohol absolute, USP	100.00	g
400.00	mg	4	Propylene glycol	400.00	g
49.00	mg	5	Sodium benzoate	49.00	g
15.00	mg	6	Benzyl alcohol	15.00	g
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	cy	8	Nitrogen gas, NF	QS	cy
QS	mL	9	Sodium hydroxide for pH adjustment	QS	mL
QS	mL	10	Hydrochloric acid for pH adjustment	QS	mL

Manufacturing Directions

Note: The following operations must be carried out under aseptic conditions. All containers and filters must be sterilized. The equipment that cannot be sterilized must be washed with 3% solution of benzyl alcohol and rinsed with sterilized water. Protect the solution from light. If directions are not followed strictly, diazepam may crystallize out.

1. Add items 1 and 2 to item 3 previously heated to 30°C to 35°C and stir to complete solution.
2. Separately dissolve item 4 in item 6.
3. Separately dissolve item 5 in the first portion of item 7 and filter through 0.6-μm Millipore® filter.
4. Pool together solutions from steps 1 and 2 Cautiously add solution in step 3 with stirring.
5. Bring to volume with item 7.
6. Check and adjust pH to 6.5 to 7.2 with item 9 or 10.
7. Filter the solution through a 0.22-μm filter and collect filtrate in a glass container.
8. Fill into rectal tubes (2.9 mL fill volume; label 2.5 mL).

Dibenzazepine Carboxamide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	5H-dibenz(b,f)azepine-5-carboxamide	2.50	
47.50	mg	2	Glucose anhydrous for injection	47.50	g
QS	ft^3	3	Nitrogen gas, NF	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve item 1 under a blanket of item 3 in a suitable quantity of item 4 with stirring at 60°C to 80°C.
2. After cooling to room temperature, add item 2 and dissolve by stirring under item 3 purging.
3. Make up the volume.
4. Filter with a 0.22-μm membrane filter.
5. Fill into type I flint glass vials.
6. Sterilize by autoclaving at 121°C for 15 minutes.

Diclofenac Injectable Solution (75 mg/3 mL)

Formulation

Diclofenac sodium, 7.5 g; propylene glycol [1], 50.0 g; Kollidon 17 PF [1], 5.0 g; benzyl alcohol, 12.0 g; water for injectables, to 300 mL.

Manufacturing Directions

Dissolve Kollidon 17 PF in the mixture of propylene glycol, benzyl alcohol and water and add diclofenac sodium and stir until a clear solution is obtained.

The sterilization could be made by aseptic filtration (0.2 μm).

Diclofenac Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
75.00	mg	1	Diclofenac sodium	25.00	g
120.00	mg	2	Benzyl alcohol, NF	40.00	g
630.00	mg	3	Propylene glycol, USP	210.00	g
3.00	mg	4	Sodium metabisulphite	1.00	g
1.15	mg	5	Sodium hydroxide	383.33	mg
QS	mg	6	Sodium hydroxide[a]	QS	mg
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	–	8	Nitrogen, NF	QS	–

[a] For pH adjustment, if necessary, to be used as 0.1 N sodium hydroxide solution, freshly prepared in water for injection.

Manufacturing Directions

Note: N_2 gas protection must be used throughout process. The solution must be prepared in a glass-lined or a 316 or higher temper-grade steel tank.

1. Preparation of water.
   a. Obtain a sample from the water for injection source to be used for rinsing and mixing and verify that it meets conductivity limit of NMT 3.0 mS and pH range of 5 to 7.
   b. Test the rinse draining from the tank for conductivity and oxidizable substances prior to batch preparation.
2. Preparation of solution.
   a. Boil ca. 1.5 L item 7 for 5 minutes in a jacketed pressure vessel.
   b. Transfer 500 mL of the boiling item 7 from step 2a to a suitable 316 stainless steel container.
   c. Allow the remaining item 7 from step 2a to cool to ambient temperature while bubbling through filtered N_2 gas.
   d. Dissolve by stirring item 4 and item 5 into the hot 500 mL item 7 from step 2b.
   e. Transfer item 3 to a separate glass container; add and dissolve item 1 and item 2. Stir until completely dissolved.
   f. Add the solution from step 2e to the solution of step 2d. Mix well with stirring while bubbling through filtered N_2 gas.
   g. Check pH (range 8.0–9.0). Adjust pH if necessary with freshly prepared 0.1 N sodium hydroxide solution.
   h. Make up to 1 L with item 7 saturated with N_2 gas cooled to ambient temperature from step 2c.
   i. QC sample.
   j. Transfer the solution from step 2h to a stainless steel pressure vessel and seal under filtered N_2 gas protection until filtration.
   k. Filter solution from the stainless steel pressure vessel through a sterilized filtration setup fitted with an approved prefilter and an approved 0.22-μm membrane filter into a sterilized glass container. Bubble sterile-filtered N_2 gas through the filtered solution and seal under sterile-filtered N_2 gas protection. *Note*: Perform the bubble point test on a 0.22-μm membrane filter before and after filtration.
   l. Prepare for sterilization an approved 0.22-μm membrane filter fitted to filtration unit, approved 0.2-μm gas filter, surge bottle, tubing, and filling unit.
3. Preparation of ampoules. Use type I 3-mL amber glass ampoules, USP.
   a. Wash and dry the ampoules and then load into appropriate covered stainless steel trays for sterilization.
   b. Sterilize the ampoules by using dry heat at 200°C (–0°C, +50°C) ampoule temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for duration of cycle. *Note*: This cycle or a cycle providing equivalent heat input may be used.
   c. Transfer ampoules to the aseptic filling area.
   d. Filling. *Note*: Careful protection with sterile-filtered N_2 gas is essential for stability.
   e. Aseptically connect glass container containing the injection solution, sterile filtration setup, sterile surge bottle, N_2 gas filter, and filling unit.
   f. Filter the injection solution into the surge bottle and adjust flow rate through filter equal filling rate to prevent any surge on the filter.
   g. Flush ampoules with sterile-filtered N_2 gas before filling.
   h. Aseptically fill the solution into each clean, dry, sterile ampoule. Flush with sterile-filtered N_2 gas and heat seal. *Note*: Perform bubble point test on filters before and after filtration.
   i. Sample. Inspect ampoules.
   j. Sample.

Diclofenac–Lecithin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
7.50	mg	1	Diclofenac	7.50	g
1.00	mL	2	Methylene chloride	1.00	L
1.00	mg	3	Lecithin[a]	1.00	g

[a] The quantity may be varied 50% on each side of the listed amount.

Manufacturing Directions

1. Dissolve item 3 in item 2.
2. Filter through a 0.2-μm membrane filter.
3. Add item 1 (micronized to less than 20-μm size).
4. Homogenize or sonicate the suspension to deagglomerate the suspension.
5. Fill 10 mL into each vial (to contain 75 mg of item 1).
6. Remove item 2 under vacuum to leave in the vial a lecithin-coated powder of item 1.
7. Reconstitute with 2.0 mL of water for injection containing 0.9% sodium chloride and made isotonic with mannitol and sodium chloride.

Diclofenac with Acetylcysteine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Diclofenac sodium	25.00	g
333.33	mg	2	1,2-Propylene glycol	333.33	g
0.033	mg	3	Ethyl lactate	0.033	g
0.666	mg	4	Glutathione (or *N*-acetylcysteine)	0.666	g
QS	mL	5	Sodium hydroxide for pH adjustment (0.1 N)	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	ft^3	7	Nitrogen gas, NF	QS	

Manufacturing Directions

1. In ca. 0.8 L of item 6, under purging of item 7, dissolve item 4.
2. Add item 2 and dissolve after grinding it to an average particle size of ca. 100 μm or less.
3. Check and adjust pH to 8.3 (8.1–8.5) with item 5.
4. Add item 3 and dissolve.
5. Make up the volume with item 6.
6. Filter using a 0.20-im membrane filter (nylon, polypropylene, or acrylic copolymer).
7. Fill ampoules.
8. Sterilize by autoclaving at 121°C for 15 minutes.

Diclofenac Lyophilized Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
18.00	mg	1	Sodium chloride, USP	18.00	g
75.00	mg	2	Diclofenac sodium, micronized (less than 20 μm)	75.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable jacketed (cold) stainless steel vessel, add item 1 to item 3 and dissolve.
2. Filter through a 0.20-mm filter membrane.
3. Transfer the solution to a sterilization vessel and sterilize in autoclave at 120°C for 20 minutes.
4. Allow to cool to 5°C.
5. Add item 2 and suspension deagglomerated in a homogenizer or ultrasonic disintegrator.
6. Fill the crystalline suspension at 5°C into 1-mL sterilized vials.
7. Freeze the vials at –45°C, lyophilize, and seal.

Diclofenac Lyophilized Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
75.00	mg	1	Diclofenac sodium, micronized (less than 20 μm)	75.00	g
5.40	mg	2	Sodium chloride, USP	5.40	g
20.00	mg	3	Mannitol	20.00	g
0.07	mg	4	Pluronic® F-68	0.07	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable stainless jacketed vessel, dissolve items 2, 3, and 4 in 0.7 L of item 5.
2. Filter solution through a 0.20-mm membrane filter after transferring it to a sterilization vessel.
3. Autoclave the solution at 120°C for 15 minutes.
4. Transfer the solution to mixing vessel, cool to 5°C, and add item 1.
5. Mix in a homogenizer or sonicator to deagglomerate.
6. Fill 1 mL into type I vials, loosely stopper, freeze at -45°C, lyophilize, and seal.

Dicyclomine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Dicyclomine hydrochloride, USP	10.00	g
9.00	mg	2	Sodium chloride, USP	9.00	g
5.00	mg	3	Chlorobutanol anhydrous, USP	5.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Acetic acid for buffering	QS	mL
QS	mL	6	Sodium acetate for buffering	QS	mL

Digoxin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.10	mg	1	Digoxin	0.10	g
0.40	mL	2	Propylene glycol	0.40	
0.10	mL	3	Alcohol, USP	0.10	L
1.70	mg	4	Sodium phosphate	1.70	g
0.80	mg	5	Citric acid anhydrous	0.80	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	ft^3	7	Nitrogen gas	QS	

Note: For adult dosage the quantity of item 1 is 0.25 mg/mL.

Manufacturing Directions

1. Take 0.9 L of item 6 and purge with item 7.
2. Add and dissolve items 2 and 3; mix well.
3. Add and dissolve items 4 and 5 (for pH adjustment); mix well.
4. Check pH to 6.8 to 7.2; do not adjust.
5. Make up volume.
6. Filter through a 0.22-μm membrane filter.
7. Fill 1 mL for pediatric (0.1 mg) dosage into type I glass ampoules.
8. Sterilize.

Dihydroergotamine Mesylate Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Dihydroergotamine mesylate, 10% excess	2.20	g
153.00	mg	2	Glycerin, USP	153.00	g
48.25	mg	3	Ethanol, USP, 190 proof	48.25	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	ft^3	7	Nitrogen gas NF	QS	

Manufacturing Directions

Caution: This product is highly susceptible to oxidation and should be continuously bubbled and blanketed with item 7 during all stages of manufacture. Use item 7 filtered through a 0.45-μm Millipore® or equivalent. Oxygen level should be less than 1 ppm at all times. Protect from light. All tubing must be stainless steel, Teflon (FEP), or silicone.

1. Preparation.
   a. Heat sufficient item 6 to 95°C. Hold at this temperature for 1 hour. Begin bubbling item 7 and continue to heat for a further 1 hour. Cool slowly to NMT 22°C while continuing to bubble item 7.
   b. Load item 2 into a suitable stainless steel or glass-lined tank.
   c. Load sufficient item 3 into a suitable stainless steel or glass-lined container. Bubble item 7 for at least 2 hours.
   d. Check oxygen concentration in the item 6 from step 1a. Continue item 7 bubbling until concentration is less than 1 ppm.
   e. Take sample for testing.
   f. Flush a suitable stainless steel or glass-lined tank with item 7 and then transfer ca. 700 mL of item 6 from step 1d and begin bubbling with item 7. From here on provide continuous item 7 blanket.
   g. Add ca. 40 mL of water from step 1d to item 2 in step 1b and bubble with item 7 at a minimum pressure of 1 kg for at least 1 hour. Continue bubbling until used.
   h. Weigh item 3 and container from step 1-c. Add 48.25 g of item 3 to the water in step 1f. Stir or mix by recirculation for at least 5 minutes.
   i. Dilute approximately 0.03 mL of acid item 4 with item 6 to make a 20% solution. Ensure that oxygen level is less than 1 ppm.
   j. Measure pH and adjust to 3.25 with solution in step 1i.
   k. Take sample. *Note*: Use protective clothing and mask; wear gloves while adding item 1.
   l. Add the item 1 to the batch and stir until completely dissolved
   m. Add the item 2/water mix from step 1g to the batch and adjust the volume to 995 mL with water from step 1d. Stir or recirculate for at least 15 minutes. Dissolve 4 g of sodium hydroxide in 100 mL water from step 1d.
   n. Measure and adjust pH to 3.75 with solution in step 1n. Stir for at least 30 seconds and recirculate for at least 5 minutes between each addition. Record final pH and amount used.
   o. Take testing samples.
   p. QS to 1 L with water.
   q. Just prior to filtration, take testing samples.
2. Filtration.
   a. Filter the solution through a Millipore filter unit or equivalent fitted with a 0.22-im pore-size filter previously sterilized by heating in an autoclave for 30 minutes at 121°C. Discard the first portion of filtrate. Record amount discarded.
   b. Carry out a bubble pressure leak test (21–28 psi) on the filter membrane to verify its integrity. Record bubble point pressure.
   c. Collect the filtrate in a suitable stainless steel or glass, clean sterile container under filtered item 7. The container should be sterilized at 121°C for 30 minutes. Continue bubbling with item 7.
   d. At the end of filtration, carry out the bubble pressure leak test. Record bubble point pressure.
3. Filling.
   a. Wash 100-mL amber glass bottles with distilled water only. Then sterilize bottles by using dry heat.
   b. Wash stoppers with distilled water only and sterilize by heating at 121°C in an autoclave for 30 minutes.
   c. Sterilize roll-on pilfer-proof caps by heating in an autoclave at 110°C for 1 hour.
   d. Set up a suitable liquid filling machine, ensuring that all fittings and tubing are clean and sterile.
   e. Fill into 100-mL sterilized, amber glass bottles from step 3-a. Prior to liquid addition, purge bottles with item 7. When each bottle is full, flush the headspace with item 7. Immediately seal by using sterilized stoppers from step 3-c.
   f. On start-up and after stoppages, take samples for testing.

Dihydroergotamine Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Dihydroergotamine mesylate	1.00	g
0.061	mL	2	Alcohol, USP	61.00	mL
QS	mL	3	Methanesulfonic acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
150.00	mg	5	Glycerin	150.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In sufficient quantity of item 6, add and dissolve item 5.
2. Add items 2 and 5; mix well.
3. Add and dissolve item 1.
4. Check and adjust pH to 3.2 to 4.0 with items 3 and 4.
5. Filter through a 0.22-μm membrane filter and sterilize.

Dihydroergotamine Mesylate Nasal Spray

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	Dihydroergotamine mesylate	4.00	g
10.00	mg	2	Caffeine anhydrous	10.00	g
50.00	mg	3	Dextrose anhydrous, USP	50.00	g
QS	ft^3	4	Carbon dioxide	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Use amber type I glass ampoules.

Diisopropylphenol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.028	mM	1	2,6-Diisopropylphenol	28.00	mM
1.00	mL	2	2,5-di-O-methyl-1,4:3,6-dianhydro-D-glucitol	1.00	L

Manufacturing Directions

1. Mix items 1 and 2 in a suitable vessel. Stir for 15 minutes in aseptic conditions.
2. Check pH to 5.3 (do not adjust).
3. Filter through a 0.22-μm membrane filter and fill into ampoule or vial.

Diltiazem Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Diltiazem hydrochloride	5.00	g
0.75	mg	2	Citric acid anhydrous	0.75	g
0.65	mg	3	Sodium citrate dihydrate	0.65	g
71.40	mg	4	Sorbitol solution, USP	714.00	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable stainless steel vessel, take approximately 0.9 L of item 7.
2. Add item 4 and mix.
3. Add items 2 and 3; mix well.
4. Check and adjust pH to 3.7 to 4.1 with item 5 or 6.
5. Filter through presterilized assembly by using a 0.22-μm membrane filter.
6. Fill appropriate volumes (5 or 10 mL) into type I glass vials.
7. Sterilize by autoclaving.

Lyo-Ject® syringe, 25-mg syringe, is available in a dual-chamber disposable syringe. Chamber 1 contains lyophilized powder composed of diltiazem hydrochloride, 25 mg, and mannitol, USP, 37.5 mg. Chamber 2 contains sterile diluent composed of 5 mL water for with 0.5% benzyl alcohol, NF, and 0.6% sodium chloride, USP. Monovial® for continuous IV infusion is available in a glass vial with transfer needle set. The vial contains lyophilized powder composed of diltiazem hydrochloride, 100 mg, and mannitol, USP, 75 mg.

Dimenhydrinate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Dimenhydrinate, USP	50.00	g
0.50	mL	2	Propylene glycol, USP	0.50	L
0.05	mL	3	Benzyl alcohol, NF	0.05	L
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	mL

Dimethyl Sulfoxide Injection

Bill of Materials (Batch Size 120 kg)					
Scale/mL		Item	Material	Qty	UOM
0.455	mL	1	Dimethyl sulfoxide, 5% excess; sp. gr. 1.1	54.60	L
60.0	mL	2	Water for injection, USP	60.0	L

Manufacturing Directions

1. Mix items 1 and 2 in a suitable stainless steel tank and mix vigorously until a clear solution is obtained.
2. Filter mixture from step 1 by using only polyethylene tubing, a prefilter of 0.22-μm sterilizing membrane, and a presterilized Pyrex bottle, which serves as reservoir.
3. Aseptically fill into bottles—type I clear glass bottles (50 mL) size Kimble, caps low density PE (Union Carbide DMDA 0160-MP7) washed with filtered Freon (3-μm cartridge filter) and gas sterilized with ethylene oxide. Do not autoclave.
4. Sample for testing.

Dimethyl Sulfoxide Irrigation

This is dimethyl sulfoxide (DMSO) 50% w/w aqueous solution for intravesical instillation. Each milliliter contains 0.54 g dimethyl sulfoxide. Intravesical instillation for the treatment of interstitial cystitis. Not for IM or IV injection.

Dinoprostone Cervical Gel

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.20	mg	1	Dinoprostone[a]	0.20	g
96.00	mg	2	Colloidal silicon dioxide	96.00	g
1104.0	mg	3	Triacetin (ca. to QS to 1 L)	1104.00	g

[a] Naturally occurring form of prostaglandin E_2 (PGE_2); dispense 2.5 mL (3 g) into tube for endocervical application.

Diphenhydramine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Diphenhydramine hydrochloride, USP[a]	10.00	g
5.00	mg	2	Chlorobutanol anhydrous, USP	5.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] Or 50 mg/mL; multidose vial contains benzethonium chloride, 0.1 mg/mL; pH adjusted 5.0 to 6.0 with item 3 or 4.

Diphenylmethyl Piperazine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	1-Diphenylmethyl-4-[(2-(4-methyl-phenyl)-5-methyl-1H-imidazol-4-yl) methyl] piperazine	4.00	g
4.13	mg	2	Tartaric acid	4.13	g
5.78	mg	3	Citric acid	5.78	g
2.64	mg	4	Methanesulfonic acid	2.64	g
45.10	mg	5	Sorbitol	45.10	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In sufficient quantity of item 6, add and dissolve items 2 and 3 in a suitable stainless steel vessel.
2. Add item 1 and dissolve.
3. Add item 5 and dissolve.
4. Bring to volume with item 6.
5. Filter using a 0.22-μm filter and fill.

Dipyrone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
500.00	mg	1	Dipyrone	500.00	g
4.00	mg	2	Chlorobutanol	4.00	g
2.00	%	3	Benzyl alcohol, NF	20.00	mL
QS	mL	4	Water for injection, USP	QS to 1	L
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Hydrochloric acid for pH adjustment	QS	
QS		7	Nitrogen gas, NF	QS	

Note: Also for veterinary use.

Manufacturing Directions

1. Dissolve item 1 in approximately 0.5 L of item 4 heated to 60°C to 70°C under constant stirring until dissolved completely.
2. Add items 2 and 3 with constant stirring to complete solution.
3. Bring the solution to room temperature and make up the volume with item 4.
4. Bubble item 7 thoroughly and let stand for 30 minutes.
5. Check pH (6.8–7.0), adjust with 10% item 6 or 4% item 5 as needed, sample.
6. Filter solution through a 0.22-μm filter assembly.
7. Fill flint ampoules 5.2 mL under item 7 cover.
8. Terminal sterilization at 121°C for 30 minutes.
9. Sample for leakage and final testing.

Dipyrone, Papaverine HCl, and Atropine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
500.00	mg	1	Dipyrone	500.00	g
20.00	mg	2	Papaverine hydrochloride	20.00	g
0.50	mg	3	Atropine sulfate	0.50	g
1.00	mg	4	Sodium metabisulfite	1.00	g
5.00	mg	5	Chlorobutanol	5.00	g
0.0013	mL	6	Benzyl alcohol, NF	1.30	mL
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS		8	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Bring item 7 to boiling; cool to room temperature.
2. Add item 6 and dissolve rapidly, add item 5, mix again for not less than 5 minutes.
3. Add items 1 to 3 and bring volume.
4. Provide and keep item 8 cover throughout.
5. Measure pH (3.8–4.2); do not adjust pH.
6. Filter through a presterilized filtering assembly by using a 0.22-μm filter.
7. Sterilize empty ampoules at 200°C for 4 hours.
8. Fill 3.2 mL for 3.00-mL fill volume into amber type I glass ampoules with pre- and post-item 8 flush.
9. Terminally sterilize in an autoclave at 121°C for 30 minutes.
10. Sample for final testing, clarity, and particle test.

Disodium Edetate Injection (150 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150.00	mg	1	Disodium edetate anhydrous, use disodium edetate dihydrate, USP	150.00	g
QS	mg	2	Sodium hydroxide	QS	mg
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Heat ca. 70% of final volume of item 3 in a glass-lined or stainless steel mixing tank. Add and dissolve item 1. Cool solution. Check pH (range 6.5–7.5). Readjust with dilute item 2 if necessary.
2. Prefilter solution through appropriate filtration setup.
3. Filter and fill into clean ampoule and seal. Steam sterilize. Sample.

Disulfonic Acids Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
121.30	mg	1	S-Adenosyl-D-methionine salts of disulfonic acids	121.30	g
66.66	mg	2	Lysine	66.66	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In sufficient quantity of item 3, dissolve item 1, filter, and lyophilize.
2. Prepare diluent by using item 2 and QS to 1 L.

Dobutamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.22	mg	1	Sodium metabisulfite, NF	0.22	g
12.50	mg	2	Dobutamine base, use dobutamine HCl, USP	12.50	g
QS	mL	3	Hydrochloric acid[a]	QS	mL
QS	mL	4	Sodium hydroxide[a]	QS	mL
QS	—	5	Nitrogen gas, NF	QS	—
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] For pH adjustment if necessary.

Manufacturing Directions

1. Transfer an appropriate volume of item 6 into a glass-lined tank while sparging with N_2 gas.
2. Mix and dissolve items 1 and 2. Continue N_2 sparging.
3. Check pH (range 2.7–3.3). If necessary, adjust pH with item 3 or 4 solution.
4. QS with N_2-protected item 6 to final volume and mix.
5. Check pH (range 2.7–3.3). If necessary, adjust pH with item 3 or 4 solution.
6. Discontinue N_2 sparge and switch to N_2 gas protection.
7. Sample for in-process control, dobutamine assay, and pH determination.
8. Filter solution through a previously cleaned and rinsed approved 0.45-μm (or finer) membrane filter. If required, an approved prefilter may be used.
9. During filling, filter solution through an approved 0.45-μm (or finer) membrane filter. If required, an approved prefilter may be used.
10. Fill clean empty vials. Protect the headspaces of filled vials by using filtered N_2 gas. Apply stoppers and overseals.
11. Sterilize product by using an approved autoclave cycle. QC samples.

Dopamine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Dopamine hydrochloride, USP	40.00	g
9.12	mg	2	Sodium metabisulfite, NF	9.12	g
10.00	mg	3	Acid citric, USP, anhydrous powder	10.00	g
QS	mg	4	Acid citric, USP, anhydrous powder[a]	QS	mg
5.00	mg	5	Sodium citrate dihydrate, USP, ampoule granules	5.00	g
QS	mg	6	Sodium citrate dihydrate, USP, ampoule granules[a]	QS	mg
QS	–	7	Nitrogen gas, NF	QS	–
QS	mL	8	Water for injection, USP	QS to 1.00	L

[a] Use for pH adjustment only; use 80 mg of item 1 for 80-mg/mL label. Other ingredients remain the same.

Manufacturing Directions

1. Preparation.
   a. Add item 8 to ca. 110% of final volume into a suitable vessel.
   b. Heat item 8 to 90°C to 100°C and hold at that temperature for 10 minutes and commence bubbling N_2 gas through the solution. Continue N_2 gas protection through the remainder of solution manufacturing. Draw off 20% of final volume into another suitable vessel under N_2 protection and hold for solution QS. Lower the temperature to between 45°C and 55°C through solution QS.
   c. Add and dissolve items 2, 3, and 5. Mix well without excessive agitation.
   d. Add and dissolve item 1 with minimal agitation. To ensure an accurate pH measurement, allow the pH sample solution to cool to 20°C to 25°C. Minimize excessive agitation of solution with mixer. Supplement this stirring by bubbling N_2 gas into the solution. Do not allow solution to vortex.
   e. QS to final volume with previously boiled N_2-protected item 8.
   f. Place lid on mix tank and establish N_2 atmosphere in the tank headspace. Cool the solution to 25°C (range 20–30°C).
   g. Check the pH (range 3.2–3.5). If more than 3.5, adjust to pH 3.3 with item 4. If less than pH 3.2, adjust to pH 3.3 (range: 3.2–3.5) with item 6.
   h. Filter solution through a previously rinsed filtration setup by using an approved 0.45-μm or finer membrane and an approved prefilter into a clean glass-lined or 316 stainless steel tank, protected with N_2 gas by bubbling and flushing headspace. Sample.
2. Filling. Ampoule: Use type I 5-mL glass ampoules, USP.
   a. Fill specified amount into each clean, dry ampoule. Flush the headspace with filtered N_2 gas and seal the ampoule.
   b. Inspect. Sample.
3. Sterilization.
   a. Sterilize at 115°C at an F_0 range of 8 to 18. Use water spray cooling and terminal air overpressure to maintain autoclave pressure. Sample.

Doxapram Hydrochloride Injection, USP

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Doxapram hydrochloride	20.00	g
9.00	mg	2	Benzyl alcohol	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Adjust pH to 3.5 to 5.0 with item 3 or 4.
2. Fill 20-mL multiple-dose vial.
3. Sterilize by autoclaving.

Doxercalciferol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Doxercalciferol	2.00	mg
4.00	mg	2	Polysorbate 80	4.00	g
1.50	mg	3	Sodium chloride	4.00	g
10.00	mg	4	Sodium ascorbate	10.00	g
7.60	mg	5	Sodium phosphate dibasic	7.60	g
1.80	mg	6	Sodium phosphate monobasic	1.80	g
1.10	mg	7	Disodium edetate	1.10	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

Description

A synthetic vitamin D analog that undergoes metabolic activation in vivo to form 1(alpha),25-dihydroxyvitamin D_2 (1(alpha),25-$(OH)_2$ D_2), a naturally occurring, biologically active form of vitamin D_2.

Doxorubicin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Doxorubicin hydrochloride	2.00	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
10.00	mg	4	Lactose NF	10.00	g
0.20	mg	5	Methyl paraben	0.20	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	ft^3	7	Nitrogen gas, NF	QS	

Manufacturing Directions

1. In a suitable stainless steel vessel, take approximately 0.9 L of item 6. Heat to 70°C to 80°C and add and mix item 5. Dissolve completely.
2. Cool to room temperature. Begin purging item 7 and maintain cover throughout.
3. Add and dissolve items 2 and 4. Mix well.
4. Add item 1 and mix vigorously.
5. Check and adjust pH using item 3 to 3.0 (2.9–3.1).
6. Filter through a 0.22-μm membrane filter and fill into vials 5-mL (10-mg dose) or higher proportional volumes.
7. Lyophilize.

Doxycycline Hyclate Injection

Bill of Materials (Batch Size 50 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Doxycycline hyclate, 5% overage	1.3125[a]	kg
120.00	mg	2	Ascorbic acid USP, 5% overage	6.30	kg
75.00	mg	3	Mannitol, USP	3.75	kg
QS	mL	4	Water for injection, USP	QS to 50.00	L

[a] Actual quantity to be recalculated depending on the potency of the material.

Manufacturing Directions

1. Place approximately 35 L of item 4 into a suitable mixing tank, add item 2 into it, and mix thoroughly to a complete solution.
2. Add item 1 with constant mixing until clear.
3. Add item 3 to the mixing tank and mix to a complete solution.
4. QS to final volume with item 4. If the solution meets specifications, filter through a 0.22-μm filter into a sterile receiving jar.
5. Lyophilization. Chill the shelves to −40°C or less and load chamber with vials kept covered with clean, sterile covers. Let the product freeze. Proceed when thermocouples register −40°C or lower for a minimum of 4 hours. Start condenser, let it achieve a temperature of −50°C or lower, start vacuum pump, and let the chamber pressure drop to 200 μm or lower. Set shelf temperature to +25°C and let the product temperature rise to within 1°C of the set point. Mark time and let the cycle run for a minimum of an additional 48 hours. At the end of the cycle, bleed the chamber with air, open chamber, remove six representative vials (two from each of the top, middle, and bottom shelves), and close the door. Test samples for moisture. If all samples contain 2% or less, stopper the vial, terminate cycle, and remove vials for sealing. If not, then extend the cycle and record action.
6. Treat stoppers by adding rubber detergent to RO water with gentle agitation. Add stoppers, autoclave at 121°C (minimum) for not less than 20 minutes. Drain solution, rinse 3 times with 57°C±3°C water for injection. Add sufficient water to cover the stoppers during each rinse. Siliconize stoppers if needed by adding 118.2 mL of silicone solution; drain and autoclave at 121°C (minimum) for not less than 30 minutes. Dry for not less than 8 hours at 100°C; use additional time if necessary.

Doxycycline Hyclate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Doxycycline as doxycycline hyclate equivalent	100.00	g
480.00	mg	2	Ascorbic acid	480.00	g

Note: Use 960.00 mg of item 2 for 200 mg of doxycycline dose.

Doxycycline Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Doxycycline, use doxycycline hydrochloride	126.96	g
167.95	mg	2	Phosphoric acid (85%)	167.95	g
34.92	mg	3	Magnesium oxide	34.92	g
20.00	mg	4	Lidocaine	20.00	g
10.00	mg	5	Monothioglycerol	10.00	g
2.00	mg	6	Propyl gallate	2.00	g
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable quantity of item 7, add item 1 with stirring.
2. Add item 3 and mix.
3. Check and adjust pH to 2.5 (2.3–2.6) with item 2.
4. Add and mix items 4, 5, and 6.
5. Make up volume with item 7.
6. Filter and sterilize.

Ebselen Liposomal Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.11	mg	1	Ebselen	0.11	g
13.33	mg	2	DPPC (Dipalmitoylphosphatidylcholine)	13.33	g
1.33	mg	3	DPPG (Dipalmitoylphosphatidylglycerol)	1.33	g
6.45	mg	4	Cholesterol	6.45	g
0.025	mL	5	Methanol	0.25	L
0.025	mL	6	Chloroform	0.25	L
QS	mL	7	Acetate buffer pH 4.0 in water for injection, USP	QS to 1.00	L
QS	ft^3	8	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Dissolve items 1, 2, and 3 in items 5 and 6.
2. Remove solvents in step 1 under vacuum.
3. Hydrate the film with item 7 under item 8.
4. Add glass beads and stir to form liposomes.
5. Filter under sterile condition and fill into ampoules under cover of item 8.

Edetate Sodium, Polyvinyl Alcohol, Sodium Sulfacetamide, Sodium Thiosulfate Ophthalmic Drops with Thimerosal

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Water purified (distilled), USP, ca.	10.00	L
14.00	mg	2	Polyvinyl alcohol, 20–90	630.00	g
0.0001	mL/mL	3	Polysorbate 80, NF (use a 10% solution)	45.00	mL
Part II					
		4	Water purified (distilled), USP, ca.	250.00	L
0.6805	mg	5	Potassium phosphate monobasic, NF	30.62	g
5.3620	mg	6	Sodium phosphate dibasic heptahydrate, USP[a]	241.30	g
0.1274	mg	7	Disodium edetate, USP	5.73	g
306.00	mg	8	Sulfacetamide sodium, USP (2% overage)	13.77	kg
		9	5 N Hydrochloric acid, NF[b]	QS	mL
3.14	mg	10	Sodium thiosulfate pentahydrate, USP[c]	141.30	g
Part III					
		11	Water purified (distilled), USP, ca.	200.00	mL
0.05	mg	12	Thimerosal, USP[d]	2.25	g
		13	Water purified (distilled), USP	QS to 45.00	L

[a] Equivalent to 2.8393 mg/mL sodium phosphate dibasic anhydrous.
[b] Use for pH adjustment only.
[c] Equivalent to 2.0 mg/mL sodium thiosulfate anhydrous.
[d] The amount of thimerosal to be added must be calculated on the basis of the assay value of the raw material lot(s) used.
Assay Value:_____%
2.25 g × 100.0%/Assay Value (%) = ____ g of thimerosal required.

Manufacturing Directions

Part I

1. Measure out ca. 10 L of item 1 into a stainless steel pressure vessel.
2. Begin mixing with a suitable mixer.
3. Heat item 1 to 85°C to 90°C.
4. Begin mixing item 1 with a propeller mixer.
5. Add item 2 slowly to the vortex.
6. Mix for at least 90 minutes until item 2 is completely dissolved.
7. After mixing item 2 for at least 90 minutes, add item 3 and mix thoroughly.
8. Cool to room temperature, with force cooling.

Part II

1. Measure out ca. 25 L of item 4 into a suitable mixing tank calibrated for a final QS of 45 L. Begin mixing.
2. Add items 5 to 8, in order, allowing each to dissolve completely before adding the next.
3. After item 8 is completely dissolved, mix part II for at least 15 minutes.
4. Sample for pH (range 7.3–7.5). If necessary, adjust the pH to 7.3 to 7.5 with item 9.
5. Add item 10 and mix until it is dissolved.
6. Add part I to the mixing tank containing part II, while mixing part II.
7. Use 2 to 3 L of water purified (distilled) to rinse the part I kettle, pump, and hoses.
8. Add the rinsings to the mixing tank.

Part III

1. Weigh out item 12 and carefully transfer it to a suitable flask.
2. Add 200 mL of item 13 and mix until item 12 is dissolved.
3. Add part III to combined parts I and II while mixing.
4. Rinse the flask containing item 12 with ca. 200 mL of item 13 and add the rinsings to the batch.
5. Allow any foam to dissipate and QS the batch to 45 L with item 13.
6. Mix thoroughly for at least 15 minutes.

Sterile Filtration

1. Sterilize for 1 hour (range 45–60 minutes) at 121°C (−0, +5°C) in autoclave at 15 psi the filter and 100-L stainless steel pressure vessel. Transfer to the solution preparation area.
2. Attach the prefilter and final filter and hosing sterilization chart.
3. Mix the product for at least 10 minutes before filtration.
4. Connect the sterilized Pall filter and sterile filter with the aid of N_2 pressure (15–30 lb). Discard initial 10 L of filtrate, attach sterilized hose to sterilized filter holder, and connect to sterilized 100-L stainless steel pressure vessel. *Note*: Before sterile filtration to 100-L pressure vessel, perform the bubble point test at NLT 40 psi.
5. After completion of product filtration, disconnect Pall filter from pressure vessel. Flush the sterilized filter with at least 10 L of water purified (distilled) for the bubble point test (after filtration).
6. After filtration, decontaminate the outer surface of bulk holding pressure vessel and then transfer to filling cubicle. Sample.

Sterilization

Sterilize filling unit, 20-L surge bottle or manifold of filling unit, and uniforms at 121°C (−0, +2°C) at 15 psi for 1 hour.

Sterile Filling

1. Transfer the presterilized bottles, plugs, and caps to the filling cubicle after swabbing their outer polyethylene packing with filtered methylated spirit and keep under the laminar flow hood.
2. Transfer the sterilized assembly line to filling room. Aseptically connect the sterilized filling tubing and N_2 line from the 100-L pressure vessel to surge bottle.
3. Aseptically fill 15.40 mL of sterile solution through into sterilized container by using the automatic filling, plugging, and sealing machine and apply sterile closure components (plugs and caps). *Note*: Discard 50 to 100 bottles initially during volume adjustment. While filtering, N_2 pressure should not exceed 5 to 10 lb.
4. Perform the bubble point test on 0.22-μm inline gas filter before and after filtration at 18 psi. Sample.

Edetate Sodium, Polyvinyl Alcohol, Sodium Sulfacetamide, Sodium Thiosulfate Ophthalmic Drops With Benzalkonium Chloride

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Water purified (distilled), USP	6.00	L
14.00	mg	2	Polyvinyl alcohol, 20–90	630.00	g
0.10	mg	3	Polysorbate 80, NF (use a 10% Solution)	41.75	mL
Part II					
		4	Water purified (distilled), USP	30.00	L
2.68	mg	5	Sodium phosphate dibasic heptahydrate, USP	120.60	g
0.345	mg	6	Sodium phosphate monobasic monohydrate, USP	15.53	g
0.15	mg	7	Disodium edetate, USP	6.75	g
100.00	mg	8	Sodium sulfacetamide, USP	4.50	kg
QS	mL	9	5 N Hydrochloric acid, NF[a]	QS	mL
QS	mL	10	1 N Sodium hydroxide, NF[a]	QS	mL
3.14	g	11	Sodium thiosulfate pentahydrate, USP	141.30	g
0.05	mL	12	Benzalkonium chloride, NF (10% solution)[b]	22.50	mL
QS	mL	13	1 N Hydrochloric acid, NF[a]	QS	mL
QS	mL	14	1 N Sodium hydroxide, NF[a]	QS	mL
QS	mL	15	Water purified (distilled), USP	QS to 45.00	L

[a] Used for pH adjustment

[b] The amount of benzalkonium chloride, NF (10% solution), is calculated as follows: 22.50 mL × 10.0%/assay value (%) = mL benzalkonium chloride, 10% solution, required.

Manufacturing Directions

Part I

1. Measure out ca. 6 L of item 1 into a jacketed pressure vessel; measure the temperature (NMT 30°C).
2. Begin mixing and add item 2. Adjust the mixing to the minimum speed that will allow complete dispersion and agitation. Mix for 60 to 90 minutes.
3. Heat part I to 85°C to 90°C by circulating steam. Maintain the temperature of part I at 85°C to 90°C for 15 to 20 minutes.
4. Add item 3 and mix thoroughly. Cool part I to less than 30°C with force cooling.

Part II

1. Measure out ca. 30 L of item 4 into a suitable mixing tank. Begin mixing.
2. Add the items 5 to 8, in order, allowing each to dissolve completely before adding the next.
3. After item 8 is completely dissolved, mix part II for at least 30 minutes. If necessary, adjust pH to 7.3 to 7.5 with item 9 or 10.
4. Add item 11 and mix until it is completely dissolved. Transfer part I into the tank containing part II. Add item 12 and mix thoroughly. QS the batch to 45 L with item 15. If necessary, adjust the pH to 7.3 to 7.5 with item 13 or 14. Mix thoroughly for at least 30 minutes.
5. Sterile filter with the aid of N_2 pressure. Perform the bubble point test.
6. Aseptically fill sterile solution into sterilized containers. Perform the bubble point test. Sample.

Edrophonium Injectable

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Edrophonium	10.00	g
4.50	mg	2	Phenol liquefied	4.50	g
2.00	mg	3	Sodium sulfite	2.00	g
0.20	M	4	Citric acid anhydrous	0.20	M
0.20	M	5	Sodium citrate	0.20	M
QS	mL	6	Hydrochloric acid for pH adjustment	QS	
QS	mL	7	Sodium hydroxide for pH adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5.4.

Electrolyte Maintenance Fluid (For Maintenance)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	%	1	Dextrose anhydrous, USP, 10% excess	55.00	g
0.28	%	2	Sodium acetate, 5% excess	2.94	g
0.09	%	3	Sodium chloride, 5% excess	0.96	g
0.15	%	4	Potassium chloride, 5% excess	1.575	g
0.13	%	5	Dibasic potassium phosphate, 5% excess	1.36	g
0.020	%	6	Sodium metabisulfite, 5% excess	0.22	g
QS		7	Glacial acetic acid, NF	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve items 2 to 6 in 0.9 L of item 4.
2. Adjust pH to 5.0 with item 7. Adjust with item 7 (ca. 1.1 mL); pH must not exceed 5.0.
3. Add item 1 and mix.
4. Filter using at least a 0.45-μm filter before final filtration with 0.22-μm filter and fill into type I 540-mL glass bottles.
5. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers pre-washed and sterilized at 116°C for 30 minutes; use triple aluminum seals and suitable plastic hangers.
6. Sterilized filled bottle by autoclaving at 121°C for 20 minutes; do not exceed temperature by 3°C or time by 2 minutes either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.

Electrolyte Maintenance Fluid (For Rehydration)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.0	mg	1	Dextrose anhydrous, USP, 10% excess	55.00	g
3.70	mg	2	Sodium chloride NF, 5% excess	3.88	g
1.30	mg	3	Potassium chloride NF, 5% excess	1.60	g
3.70	mg	4	Ammonium chloride NF, 5% excess	3.88	g
0.15	mg	5	Sodium sulfite, NF, 5% excess	0.156	g
QS	mL	6	Hydrochloric acid for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS		8	Glacial acetic acid, NF, for pH adjustment	QS	

Manufacturing Directions

The general directions are common to all LVPs containing dextrose. Read directions for dextrose 5%.

1. To 0.8 L of item 7 add items 2, 3, and 4, and stir and dissolve.
2. Check and adjust pH to 4.8 to 5.0 with item 6. (Do not adjust if in this range.)
3. Add items 1 and 5 and make up volume.
4. Check and adjust pH again to 4.8 to 5.2 with item 8.
5. Filter using at least a 0.45-μm filter before final filtration with 0.22-(μm filter and fill into type I 540-mL glass bottles.
6. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers prewashed and sterilized at 116°C for 30 minutes; use triple aluminum seals and suitable plastic hangers.
7. Sterilized filled bottle by autoclaving at 121°C for 20 minutes; do not exceed temperature by 3°C or time by 2 minutes either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.

Electrolyte Maintenance Fluid (Maintenance, Pediatric)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	%	1	Dextrose anhydrous, USP, 10% excess	55.00	g
0.315	%	2	Sodium acetate, 5% excess	3.30	g
0.13	%	3	Potassium chloride, 5% excess	1.365	g
0.031	%	4	Magnesium chloride, 5% excess	0.334	g
0.026	%	5	Dibasic potassium phosphate, 5% excess	0.273	g
0.021	%	6	Sodium metabisulfite, 5% excess	0.224	g
QS		7	Glacial acetic acid, NF	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve items 2 to 5 in 0.9 L of item 8.
2. Adjust pH to 5.0 using item 7.
3. Add item 1 and mix.
4. Make up the volume and check pH again and adjust between 4.8 and 5.0.
5. Filter by using at least a 0.45-μm filter before final filtration with 0.22-μm filter and fill into type I 540-mL glass bottles.

Electrolyte Maintenance Fluid: Maintenance (45 mEq)

1. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers prewashed and sterilized at 116°C for 30 minutes; use triple aluminum seals and suitable plastic hangers.
2. Sterilized filled bottle by autoclaving at 121°C for 20 minutes; do not exceed temperature by 3°C or time by 2 minutes either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.

Electrolyte Maintenance Fluid

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Dextrose hydrous, USP (use 23.89 g if using anhydrous)	26.25	g
2.05	mg	2	Sodium chloride, USP	2.05	g
0.98	mg	3	Sodium citrate, USP	0.98	g
2.16	mg	4	Potassium citrate monohydrate	2.16	g
QS	mg	5	Citric acid, USP, anhydrous, for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

5 Electrolyte Maintenance Fluid Rehydration (75 mEq)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Dextrose hydrous, USP (use 23.89 g if using anhydrous)	26.25	g
3.80	mg	2	Sodium chloride, USP	3.80	g
0.98	mg	3	Sodium citrate, USP	0.98	g
2.16	mg	4	Potassium citrate monohydrate	2.16	g
QS	mg	5	Citric acid, USP, anhydrous, for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Electrolyte Maintenance Fluid Rehydration (90 mEq)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Dextrose hydrous, USP, (use 23.89 g if using anhydrous)	26.25	g
4.68	mg	2	Sodium chloride, USP	4.68	g
0.98	mg	3	Sodium citrate, USP	0.98	g
2.16	mg	4	Potassium citrate monohydrate	2.16	g
QS	mg	5	Citric acid, USP, anhydrous, for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add item 1 to ca. 80% of item 6 in a previously cleaned mixing tank.
2. Add and dissolve items 3, 2, and 4, in order. Mix to dissolve.
3. Check pH to 6.0 to 6.5; adjust if necessary with item 5.
4. Filter using a 0.45-μm prefilter and 0.22-μm membrane filter.
5. Fill and steam sterilize.

Electrolytes, TPN Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
16.07	mg	1	Sodium chloride, USP	16.07	g
16.54	mg	2	Calcium chloride, USP	16.54	g
74.55	mg	3	Potassium chloride, USP	74.55	g
25.41	mg	4	Magnesium chloride, USP	25.41	g
121.00	mg	5	Sodium acetate, USP	121.00	g
QS	mL	6	Hydrochloric acid, reagent grade, for pH adjustment		
QS	mL	7	Water for injection, USP		

Manufacturing Directions

1. Prepare the solution in a glass-lined or 315 or higher temper-grade stainless steel tank.
2. Add item 7 to ca. 70% of the final volume into the tank.
3. Add and dissolve items 1 to 5 with mixing.
4. QS with item 7 and mix.
5. Check and record pH adjust with item 6 if necessary.
6. Filter the solution through a previously rinsed filtration setup, using an approved 0.45-μm membrane with an approved prefilter into a glass-lined or stainless steel tank.
7. Fill into clean vials by using the surge bottle.
8. Autoclave at 121°C for 20 minutes.
9. Inspect and finish.
10. Sample for testing.

Emetine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
30.00	mg	1	Emetine hydrochloride, USP	50.00	g
QS	mL	2	Sodium hydroxide for pH adjustment	QS	
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve item 1 in 0.9 L of item 4. Make up the volume.
2. Check and adjust pH to 3.0 (2.7–3.3) with items 2 and 3.
3. Filter through presterilized filtration assembly through a 0.45-μm prefilter and a 0.22-μm filter into a sterilized staging vessel.
4. Fill 1.1 mL into presterilized type I glass ampoule aseptically. *Do not* autoclave.

Enalaprilat Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Enalaprilat	5.40	g
11.40	mg	2	Sodium phosphate dibasic anhydrous	11.40	g
9.00	mg	3	Benzyl alcohol	9.00	g
QS	mL	4	Water for injection	QS to 1.00	L

Ephedrine and Pyrilamine Maleate Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Pyrilamine maleate, NF	25.00	g
10.00	mg	2	Ephedrine HCl, NF	10.00	g
3.00	mg	3	Chlorobutanol anhydrous, USP	3.00	g
QS	mL	4	Water for injection	QS to 1.00	L

Ephedrine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Ephedrine sulfate, USP	50.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: The solution must be prepared in a glass-lined or a 316 or higher temper-grade stainless steel tank cleaned according to approved plant basic operating procedures.

1. Add item 2 to tank to ca. 90% of the final volume.
2. Add and dissolve item 1 with mixing.
3. QS with item 2 to final volume and mix until drug is dissolved and solution is uniform. Check pH (range 5–6.5).
4. Filter solution through a previously rinsed filtration setup, using an approved 0.45-μm or finer membrane with an approved prefilter. Filter solution into a clean glass-lined or 316 stainless steel holding tank. Sample.
5. With the 0.22-μm inline filter, fill specified dose into each clean, dry ampoule, and seal and sterilize in a steam autoclave at 121°C for 15 minutes. Sample.

Epinephrine Auto Injector Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Epinephrine	1.80	g
5.40	mg	2	Sodium chloride	5.40	g
1.50	mg	3	Sodium metabisulfite	1.50	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	ft^3	6	Nitrogen gas, NF	QS	

Manufacturing Directions

Note: This preparation requires strict control on exposure to light and air.

1. Take 0.9 L of item 5 and pass item 6 for 20 minutes, covered and protected from light.
2. Add and dissolve items 2 and 3.
3. Add item 1 and dissolve.
4. Check and adjust pH with item 4 to 2.2 to 5.0.
5. Filter through 0.22-μm membrane filter into emergency-use syringes.

Epinephrine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1	mg	1	Epinephrine, USP	1.00	g
9	mg	2	Sodium chloride, USP	9.00	g
5	mg	3	Chlorobutanol anhydrous, USP	5.00	g
2	mg	4	Sodium bisulfite, USP	2.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Hydrochloric acid for pH adjustment	QS	

Epoetin-Alpha for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2000	U	1	Epoetin alpha[a]	2000,000	U
2.50	mg	2	Albumin (human)	2.50	g
5.80	mg	3	Sodium citrate	5.80	g
5.80	mg	4	Sodium chloride	5.80	g
0.06	mg	5	Citric acid	0.06	g
QS	mL		Water for injection, USP	QS to 1.00	L

[a] Other strengths to 40000 U require adjustment of ingredients; adjust pH to 6.9 (range 6.6–7.2).

Epoprostenol Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	mg	1	Epoprostenol sodium equivalent to epoprostenol	0.50	g
3.76	mg	2	Glycine	3.76	g
2.93	mg	3	Sodium chloride	2.93	g
50.00	mg	4	Mannitol	50.00	g
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 10.2 to 10.8; freeze dry; diluent includes glycine; sodium hydroxide in water for injection.

Ergocalciferol Injection (Vitamin D)

Bill of Materials (Batch Size 2 L)					
Scale/mL		Item	Material	Qty	UOM
400.00	IU	1	Ergocalciferol, USP = $8 \times 10^5/40 \times 10^6$ potency of raw material	800000 20.00	IU mg
50.00	mg	2	Polysorbate 20, NF	100.00	g
500.00	mg	3	Glycerin, NF	1.00	kg
QS	mL	4	Water for injection, USP	2.00	L
QS	–	5	Nitrogen gas, NF	QS	–
QS	mL	6	Sodium hydroxide, 10%, for pH adjustment	QS	mL

Manufacturing Directions

1. Put item 2 into a clean compounding tank and place it on a hot plate, heat it to approximately 40°C and not exceeding 60°C, keep nitrogen blanket over tank throughout.
2. Add item 1 with constant stirring to step 1. Keep stirring until a clear solution is obtained.
3. Stop heating; while agitating, add in portions item 3 to the tank.
4. Bring within approximately 100 mL of the final volume with item 4. Mix thoroughly and check pH.
5. If necessary, adjust pH to between 5.0 and 7.0 with item 6. Do not adjust pH if within this range already.
6. Bring to final volume with item 4, check pH, and if approved, filter through a 0.22-μm filter into a sterile jar. Keep N_2 cover. Fill with N_2 postfill flush.

Ergonovine Maleate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.25	mg	1	Ergonovine maleate, USP, 7% excess	267.50	mg
0.20	mg	2	Acid maleic, BP	200.00	mg
QS	–	3	Nitrogen, NF	QS	–
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Precautions: Prepare solution in a clean glass-lined tank. Use N_2 protection throughout. Product is heat sensitive and must be refrigerated. Do not freeze.

1. Add item 4 to ca. 90% of the final volume into a glass-lined tank protected from light.
2. Bubble filter item 3 into item 4 for 10 minutes. Blanket with item 3.
3. Add and dissolve item 1 and 0.4% solution of item 2 (30 mL of a 0.4% item 2 solution needed for 1 L of final solution) with mixing.
4. Check pH (range 2.7–3.5). Adjust to pH 3 with remaining portion of 0.4% solution of item 2.
5. QS with item 4 to final volume. Sample.
6. Sterilize an approved 0.2- or 0.22-μm membrane filter with an approved prefilter.
7. Filter the solution through the sterilized filter unit into a sterile glass-lined holding container.
8. Sterilize sulfur-treated ampoules, using dry heat at 245°C for at least 3 hours and 25 minutes or an equivalent cycle.
9. Connect bulk solution container by using aseptic technique to the filling machines.
10. Aseptically fill the specified dose into each clean, sterile ampoule.
11. Flush the headspace of each ampoule with sterile-filtered item 3. Immediately seal. Sterilize and sample.

Ergonovine Maleate Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.20	mg	1	Ergonovine maleate, NF	0.20	g
0.50	mL	2	Liquefied phenol, USP	0.50	g
QS	mL	3	Water for injection, USP	1.00	L
QS	mL	4	Hydrochloric acid for pH adjustment	QS	

Erythromycin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Erythromycin, use erythromycin, USP, base special[a]	66.42	g
—	mL	2	Lactobionic acid, 12% w/v[b]	272.28	mL
QS	mg	3	Charcoal activated USP[c]	QS	g
9.00	mg	4	Benzyl alcohol, NF, for ampoules (15% excess)	12.38	g
QS	—	5	Nitrogen, NF	QS	—
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] Qty based on a theoretical potency of 900 μg/mg; to be recalculated depending on actual potency.
[b] Include 5% excess for pH adjustment. The ratio between erythromycin base and lactobionic acid should remain constant.
[c] Amount of charcoal depends on area of filter. Use ca. 440 g/m^2 of filter surface area.

Manufacturing Directions

Note: Lactobionic acid is an irritant. Avoid contact with skin and eyes. Solution must be kept refrigerated prior to use.

1. Preparation of erythromycin lactobionate. *Note*: Total procedure for addition of lactobionic acid to erythromycin should not take less than 1.5 hours; all steps must be completed within a 12-hour period.
   a. Add ca. one-third of item 1 to 50% of the final volume of item 6 that has been previously cooled to 5°C to 10°C. Mix slowly; vigorous agitation will produce foaming and prevent adequate mixing. Maintain temperature of solution at 18°C or less throughout processing.
   b. To this item 1 slurry, slowly add 86 mL of item 2 solution, the addition taking approximately 20 minutes. Mix for an additional 10 minutes. item 2 must be added slowly in small amounts to prevent localized low pH in slurry and to give sufficient time for the reaction to occur. Reaction is completed when solution is almost clear.
   c. Add another one-third of item 1 followed by the slow addition of 86 mL of item 2 solution until the reaction is completed.
   d. Add remainder of item 1 followed by the slow and careful addition of the remaining item 2 solution until pH 7.4 is reached.
   e. Add item 6 to 88% of the final volume and mix until drug is dissolved.
   f. Check pH (range 7.0–7.5). If pH is more than 7.5, adjust down to pH 7.4 cautiously with item 2. Add in small quantities with thorough mixing and check pH after each addition. If pH falls less than 7.0, adjust up to 7.4 with small, careful additions of item 1 base. Stir at least 30 minutes after each addition and recheck pH after each addition.
   g. Make a slurry of item 3 and add to the solution. Discontinue cooling, but keep temperature less than 18°C at all times. Mix for 1 hour.
   h. Filter through a previously rinsed filter press or equivalent cellulose filters. Remove item 3 by recirculation through press. Recirculate for at least 15 minutes until solution is clear of item 3.
   i. Filter solution through a previously rinsed approved filtration setup by using a 0.45-μm or finer membrane filter connected in series prefilter. Recirculate for at least 15 minutes and filter into a glass-lined or 316 stainless steel tank.
   j. QS to final volume with item 6. Mix until ingredients are dissolved and solution is uniform. Sample.
   k. Store solution in refrigerator (2–6°C) until filled. Filling of this solution should be completed as soon as possible, but NMT 6 days after the solutions are prepared.
   l. Prepare a sterile 0.22-μm membrane filtration setup.
2. Preparation of bottles. Use type I glass, 50-mL bottles.
   a. Wash, dry, and stack bottles in a container suitable for sterilizing.
   b. Sterilize bottles by using dry heat at 200°C (–0, +50°C) bottle temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for duration of the cycle.
3. Preparation of stoppers. Stopper: West, Faultless, or Selgas. Sterilize by autoclaving at 121°C for 60 minutes and vacuum dry at a temperature less than 90°C.
4. Filtration.
   a. Connect tank, sterile 0.22-μm membrane and sterile surge bottles to filling equipment by using aseptic technique.
   b. Apply N_2 gas pressure to tank to provide adequate filtration rate. (Do not apply more than 10 lb.) Sample.
5. Filling.
   a. Fill solution into each clean, dry sterile bottle and prestopper with lyophilization stoppers.
   b. Place filled bottles in sterile metal trays and introduce them into the previously sterilized chamber. Do not allow filled or bulk solution to warm to temperature. Freeze or refrigerate solution until lyophilized.
   c. Freeze product to −35°C to −38°C for blown vials or −25°C to −30°C when using tubing vials. Freezing temperature below those specified will cause excessive breakage.
   d. Apply 100 to 200 μm vacuum and set shelf temperature controller at 38°C. Set condenser temperature less than −50°C.
   e. Increase shelf temperature as product temperature approaches shelf temperature until product temperature reaches 38°C (±2°C). Hold at this temperature for at least 4 hours.
   f. Release vacuum with sterile N_2 gas and aseptically remove bottles from chamber. Aseptically apply stoppers and seal. Sample.

Esmolol Hydrochloride Injection Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Esmolol hydrochloride	10.00	g
5.90	mg	2	Sodium chloride	5.90	g
2.80	mg	3	Sodium acetate trihydrate	2.80	g
0.546	mg	4	Glacial acetic acid	0.546	g
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Hydrochloric acid for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5.0 (4.5–5.5); package in nonlatex bags.

Concentrate

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Esmolol hydrochloride	250.00	g
250.00	mg	2	Propylene glycol	250.00	g
250.00	mg	3	Alcohol, USP	250.00	g
17.00	mg	4	Sodium acetate trihydrate	17.00	g
0.00715	mL	5	Glacial acetic acid	7.15	mL
QS	mL	6	Hydrochloric acid for pH adjustment		
QS	mL	7	Sodium hydroxide for pH adjustment		
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.5 to 5.5.

Estradiol Cypionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Estradiol cypionate, USP	2.00	g
20.00	mg	2	Benzyl alcohol, NF	20.00	g
QS	mL	3	Cottonseed oil, USP	QS to 1.00	L

Note: Adjust fill volume for different strengths.

Estradiol Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	mg	1	Estradiol, NF	0.50	g
1.00	mg	2	Carboxymethylcellulose sodium, USP	1.00	g
1.00	mg	3	Sodium phosphate, USP	1.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
1:10	M	5	Benzalkonium chloride 50%, USP	1.10	M
QS	mL	6	Water for injection, USP	1.00	L
QS	mL	7	Acetic acid for buffering	QS	QS
QS	mL	8	Sodium acetate for buffering	QS	QS

Note: Adjust quantity of item 1 for 1 mg/mL strength.

Estradiol Valerate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Estradiol valerate, USP	10.00	g
20.00	mg	2	Benzyl alcohol, NF	20.00	g
QS	mL	3	Sesame oil, USP	QS to 1.00	L

Estrogenic Substances in Oil Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.50	mg	1	Estrone, NF	1.50	g
0.50	mg	2	Estrogenic substances, combined with item 1 = 2 mg	0.50	g
40.00	mg	3	Benzyl alcohol, NF	40.00	g
QS	mL	4	Sesame oil, USP	QS to 1.00	L

Estrone, Estradiol, and Cyanocobalamin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Estrone, NF	2.00	g
2.00	mg	2	Estradiol, NF	2.00	g
1000.00	mg	3	Cyanocobalamin, USP	1000.00	mg
1.00	mg	4	Carboxymethylcellulose sodium, USP	1.00	g
1.00	mg	5	Sodium phosphate, USP	1.00	g
9.00	mg	6	Sodium chloride, USP	9.00	g
15.00	mL	7	Benzyl alcohol, NF	15.00	g
QS	mL	8	Water for injection, USP	QS to 1.00	L
QS	mL	9	Hydrochloric acid for pH adjustment	QS	
QS	mL	10	Acetic acid for buffering	QS	
QS	mL	11	Sodium acetate for buffering; see item 10	QS	

Estrone Sterile Suspension Veterinary Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Estrone, NF	5.00	g
1.00	mg	2	Carboxymethylcellulose, USP	1.00	g
1.00	mg	3	Sodium phosphate, USP	1.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
1:10	M	5	Benzalkonium chloride, 50%, USP	1.10	M
QS	mL	6	Water for injection, USP	1.00	L
QS	mL	7	Acetic acid for buffering	QS	
QS	mL	8	Sodium acetate for buffering; see item 7	QS	

Etanercept Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Etanercept	25.00	g
40.00	mg	2	Mannitol	40.00	g
10.00	mg	3	Sucrose	10.00	g
1.20	mg	4	Tromethamine	1.20	g
5QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Lyophilized powder is reconstituted with 1.0 mL of water for injection containing 0.9% benzyl alcohol.

Etorphine Hydrochloride Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Etorphine hydrochloride (M-99)	1.00	g
3.40	mg	2	Sodium hydroxide, USP	3.40	g
0.50	mg	3	Disodium edetate	0.50	g
14.00	mg	4	Citric acid, USP	14.00	g
0.50	mg	5	Propylene glycol, USP	0.50	g
5.00	mg	6	Benzyl alcohol, NF	5.00	g
QS	mL	7	Water for injection, USP	QS to 1.00	L

Exemestane Aqueous Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Exemestane (micronized)	100.00	g
1.80	mg	2	Methyl paraben	1.80	g
0.20	mg	3	Propyl paraben	0.20	g
8.30	mg	4	Sodium chloride	8.30	g
30.00	mg	5	Polyethylene glycol 400	30.00	g
2.00	mg	6	Polysorbate 80 (Tween®)	2.00	g
1.50	mg	7	Methylcellulose	1.50	g
5.00	mg	8	Lecithin	5.00	g
1.00	mg	9	L-Methionine	1.00	g
0.50	mg	10	Edetate sodium	0.50	g
0.694	mg	11	Sodium phosphate monobasic hydrate	0.694	g
0.588	mg	12	Sodium phosphate dibasic dodecahydrate	0.588	g
QS	mL	13	Sodium hydroxide for pH adjustment		
QS	mL	14	Hydrochloric acid for pH adjustment		
QS	mL	15	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 0.2 L of item 15 in a suitable vessel and add and disperse items 8 and 7 (adding in that order to the vessel). Mix to obtain a homogenous dispersion.
2. Autoclave at 121°C for 15 minutes the preparation in step 1.
3. In another vessel, take 0.8 L of item 15 and add and dissolve all other ingredients except item 1.
4. Pass the solution in step 3 through a 0.22-μm filter to sterilize.
5. Add preparation in step 4 to preparation in step 2 under aseptic conditions.
6. Check and adjust pH to 6.0 to 7.0 with item 13 or 14.
7. Add item 1 (presterilized by heat) and homogenize to form a smooth suspension.
8. Fill.

Famotidine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Famotidine	10.00	g
4.00	mg	2	L-Aspartic acid	4.00	g
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
20.00	mg	4	Mannitol	20.00	g
0.90	%	5	Benzyl alcohol[a]	0.90	%
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a]For multidose injection only. Adjust pH with item 2 or 3 to 5.7 to 6.4.

Fenoldopam Mesylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Fenoldopam mesylate equivalent to fenoldopam	10.00	g
3.44	mg	2	Citric acid	3.44	g
518.00	mg	3	Propylene glycol	518.00	g
0.61	mg	4	Sodium citrate dihydrate	0.61	g
1.00	mg	5	Sodium metabisulfite	1.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Fentanyl Citrate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
78.55	mg	1	Fentanyl citrate, USP	78.55	mg
QS	mg	2	Sodium hydroxide, reagent-grade pellets	QS	mg
QS	mL	3	Hydrochloric acid, reagent-grade bottles	QS	mL
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add item 4 to the stainless steel tank to ca. 95% of the final volume.
2. Add and dissolve item 1 with mixing. After drug addition, maintain protection from undue light exposure.
3. Check pH. Adjust to 4.5 if necessary (range 4.3–4.7) with item 2 or 3 (1% each).
4. QS to final volume with item 4 and mix well, check pH, and adjust as in step 3.
5. Filter through a previously rinsed filtration setup by using an approved 0.45-μm or finer membrane, with an approved prefilter, into a clean glass-lined or 316 stainless steel tank. Sample. Before starting to fill, flush 3 to 4 L to clean equipment of residual water and to set dosage. Discard.
6. Using an inline filter, fill specified amount into each clean, dry type I glass ampoule. Seal.
7. Sterilize in steam autoclave at 115°C and an F_0 range of 8 to 20. Cooling water rate should be controlled to minimize thermal shock. Alternatively, sterilize in steam autoclave at 122°C and an F_0 range of 8 to 20. Sample.

Filgrastim Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.30	mg	1	Filgrastim	0.30	g
0.59	mg	2	Sodium acetate	0.59	g
50.00	mg	3	Sorbitol	50.00	g
0.004	%	4	Polysorbate 80	0.004	%
0.035	mg	5	Sodium chloride	0.035	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Flosulide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Flosulide	10.00	g
50.00	mg	2	*N*-Methyl pyrrolidone	50.00	g
50.00	mg	3	Dimethylacetamide	50.00	g
300.00	mg	4	Polyethylene glycol 400	300.00	g
20.00	mg	5	Benzyl alcohol	20.00	g
0.50	mg	6	Alpha-tocopheryl acetate	0.50	g
QS	mL	7	Propylene glycol, USP	QS to 1.00	L

Fluconazole Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Fluconazole	2.00	g
9.00	mg	2	Sodium chloride	9.00	g
56.00	mg	3	Dextrose anhydrous, USP	56.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Use either item 2 or 3; packaged in plastic bags and sterilized by autoclaving.

Flumazenil Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.10	mg	1	Flumazenil	1.00	g
1.80	mg	2	Methyl paraben	1.80	g
0.20	mg	3	Propyl paraben	0.20	g
9.00	mg	4	Sodium chloride	9.00	g
0.10	mg	5	Disodium edetate	0.10	g
0.10	mg	6	Acetic acid, glacial	0.10	g
QS	mL	7	Sodium hydroxide for pH adjustment	QS	
QS	mL	8	Hydrochloric acid for pH adjustment	QS	
QS	mL	9	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 4.0 with item 7 or 8.

Folic Acid and Niacinamide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
15.00	mg	1	Folic acid, USP, 15% excess	19.16	g
150.00	mg	2	Niacinamide, USP, 15% excess	191.60	g
0.5	%	3	Liquefied phenol, NF	5.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS		7	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Maintain cover of item 7 throughout the manufacturing process.
2. Dissolve item 2 in 0.6 L of item 4.
3. Add item 1 into step 1 to make a suspension and dissolve it by slow addition of 40% of item 6 until dissolved; do not overadd item 6.
4. Dissolve item 3 in 0.1 L of item 4 and add this solution to that of step 2 slowly.
5. Make up volume. Check and adjust pH to 6.8 (6.5–7.0)
6. Filter through a 0.45-μm prefilter and 0.22-μm filter into a presterilized staging assembly.
7. Fill 10.5 mL into type I 10-mL amber glass vials presterilized aseptically under cover of item 7.

Follitropin-Beta for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
75.00	IU	1	Follitropin-beta	75,000	IU
25.00	mg	2	Sucrose	25.00	g
7.35	mg	3	Sodium citrate Dihydrate	7.35	g
0.10	mg	4	Polysorbate 80	0.10	g
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 7.0; 1 mL per vial lyophilized.

Furaltadone Injectable Solution (50 mg/mL)

Formulation

Furaltadone, 5.00 g; tartaric acid, 1.25 g; Kollidon 12 PF [1], 25.00 g; water of injectables, add 100 mL.

Manufacturing Directions

Dissolve the solid substances in water at approximately 50 °C.

The sterilization can be made by aseptic filtration or by heating (120°C, 20 minutes).

Remark

To prevent of discoloration of Kollidon in the solution during storage, 0.2% to 0.5% of cysteine could be added as antioxidant.

Furosemide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Furosemide, USP	10.00	g
7.50	mg	2	Sodium chloride, USP	7.50	g
1.34	mg	3	Sodium hydroxide, NF	1.34	g
QS		4	Sodium hydroxide, NF, for pH adjustment	QS	
QS		5	Hydrochloric acid, reagent grade, NF	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS		7	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Preparation of water. Check item 6 to be used for solution preparation and verify that it meets conductivity limit of NMT 1.0 mS/s and pH range of 5.0 to 7.0.
2. Preparation of solution. *Caution*: Product is light sensitive. Protect from light as much as possible throughout the processing.
   a. Put 900 mL of item 6 into the preparation vessel and bubble N_2 gas (item 7) to expel dissolved oxygen gas. Monitor the O_2 sensor display (O_2% limit = NMT 1).
   b. Put 300 mL of item 6 into another preparation vessel and bubble item 7 for 20 minutes.
   c. Add and dissolve items 2 and 3 into the step 2a preparation vessel.
   d. Add item 1 into step 2c solution and stir until it is completely dissolved and the solution is clear.
   e. Check pH (range 8.5–9.1).
   f. Adjust pH if necessary with 10% sodium hydroxide solution or 1 N hydrochloric acid solution.
   g. After adjusting pH, make up volume to 1 L by item 6 from step 2b and mix it for 15 minutes, followed by bubbling item 7 for 20 minutes.
   h. Check final pH (range 8.5–9.1).
   i. Take sample for assay.
3. Preparation of ampoules. Use sterilized type I 2-mL amber glass ampoules, USP.
4. Preparation of filtration assembly and machine parts for production. Clean and sterilize filtration assembly and machine parts in the autoclave as per USP 24.
5. Integrity testing. Before starting the sterile filtration, check the integrity of filter cartridge.
6. Aseptic filling. Fill 2.15 mL (range 2.1–2.2 mL) solution from the bulk into each sterile dry clean ampoule and seal it.
7. Terminal sterilization. Load the filled ampoules inside the autoclave chamber. Run the cycle at a sterilization temperature of 121.1°C and an exposure time of 20 minutes.
8. Ampoules leak test. Perform the leak test.
9. Optical checking. Check the ampoules under the optical checking machine.

Gentamicin and Prednisolone Ophthalmic Drops

Bill of Materials (Batch Size 42 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Water purified (distilled), USP	6.00	L
0.65[a]	mg	2	Hydroxypropyl methylcellulose, F-4M	39.90	g
Part II					
		3	Water purified (distilled), USP	10.00	L
4.50	mg	4	Polyvinyl alcohol, 20–90	918.80	g
0.50[b]	mg	5	Polysorbate 80, NF (use a 10% solution)	b	mL
Part III					
		6	Water purified (distilled), USP	40.00	L
4.50	mg	7	Sodium citrate, dihydrate, USP	295.30	g
3.30[c]	mg	8	Gentamicin sulfate, USP	216.60[d]	g
6.80[a]	mg	9	Sodium chloride, USP	441.30	g
0.15	mg	10	Disodium edetate, USP	9.80	g
0.05	mg	11	Benzalkonium chloride, NF (10% solution)	32.80[e]	mL
QS	mL	12	1 N Hydrochloric acid, NF[a]	QS[f]	mL
QS	mL	13	1 N Sodium hydroxide, NF[a]	QS[f]	mL
		14	Water purified (distilled), USP	60.00	L
		15	Sterile filtrate, QS parts I, II, and III	38.40	L
Part IV					
10.00	mg	16	Prednisolone acetate, USP	420.00	g
Part V					
		17	Water purified (distilled) USP	2.88	L

[a] Includes amount contained in hydroxypropyl methylcellulose micronizing diluent. It contains 0.5% hydroxypropylmethyl cellulose F-4M and 0.9% sodium chloride.
[b] Required amount is contained in the micronization of pred acetate, the specific gravity of polysorbate 80 is 1.08g/mL.
[c] The amount of gentamicin sulfate equivalent to 3.0 mg/mL of gentamicin base.
[d] The amount of gentamicin sulfate is calculated as follows: 216.6 g $\times$ 1000 mg/ mg/manufacturer's assay value $=$ g of gentamicin sulfate required.
[e] The amount of benzalkonium chloride, 10% solution, to be added must be calculated on the basis of the assay value of the raw material lot used as follows: 32.8 mL $\times$ 10.0%/assay value (%) $=$ mL benzalkonium chloride, 10% solution, required.
[f] For pH adjustment.

Manufacturing Directions

Part I

1. Measure out ca. 30 L of item 1 into a stainless steel pressure vessel. Begin mixing with a suitable mixer and heat it to 80°C to 90°C.
2. Measure out 3 L of heated item 1 into a stainless steel pressure vessel. Begin mixing it with a propeller mixer. Add item 2 slowly to the vortex and mix until it is thoroughly dispersed.
3. Transfer the dispersion to a glass bottle, rinse the container, and add the rinsings to the glass bottle. Place the glass bottle in the water sink and begin mixing.
4. Add item 1 to the bottle to bring the volume to ca. 6 L. Fill the water sink with cold water purified (distilled). Cool the dispersion to less than 30°C.
5. Cover the mouth of the bottle with two layers of aluminum foil. Secure the aluminum foil with two rubber bands. Place the bottle in the refrigerator, chill for at least 12 hours at 15°C or less until item 2 is completely hydrated.

Part II

1. Measure out ca. 30 L of item 3 into a stainless steel-jacketed pressure vessel. Heat it to 85°C to 90°C.
2. When the temperature reaches 85°C to 90°C, turn off the heat source and begin mixing vigorously. Measure out 10 L of heated item 3 into a 20-L glass bottle. Add item 4 slowly to the vortex. Mix for at least 90 minutes until all dissolved.
3. Add item 5 and mix well. Cool to room temperature with continuous agitation by placing in cold water bath.

Part III

1. Measure out ca. 40 L of item 6 into a mixing tank. Begin mixing. Add the items 7 to 11, in order, allowing each to mix thoroughly or dissolve completely before adding the next.
2. Mix thoroughly. Avoid excess foam formation. Add part I to the mixing tank containing part III, while mixing part III. Transfer part II into the mixing tank containing combined parts I and III.
3. Use 1 to 2 L of water purified (distilled) to rinse the part II kettle and any equipment used to transfer part II. Add the rinsings to the mixing tank.
4. Sample for pH. If necessary, adjust pH to 6.4 to 6.6 with item 12 or 13.
5. QS combined parts I, II, and III to 60 L with item 14. Mix parts I, II, and III (base) thoroughly for at least 15 minutes. Avoid excess foam formation. Sample.
6. Mix the product for at least 10 minutes before filtration. Sterile-filter with the aid of N_2 pressure (15–30 lb) into a sterilized 100-L stainless steel pressure vessel. Perform the bubble point test.

Part IV

Prednisolone acetate micronized.

Part V

1. Measure out and transfer item 17 into a suitable glass bottle. Seal the mouth of the bottle with two layers of aluminum foil paper and two layers of parchment paper.
2. Sterilize it by autoclaving for at least 80 minutes at 121°C. Remove the bottles from the autoclave and allow it to cool to room temperature.

Mixing Procedure

1. Grind the steroid for at least 6 hours before mixing.
2. Aseptically receive 38.4 L of sterile-filtered base (combined parts I, II, and III) into a sterilized glass bottle and place the glass bottle on a magnetic mixing table.
3. Place the bottle and magnetic mixer in front of a laminar air flow hood. Aseptically add a sterilized magnetic stirring bar to the glass bottle containing the base. Adjust the mixing speed such that a 0.5-in deep vortex is formed.
4. Aseptically pour the ground item 16 from the grinding jar, through a sterilized funnel, into the bottle containing the base. The volume of the suspension in the bottle should be 42 L.
5. Allow the product to mix with a 0.5-in deep vortex for at least 2 hours.
6. Homogenize the product suspension by using a sterilized homogenizer. Allow the product to mix in the receiving bottle after completion of homogenization for at least 2 hours. Sample.
7. Aseptically fill sterile solution through P2 sintered glass into sterilized container. Perform the bubble point test. Sample.

Gentamicin Injection (20 mg/2 mL)

Bill of Materials (Batch Size 10 L)					
Scale/mL		Item	Material	Qty	UOM
10	mg	1	Gentamicin base, 3% excess (use equivalent amount of gentamicin sulfate), USP	103.0	g
1.2	mg	2	Methyl paraben, USP	12.0	g
0.2	mg	3	Propyl paraben, USP	2.0	g
0.11	mg	4	Sodium edetate, USP	1.1	g
QS		5	Sulfuric acid, reagent-grade pellets, for pH adjustment	QS	
QS		6	Sodium hydroxide pellet for pH adjustment		
QS	mL	7	Water for injection, USP	QS	
QS		8	Nitrogen gas, NF	QS	

Gentamicin Injection (80 mg/2 mL)

Bill of Materials (Batch Size 10 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Gentamicin base, 3% excess (use equivalent amount of gentamicin sulfate), USP	412.00	g
1.80	mg	2	Methyl paraben, USP	18.00	g
0.20	mg	3	Propyl paraben, USP	2.00	g
0.11	mg	4	Sodium edetate, USP	1.10	g
QS		5	Sulfuric acid, reagent-grade pellets, for pH adjustment	QS	
QS		6	Sodium hydroxide pellets for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 10.00	L
QS		8	Nitrogen gas, NF	QS	

Note: Qty of gentamicin sulfate = (1000 ∞ weight of gentamicin base)/(potency of gentamicin as base).

Manufacturing Directions

1. Preparation of water.
   a. Check the water for injection used for solution preparation and verify that it meets conductivity NMT 1 pS/cm.
   b. Take the sample for pH (range 5.0–7.0)
2. Preparation of solution.
   a. Put 3 L of water for injection into the first 20-L preparation vessel and bubble N_2 gas to expel dissolved O_2 for 20 minutes.
   b. Put 9 L of water for injection (hot water, 82–85°C) in a second 20-L preparation vessel. Check and record water temperature.
   c. Add and dissolve methyl paraben and propyl paraben in water for injection from step 2b with stirring until clear solution is obtained.
   d. Bubble N_2 gas through solution for 20 minutes and allow to cool to 30°C or less. Record temperature.
   e. Add and dissolve sodium EDTA into solution of step 2d. Mix until dissolved.
   f. Add and dissolve gentamicin sulfate into solution of step 2f and make a clear solution.
   g. Check and record pH (range 3.5–5.0).
   h. Adjust pH by 2 N H_2SO_4/2 N NaOH solution.
   i. Check pH after adjustment (range 3.5–5.0).
   j. Make volume up to 10 L by water for injection from step 2a and mix for 15 minutes.
   k. Take final pH (range 3.5–5.0).
   l. Bubble N_2 gas for 20 minutes.
   m. Request sample for assay.
   n. Transfer the preparation vessel to solution room.
3. Preparation of ampoules. Use type I 2-mL clear glass ampoules, USP.
   a. Assemble the machine parts (2-mL size) and set up the washing machine as per SOPs.
   b. Wash the ampoules according to SOPs.
   c. Sterilize the ampoules by using the dry heat tunnel.
   d. Set the temperature as per latest validation studies with revised cycle. Set temperature to 330°C.
4. Sterilization. Sterilize the filtration assembly and ampoule filling machine parts at 121°C for 30 minutes. Set the parameters according to current validated cycle. Sterilize the gowns at 121°C for 30 minutes. Set the parameters according to current validated cycle.
5. Integrity testing.
   a. Before starting the sterile filtration, check the integrity of filter cartridge according to SOPs.
   b. Record integrity test results of filter cartridge.
   c. Aseptically connect the N_2 line through sterile N_2 filter to inlet of the holding tank refer to SOPs.
6. Aseptic filling.
   a. Assemble the previously sterilized machine parts and set up the machine as per SOPs.
   b. Aseptically connect one end of previously sterilized filtration assembly with a 0.22-μm filtration cartridge to the outlet of the holding tank and the other end to the buffer holding tank.
   c. Operate the ampoules filling machine according to SOPs. Bleed the dosing system as described in the operating procedure. Adjust the fill volume to 2.15 mL.
   d. Fill 2.15 mL (range 2.1–2.2 mL) solution from the bulk into each sterile, dry clean ampoule and seal it.

Gentamicin Ophthalmic Drops

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Water purified (distilled), USP	10.00	L
14.00	mg	2	Polyvinyl alcohol, 20–90	630.00	g
Part II					
		3	Water purified (distilled), USP	25.00	L
8.00	mg	4	Sodium phosphate dibasic heptahydrate, USP	360.00	g
6.30	mg	5	Sodium chloride, USP	283.50	g
0.127	mg	6	Disodium edetate, USP	5.72	g
0.04	mL	7	Benzalkonium chloride, NF (10% solution)	18.00[a]	mL
3.30	g	8	Gentamicin sulfate, USP	148.50[b]	g
QS	mL	9	5 N Hydrochloric acid, NF[d]	QS	mL
QS	mL	10	1 N Sodium hydroxide, NF[d]	QS	mL
QS	mL	11	Water purified (distilled), USP	QS to 45.00	L

[a] The amount of benzalkonium chloride, 10% solution, to be added must be calculated on the basis of the assay value of the raw material lot used according to the following formula: 18 mL × 10.0%/assay value (%) = mL benzalkonium chloride, 10% solution, required.
[b] The amount of gentamicin sulfate calculated as follows: 148.5 g × 1000 mg/manufacturer's assay value = g of gentamicin sulfate required.

Manufacturing Directions

Part I

1. Measure out ca. 10 L of item 1 into a jacketed stainless steel pressure vessel. Heat it to 85°C to 90°C, turn off the heat source, and begin mixing it by a propeller mixer.
2. Add item 2 slowly to the vortex. Mix for at least 90 minutes until all of it is dissolved. Cool to room temperature, with continuous agitation, by running cold water through the kettle jacket.

Part II

1. Measure out ca. 25 L of item 3 into a mixing tank. Begin mixing and add items 4 to 7, in order, allowing each to dissolve completely before adding the next.
2. Rinse the container with water purified and add the rinsings to the batch.
3. Add item 8.
4. Pump part I into the tank containing part II and mix thoroughly for at least 30 minutes.
5. Sample for pH (range 7.4–7.5). If necessary, adjust the pH with item 9 or 10.
6. Allow any foam to dissipate and QS to 45 L with item 11. Mix thoroughly for at least 15 minutes.
7. Before filtration, mix the product for at least 10 minutes. Perform the bubble point test. Sample.
8. Aseptically fill sterile solution into sterilized containers. Perform the bubble point test.

Glycine Antagonist Injection Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.69	mg	1	Glycine antagonist[a]	1.69	g
0.72	mg	2	Tris (hydroxymethyl) aminomethane	0.72	g
7.68	mg	3	EDTA disodium salt dihydrate	7.68	mg
0.0194	mL	4	Propylene glycol	19.40	mL
50.00	mg	5	Dextrose anhydrous, USP	50.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] (E)-3-Æ2-(phenylcarbamoyl) ethenyl-4,6-dichloroindole-2-carboxylic acid.

Manufacturing Directions

1. In sufficient quantity of item 6, add and dissolve items 2 to 5.

Bolus Injection

1. Add and dissolve item 1.
2. Add item 5 and dissolve.
3. Make up volume with item 6.
4. Filter aseptically and sterilize by autoclaving.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
70.60	mg	1	Glycine antagonist[a]	70.60	g
1.30	mg	2	Tris (hydroxymethyl) aminomethane	1.30	g
10.00	mg	3	Polysorbate 80	10.00	g
300.00	mg	4	Glycofurol	300.00	g
50.00	mg	5	Mannitol	50.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a](E)-3Æ2-(phenylcarbamoyl) ethenyl!-4,6-dichloroindole-2-carboxylic acid.

Manufacturing Directions

1. In a suitable container, add item 5 to item 6 and dissolve.
2. Add and dissolve item 2.
3. In a separate container, add and mix item 1 with item 2 and item 4.
4. Add step 2 into step 3 gradually and slowly.
5. Filter through 0.2-μm membrane filter and autoclave at 131°C for 15 minutes.

Glycopyrrolate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.20	mg	1	Glycopyrrolate	0.20	g
9.00	mg	2	Benzyl alcohol	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH with item 3 or 4 to 3.0 to 4.0.

Gramicidin Ophthalmic Solution (1.3 mg/10 mL)

Formulation

1. Gramicidin, 13 mg; Cremophor RH 40 [1], 0.1 g.
2. Ethanol 96%, 1.0 g; preservatives, QS; water, 98.8 g.

Manufacturing Directions

Mix gramicidin and Cremophor RH 40, heat to approximately 65 °C, stir, and add slowly the heat solution II.

Granisetron Hydrochloride Injection Single Dose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Granisetron, use granisetron hydrochloride	1.12	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: pH 4.7 to 7.3; do not adjust.

Granisetron Hydrochloride Injection Multiple Dose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Granisetron, use granisetron hydrochloride	1.12	g
9.00	mg	2	Sodium chloride	9.00	g
2.00	mg	3	Citric acid	2.00	g
10.00	mg	4	Benzyl alcohol	10.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: pH 4.0 to 6.0; do not adjust.

Guaiacol–Iodide Solution Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Potassium guaiacolsulfonate	40.00	g
50.00	mg	2	Sodium iodide, USP	50.00	g
1.00	mg	3	Sodium metabisulfite, NF	1.00	g
20.00	mg	4	Benzyl alcohol, NF	20.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	

Haloperidol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Haloperidol, use haloperidol decanoate	70.52	g
12.00	mg	2	Benzyl alcohol	12.00	g
QS	mg	3	Sesame oil refined	QS to 1.00	L

Note: For higher strength of 100 mg, change only the quantity of active ingredient.

Hemin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
31.30	mg	1	Hemin	31.30	g
21.50	mg	2	Sodium carbonate	21.50	g
30.00	mg	3	Sorbitol	30.00	g
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Lyophilize 10 mL in each vial.

Heparin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
9.00	mg	1	Benzyl alcohol, NF	9.00	g
9.00	mg	2	Sodium chloride, USP	9.00	g
1000.00	U	3	Heparin sodium lyophilized, USP (NLT 120 U/g), adjust to specification	8.333	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Heparin sodium injection, USP, is a sterile solution. Each milliliter contains 1000, 2500, 5000, 7500, 10000, 15000, or 20000 USP U heparin sodium derived from porcine intestinal mucosa (standardized for use as an anticoagulant), in water for injection, and NMT 10 mg benzyl alcohol as a preservative. The pH range is 5.0 to 7.5. Heparin lock flush solution, USP, is a sterile solution. Each milliliter contains either 10 or 100 USP U heparin sodium derived from porcine intestinal mucosa (standardized for use as an anticoagulant), in normal saline solution, and NMT 10 mg benzyl alcohol as a preservative. The pH range is 5.0 to 7.5.

Manufacturing Directions

Note: Use only fresh pyrogen-free water for injection. Expensive solution; handle with care.

1. Preparation.
   a. Dissolve benzyl alcohol in ca. 80% of the final volume of water for injection.
   b. Add and dissolve sodium chloride and sodium heparin.
   c. Add water for injection, and QS to final volume. Mix thoroughly.
   d. Check and adjust pH (range 5.8–6.8) with 10% HCl or 10% NaOH.
   e. Sample for testing.
   f. Filter solution through a previously rinsed filtration setup, using an approved 0.45-μm membrane and an approved prefilter. Filter into a clean glass-lined or 316 stainless steel holding tank. If not filled within 24 hours, store at 2°C to 8°C. Allow to warm to room temperature before filling.
   g. Prepare for sterilization a 0.22-μm membrane filtration.
2. Preparation of bottles.
   a. Wash and dry type I glass bottles, 10 or 30 mL, and load into appropriate containers for sterilization.
   b. Sterilize at 200°C (−0°C, +50°C), bottle temperature for 225 minutes (−0, +360 minutes), while maintaining the oven temperature at 225°C (±10°C) for the duration of the cycle.
   c. Deliver the bottles to sterile filling area.
3. Preparation of stoppers. West Cpd 867 gray (92-046).
   a. Leach stoppers by boiling for 10 minutes in deionized water.
   b. Wash stoppers in a Prosperity (or equivalent) washer by using rubber cycle with 10 mL of Triton X-100.
   c. Dry in Huebsch (or equivalent) fast dryer at 55°C.
   d. Store in suitable containers until ready for use.
   e. Tray and inspect and rinse thoroughly. Wrap tray and identify properly.
   f. Sterilize at 121°C for 60 minutes.
   Note: Use completely aseptic technique in filling. This is an expensive solution.
4. Filling (10- or 30-mL vials).
   a. Connect bulk solution container, previously prepared sterile filter, and sterile surge bottle to filler by using aseptic technique.
   b. Aseptically fill either 10.5 or 31.0 mL of solution into each clean, sterile bottle. Stopper.
   c. Request sample.
   d. Apply seal and inspect.
   e. Request samples.

Hepatitis B Immune Globulin (Human)

Solvent/Detergent Treated and Filtered

Hepatitis B immune globulin (human) is a sterile solution of immunoglobulin (5±1% protein) containing antibodies to hepatitis B surface antigen (anti-HBs). The product is formulated in 0.075 M sodium chloride, 0.15 M glycine, and 0.01% polysorbate 80, pH 6.25. It contains no preservative and is intended for single use by the intramuscular (IM) route only.

Hexamethylmelamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Hexamethylmelamine	5.00	g
150.00	mg	2	Soybean oil, USP, superfine	150.00	g
12.00	mg	3	Egg phospholipid, parenteral grade	12.00	g
5.00	mg	4	Pluronic F-68®	5.00	g
22.50	mg	5	Glycerin, USP	22.50	g
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Hydrochloric acid for pH adjustment		
QS	mL	8	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable container, dissolve item 1 in item 2 by propeller mixing.
2. Add to this solution slowly item 3 while continue mixing.
3. In another vessel, mix item 4 and 5 and 0.4 L of item 8 by propeller mixing.
4. Add the solution in step 3 to the solution in step 2 slowly and with continuous propeller mixing.
5. Check and adjust pH to 7.4 (range 7.2–7.6) with item 6 or 7.
6. Make up volume with item 8.
7. This is a coarse emulsion (2- to 25-μm droplets); pass it through a Microfluidizer® at 12000 psi pressure 3 times to droplet size of 0.22-μm with distribution of size to ±26%. The size is measured by the quasielastic laser light scattering particle size determination instrument.
8. Fill into suitable parenteral container.
9. Sterilize by autoclaving at 121°C for 15 minutes. 10. Measure particle size again.

Hydrochloric Acid

Bill of Materials (Batch Size 3 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mEq	1	Hydrochloric acid concentrated, NF (11.62 N), 2% excess	516.00	mL
QS	mL	2	Water for injection USP	QS to 3.00	L

Manufacturing Directions

Note: Use glass-lined compounding tanks only, special filtration and filling equipment, and proper safety (inhalation) equipment.

1. Take approximately 500 mL of item 2 in a clearly marked compounding vessel.
2. Measure required quantity of item 1 to the compounding vessel containing item 2.
3. Add item 2 close to QS. Mix thoroughly and allow the solution to cool to room temperature.
4. QS to volume with item 2 and mix thoroughly.
5. Sample for testing.
6. After approval, sterile filter through special filter compatible with formulation (0.22 μm) and fill (flint vials, Teflon-coated stoppers, 1888 gray).

Hydrocortisone Sodium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Hydrocortisone equivalent hydrocortisone sodium phosphate	67.09	g
8.00	mg	2	Creatinine	8.00	g
10.00	mg	3	Sodium citrate	10.00	g
QS	mL	4	Sodium hydroxide for pH adjustment		
3.20	mg	5	Sodium bisulfite	3.20	g
1.50	mg	6	Methyl paraben	1.50	g
0.20	mg	7	Propyl paraben	0.20	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 7.5 to 8.5.

Hydrocortisone Sodium Succinate for Injection (Single-Unit System Lyophilized)

Bill of Materials (Batch Size 20 L)					
Scale/mL		Item	Material	Qty	UOM
63.80	mg	1	Hydrocortisone hemisuccinate, USP	1276.00	g
0.40	mg	2	Sodium phosphate monobasic anhydrous, USP	8.00	g
4.36	mg	3	Sodium phosphate dibasic anhydrous USP	87.20	g
5.25	mg	4	Sodium hydroxide, USP	110.40	g
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 20	L

Manufacturing Directions

1. Preparation of solution.
   a. Prepare a 10% solution of item 4 (110.4 g in 1104 mL) in item 6 in a clean container. Let the solution cool to room temperature.
   b. Prepare a 1 N solution of item 5 (20.0 g in 500 mL) in a clean container. Let the solution cool to room temperature.
   c. In another container, dissolve item 2 in 2000 mL of item 6. Mix to a homogenous solution.
   d. Add item 3 to the solution prepared in step 1c. Mix the tank contents to homogeneous solution.
2. Compounding.
   a. Place approximately 10 L of item 6 into a clear compounding tank. Cool to between 15°C and 18°C.
   b. Add item 1 to step 2a. Agitate to suspend the compound in water.
   c. Record temperature of suspension.
   d. Record pH of suspension.
   e. With constant stirring, carefully add solution in step 1a in small portions to the suspension. Monitor pH and temperature so that they do not rise more than 7.8 and 8°C, respectively. If they do, wait till they come down.
   f. At the end of the addition, the suspension should turn into a clear solution. If needed, add more item 4.
   g. When the solution has cleared, measure pH and temperature.
   h. Add phosphate solution to the compounding tank and mix to a homogenous solution. Check pH and temperature.
   i. Bring to final volume. Again check pH and temperature.
   j. Withdraw sample for laboratory test. After approval, filter through a sterile 0.22-μm filter protecting from light.
   k. Fill and determine fill volumes gravimetrically.
3. Lyophilization.
   a. Chill the shelves to −40°C or less.
   b. Load the chamber keeping vials covered with sterilized clean covers.
   c. Place thermocouple in representative vials on different shelves and record location.
   d. After loading, place washed sterilized center seals in the chamber and close chamber door.
   e. Product thermocouple should register −40°C or less for at least 4 hours.
   f. Start condenser and let it reach −55°C or less.
   g. Start vacuum and let chamber achieve vacuum level of 100 μm or less.
   h. Set the shelf temperature to +15°C; let it run for at least 12 hours.
   i. Raise shelf temperature to +30°C and run the cycle for an additional 36 hours at least.
   j. At the end of the cycle, bleed chamber to atmospheric pressure with sterile dry air or N_2.
   k. Withdraw six representative samples, two from each of the top, middle, and bottom shelves, and close the door.
   l. If all the samples contain moisture 2% or lower, stopper the vials and terminate the cycle, and remove vials for sealing (845 gray stopper).
   m. If any of the samples register more than 2% moisture, extend the cycle and record action.

Hydrocortisone Sodium Succinate for Injection (Nonlyophilized)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Hydrocortisone acetate	50.00	g
9.00	mg	2	Sodium chloride	9.00	g
4.00	mg	3	Polysorbate 80	4.00	g
5.00	mg	4	Carboxymethylcellulose	5.00	g
9.00	mg	5	Benzyl alcohol	9.00	g
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Hydrochloric acid for pH adjustment		
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5 to 7; 5-mL vials.

Twin-Unit System

This product comprises two solutions. Solution 1 is used in conjunction with Solution 2 for reconstitution. Each milliliter of the reconstituted solution contains 50 mg of hydrocortisone.

Hydrocortisone Sodium Succinate for Injection

Solution 1

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.46	mg	1	Sodium phosphate monobasic monohydrate, USP	0.46	g
4.37	mg	2	Sodium phosphate dibasic anhydrous, USP	4.37	g
50.0	mg	3	Hydrocortisone, use equivalent hydrocortisone hemisuccinate, USP, anhydrous (equivalent to hydrocortisone 50.0 g)	63.85	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Nitrogen gas, NF	QS	
QS	mL	7	Water for injection, USP	QS	

Manufacturing Directions

Caution: Hydrocortisone hemisuccinate is a potent drug. Avoid inhaling dust and contact with open sounds. Operators must wear face masks and rubber gloves and wash thoroughly after handling.

1. Preparation.
   a. Add water for injection to a clean 316 stainless steel mixing tank to ca. 60% of the final volume. (The tank should be equipped with baffles to insure better mixing.)
   b. Add and dissolve sodium phosphate monobasic and dibasic with mixing.
   c. Cool the sodium phosphate solution to 10°C to 14°C before proceeding and maintain this temperature range throughout solution preparation.
   d. Slowly add the hydrocortisone hemisuccinate while mixing to form a smooth dispersion.
   e. Add 2 N sodium hydroxide solution with mixing at a rate of NMT 100 mL/min until a pH of 7.5 to 7.6 is attained and the solution is essentially clear. Record pH and amount of 2 N sodium hydroxide added. *Note*: 2 N sodium hydroxide is prepared by dissolving 80 g of item 4 in 1 L water; ca. 80 mL of 2 N sodium hydroxide is needed per liter of hydrocortisone solution.
   f. Add water for injection to final volume and mix thoroughly for at least 45 minutes.
   g. Check and record pH (range 7.5–7.6). If more than 7.6, adjust with 10% hydrochloric acid (if below, use 2 N sodium hydroxide). Record pH and amount of hydrochloric acid or sodium hydroxide used.
   h. Filter solution through an approved 0.2-μm nylon filter into a clean 316 stainless steel portable tank. Use either N_2 pressure (NMT 10 psig) or a pump for filtration.
   i. Sample for testing.
   j. Store solution at 2°C to 8°C until ready for filling. Do not hold for more than 48 hours.
2. Preparation of bottles. Use type I 5-mL glass bottles.
   a. Wash, dry, and load bottles into a container suitable for sterilization.
   b. Sterilize bottles by using dry heat at 200°C bottle temperature for 225 minutes (or an equivalent cycle).
   c. Deliver bottles to the sterile filling area.
3. Preparation of stoppers. Use West Cpd No. 1811 stoppers.
   a. Wash by using rubber cycle and suitable detergents.
   b. Dry in fast dryer at 55°C.
   c. Inspect and wrap for autoclaving.

   d. Sterilize by autoclaving at 121°C for 60 minutes and vacuum dry with heat at a temperature not to exceed 90°C.
   e. Deliver to the sterile filling area.
4. Filtration.
   a. Sample for testing.
   b. Connect tank, sterile 0.2-μm filtration setup and sterile surge bottle to filling machine, using aseptic technique.
5. Filling.
   a. Aseptically fill 2.3 mL into each clean, dry sterile bottle.
   b. Place filled bottles in sterile metal trays and cover with sterile cover.
   c. Freeze product to −30°C (±5°C) and hold the product at this temperature range for at least 1 hour before increasing shelf temperature.
   d. Cool condenser to –50°C or less.
   e. Conduct vacuum level check.
   f. Control chamber pressure to 800 μm (±50 μm).
   g. Control shelf temperature at +20°C (±2°C).
   h. When product temperature reaches +10°C or higher, raise shelf temperature to 60°C (±2°C).
   i. When product temperature reaches +52°C or higher, control chamber pressure at less than 60 μm (full vacuum).
   j. Maintain product temperature greater than 50°C for 3.5 hours (±0.5 hours) before unloading. *Note*: The shelf temperature may be lowered to 25°C (±5°C) before unloading.
   k. Release vacuum with filtered N_2 gas and remove bottles from camber.
   l. Aseptically apply stoppers and seals.
   m. Inspect and send appropriate samples to QA for testing.
6. Finishing. Sample for testing.

Solution 2

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
9.54	mg	1	Benzyl alcohol, NF, for ampoule	9.54	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Nitrogen gas, NF	QS	

Manufacturing Directions

Caution: Use 316 or higher temper-grade stainless steel or steel-lined tank cleaned according to approved BOPs.

1. Preparation of solution.
   a. Collect ca. 95% of the final volume of water for injection in a tank.
   b. Add and dissolve with mixing benzyl alcohol.
   c. Add water for injection to final volume and mix thoroughly for ca. 45 minutes.
   d. Filter solution through a 0.2-μm filtration setup into a portable 316 stainless steel holding tank.
   e. Sample for testing.
   f. Store solution at room temperature before filling. *Note*: Do not hold solution more than 30 days before filling.
2. Preparation of ampoules. Use type I 2-mL glass ampoules.
   a. Wash, dry, and load ampoules in container suitable for sterilization.
   b. Sterilize ampoules by using dry heat at 200°C glass temperature for 225 minutes (or use an equivalent cycle).
   c. Deliver ampoules to the sterile filling area.
3. Filtration.
   a. Send appropriate samples for testing.
   b. Connect tank containing solution, sterile filtration setup, and sterile surge bottle to filling machine by using aseptic technique.
   c. Apply N_2 gas pressure to tank to provide adequate filtration rate (NMT 10 psig). If tank does not have a pressure heat, connect pump between tank and filter.
4. Filling.
   a. Sample for testing.
   b. Aseptically fill 2.3 mL of sterile-filtered solution into each sterile ampoule.
   c. Seal ampoules and inspect.

Hydromorphone Hydrochloride Injection Single Dose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Hydromorphone hydrochloride	1.00	g
2.00	mg	2	Sodium citrate	2.00	g
2.00	mg	3	Citric acid	2.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: For 2- and 4-mg concentration, use the same formula.

Hydromorphone Hydrochloride Injection Multiple Dose

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Hydromorphone hydrochloride	2.00	g
0.50	mg	2	Disodium edetate	0.50	g
1.80	mg	3	Methyl paraben	1.80	g
0.20	mg	4	Propyl paraben	0.20	g
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill 20 mL into vials.

Hydroxycobalamin Injection

Bill of Materials (Batch Size 308 L)					
Scale/mL		Item	Material	Qty	UOM
1000.00	mg	1	Hydroxycobalamin, NF (as acetate, 344.96 × 100___% assay)	344.96[a]	g
0.204	mg	2	Sodium acetate trihydrate, USP	62.83	g
2.18	mg	3	Glacial acetic acid, USP, for pH adjustment	136.14	g
8.20	mg	4	Sodium chloride, USP	2525.60	g
1.50	mg	5	Methyl paraben, USP	462.00	g
0.20	mg	6	Propyl paraben, USP	61.60	g
QS	mL	7	Water for injection, USP	QS to 308.00	L
QS	mL	8	Nitrogen gas, NF	QS	

[a]Take the moisture content and the assay value of hydroxycobalamin (as acetate) into calculation.

Manufacturing Directions

1. Measure ca. 33 L of item 7 into a clean stainless steel container and heat to 90°C.
2. Add items 5 and 6 to the heated water and stir to dissolve. Cool to 25°C to 30°C.
3. Measure ca. 253 L of item 7 into another stainless steel clean mixing tank and mark it accordingly.
4. Add the solution from step 2 into the mixing tank with constant agitation.
5. Add items 2, 3, and 4 into the mixing tank with constant agitation until a clear solution is obtained.
6. Add item 1 into the mixing tank with constant agitation until a clear solution is obtained.
7. Bring to final volume with item 7; check pH and sample for in-process checks.
8. Bubble item 8 continuously into the mixing tank.
9. Sterile filter through a 0.22-μm filter into an appropriate reservoir for filling.
10. Use amber type I vials, 1888 gray stoppers, and appropriate aluminum seals.

Hydroxyprogesterone Caproate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
125.00	mg	1	Hydroxyprogesterone caproate, USP	125.00	g
460.00	mg	2	Benzyl benzoate, USP	460.00	g
20.00	mg	3	Benzyl alcohol, NF	20.00	g
QS	mL	4	Castor oil, USP	QS to 1.00	L

Hydroxypropylmethylcellulose Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Hydroxypropylmethylcellulose	20.00	g
4.90	mg	2	Sodium chloride	4.90	g
0.75	mg	3	Potassium chloride	0.75	g
0.48	mg	4	Calcium chloride	0.48	g
0.30	mg	5	Magnesium chloride	0.30	g
3.90	mg	6	Sodium acetate	3.90	g
1.70	mg	7	Sodium citrate	1.70	g
QS	mL	8	Sodium hydroxide for pH adjustment	QS	
QS	mL	9	Hydrochloric acid for pH adjustment	QS	
QS	mL	10	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 6.8 to 7.6. Fill bottles and terminally sterilize.

Hyoscine Butylbromide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.0	mg	1	Hyoscin-*N*-butylbromide	20.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Hydrobromic acid, 1% solution	QS	mL
QS	mL	4	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Preparation of water. Check item 2 to be used for solution preparation and verify that it meets conductivity limit of NMT 1 mS/cm and pH range of 5 to 7.
2. Preparation of solution.
   a. Put 900 mL of item 2 into the preparation vessel and bubble N_2 gas (item 4) to expel dissolved O_2 gas. Monitor the O_2 sensor display (O_2% limit = NMT 1).
   b. Add and dissolve item 1 into step 2-a preparation vessel. Mix well with stirring to make clear solution.
   c. Check pH (range 4.0–5.2).
   d. Adjust pH if necessary with item 3 (range 4.0–5.2).
   e. After adjustment of pH, make up volume to 1 L by item 2 and mix during bubbling item 4 until oxygen % is less than 1.
   f. Check final pH (range 4.0–5.2).
   g. Take sample for assay.
3. Preparation of ampoules. Use type I 2-mL clear glass ampoules, USP. Sterilize the ampoules by using dry heat tunnel.
4. Preparation of filtration assembly and machine parts for production. Clean and sterilize filtration assembly and machine parts by autoclaving.
5. Prefiltration.
   a. Before starting the filtration, check the integrity of filter cartridge.
   b. Integrity test results of filter cartridge.
   c. Transfer the solution from the preparation vessel to mobile vessel through filtration assembly, containing a 0.45-μm filter cartridge.
   d. After filtration, transfer mobile vessel to solution room.
6. Final filtration.
   a. Before starting the final filtration, check the integrity of filter cartridge.
   b. Aseptically connect the N_2 line through sterile N_2 filter to the inlet of vessel.
   c. Aseptically connect one end of the previously sterilized filtration assembly with 0.22-μm pore-size filtration cartridge to the outlet of vessel and the other end to the buffer holding tank on the ampoule's filling machine parts.
   d. Filter the solution.
7. Aseptic filling. Fill 1.10 mL (range 1.05–1.15 mL) solution from the bulk into each sterile dry clean ampoule and seal it.
8. Terminal sterilization and leak test. Load the inverted ampoules inside the autoclave chamber and run the cycle as per following parameters: sterilization temperature 121.1°C and exposure time 20 minutes.
9. Optical checking. Check the ampoules under optical checking machine.

Ibuprofen Lysinate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Ibuprofen, use ibuprofen lysinate	12.00	g
9.33	mg	2	Sodium chloride	9.33	g
QS	mL	3	0.1 N Sodium hydroxide for pH adjustment	QS	
QS	mL	4	0.1 N Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take item 5 into a jacketed stainless steel vessel and maintain at 15°C to 30°C.
2. Begin mixing at 600 to 800 rpm and add item 2 to dissolve.
3. Add item 1 to vessel and dissolve. Add rinses. This ensures full dissolution of item 1.
4. Check and adjust pH to 7.2 to 7.6 with item 3 or 4.
5. Make up volume with item 5.
6. Transfer to filling area, filter, and autoclave at 123°C for 22 minutes.

Ibutilide Fumarate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.10	mg	1	Ibutilide fumarate (equivalent to 0.087 mg of base)	0.10	g
0.189	mg	2	Sodium acetate trihydrate	0.189	g
8.90	mg	3	Sodium chloride	8.90	mg
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 4.60 with item 4.

Idarubicin Hydrochloride Injections

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Idarubicin hydrochloride	1.00	g
25.00	mg	2	Glycerin	25.00	g
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.5; terminally sterilize.

Imiglucerase for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
21.20	U	1	Imiglucerase	21,200	U
17.00	mg	2	Mannitol	17.00	g
5.20	mg	3	Trisodium citrate	5.20	g
1.80	mg	4	Disodium hydrogen citrate	1.80	g
0.053	mg	5	Polysorbate 80	0.053	g
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Citric acid for pH adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL for 212 U and 20 mL for 424 U and lyophilize after adjusting pH.

Immune Globulin (Human) for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	IgG	50.00	g
30.00	mg	2	Albumin (human)	30.00	g
50.00	mg	3	Sucrose	50.00	g
5.00	mg	4	Sodium chloride	5.00	g
QS	mg	5	Citric acid for pH adjustment	QS	
QS	mg	6	Sodium carbonate for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: The heat treatment step employed in the manufacture of immune globulin IV (human) is pasteurization at 60°C for 10 hours in aqueous solution form with stabilizers. Lyophilized product to give 5% IgG per vial.

Infliximab Recombinant for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Infliximab	10.00	g
50.00	mg	2	Sucrose	50.00	g
0.05	mg	3	Polysorbate 80	0.05	g
0.22	mg	4	Sodium phosphate monobasic monohydrate	0.22	g
0.61	mg	5	Sodium phosphate monobasic dihydrate	0.61	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: 10 mL is lyophilized in each vial.

Insulin Aspart Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	U	1	Insulin aspart[a]	100,000	U
16.00	mg	2	Glycerin	16.00	g
1.50	mg	3	Phenol	16.00	g
1.72	mg	4	*M*-Cresol	1.72	g
19.60	mg	5	Zinc as zinc oxide	16.90	mg
1.25	mg	6	Disodium hydrogen phosphate dihydrate	1.25	g
0.58	mg	7	Sodium chloride	0.58	g
QS	mL	8	Hydrochloric acid 10% for pH adjustment		
QS	mL	9	Sodium hydroxide 10% for pH adjustment		
QS	mL	10	Water for injection, USP	QS to 1.00	L

[a] B28 asp regular human insulin analog; adjust pH to 7.2 to 7.6.

Insulin Glargine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.637[a]	mg	1	Insulin glargine	3.673	g
30.00	mg	2	Zinc (as zinc oxide equivalent)	30.00	mg
2.70	mg	3	*M*-Cresol	2.70	g
20.00	mg	4	Glycerol, 85%	20.00	g
QS	mL	5	Hydrochloric acid, 10%, for pH adjustment		
QS	mL	6	Sodium hydroxide, 10%, for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a] Equivalent to 100 U; adjust to pH 5.0 with item 5 or 6.

Insulin Human 70/30

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1000	U	1	Insulin human, USP, approximately 2% excess	1000,000	U
0.011	mg	2	Zinc oxide, USP; to give 0.025 mg/100 U	0.011	g
0.73	mg	3	Liquefied phenol, USP, equivalent to 0.65 mg/mL, calculated at 89% phenol	0.73	g
1.60	mg	4	Metacresol, USP	1.60	g
16.00	mg	5	Glycerin, USP (parenteral)	16.00	g
0.241	mg	6	Protamine sulfate, USP (purified) to provide 0.270 mg base/100 U in NPH crystallization part	0.241	g
3.78	mg	7	Sodium phosphate dibasic, USP	3.78	g
QS	mL	8	Water for injection, USP	QS	
QS	mL	9	Hydrochloric acid, 10% solution, for pH adjustment	QS	
QS	mL	10	Sodium hydroxide, 10% solution, for pH adjustment	QS	

Manufacturing Directions

This product is prepared by combining 70 parts by volume of human insulin NPH with 30 parts by volume of human insulin buffered regular.

Manufacture of NPH Insulin (Insulin Section)

1. Weigh the required amount of water for injection (775 kg) into a stainless steel manufacturing tank.
2. Add and mix accurately weighed quantities of liquefied phenol (617.9 g), metacresol (1.354 g), and glycerin (13.536 g) until adequately blended.
3. Add and mix a calculated amount of protamine sulfate purified (588.1 g) until completely dissolved.
4. Add and mix a calculated amount of insulin human (6.467 g based on potency of 25.7 U/mg and 0.9% excess) until all crystals are completely wetted.
5. Dissolve an accurately weighed amount of zinc oxide (21.49 g) in 10% hydrochloric acid solution (1.425 mL) and then add to a suitable container having a specified amount of water for injection.
6. Add the contents of the container to the insulin mixture. Mix the material until all crystals are dissolved. Determine the pH of the solution (7.35–7.55) and adjust, if necessary, to the proper range with 10% hydrochloric acid solution, or 10% sodium hydroxide solution.
7. Add additional water for injection to adjust the solution to final weight to give 846 L.

Buffer Section

1. Weigh the required amount of water for injection (800 kg) into a stainless steel manufacturing tank.
2. Add and mix accurately weighed quantities of liquefied phenol (655.2 g), metacresol (1.370 g), glycerin (13.696 kg), and sodium phosphate dibasic (6.471 kg) until all crystals are dissolved.
3. Add additional water for injection to adjust the solution to a final weight of 846 kg or 856 L.
4. Prepare a test sample representing a combination of equal volumes of insulin and buffer sections for NPH for pH determination.
5. If necessary, adjust pH of the buffer section with 10% hydrochloric acid solution or 10% sodium hydroxide solution, until the pH of an equal-parts mixture of the two bulk solutions is within proper range (7.35–7.55).
6. Separately sterilize each of the two solutions by membrane filtration.
7. Combine appropriate quantities of insulin and buffer sections for NPH aseptically and mixed in a suitable tank.
8. Aseptically adjust the pH of the resulting mixture to proper range, if necessary, by adding either 10%

hydrochloric acid solution, sterile, or 10% sodium hydroxide solution, sterile.
9. Allow the mixture to crystallize for at least 24 hours. Adjust the pH of the mixture aseptically to the proper pH range (7.35–7.55), if necessary, by adding either 10% hydrochloric acid solution, sterile, or 10% sodium hydroxide solution, sterile. After the NPH section is crystallized, take an in-process assay (to ensure 97–103% value).

Buffered Regular Insulin

1. Weigh the required quantity of water for injection (750 kg) into a stainless steel tank or glass container.
2. Add accurately weighed quantities of liquefied phenol (590.1 g), metacresol (1.293 g), glycerin (12.928 kg), and sodium phosphate dibasic (3.054 kg) and mix the contents until all components are dissolved.
3. While continuing to mix, add a calculated amount of insulin human (3.098 g based on 26.4 U/mg and 0.9% excess).
4. After the crystals are completely dissolved, dissolve the required amount of zinc oxide (10.27 g) in a measured volume of 10% hydrochloric acid solution (700 mL) and then add to a suitable container having a specified amount of water for injection (811 kg).
5. Add the contents of the container to the insulin solution.
6. Determine the pH of the solution and adjust, if necessary, to the proper pH range (7.35–7.55) with 10% hydrochloric acid solution or 10% sodium hydroxide solution.
7. Add additional water for injection to adjust the solution to final weight to yield a volume of 808 L.
8. If necessary, adjust the pH of the final solution (7.35–7.55) by adding either 10% hydrochloric acid solution or 10% sodium hydroxide solution.
9. Sterilize this solution by membrane filtration. Samples for in-process assays are routinely taken aseptically following the sterile filtration process. However, on occasion, samples may be taken prior to filtration.

NPH/Buffered Regular, Final Mixture

1. Combine aseptically the appropriate quantities of NPH insulin (70 parts) and buffered regular insulin (30 parts) and mixed in a suitable tank.
2. Aseptically adjust the pH of the final suspension to the proper pH range (7.35–7.55), if necessary, by adding either 10% hydrochloric acid solution, sterile, or 10% sodium hydroxide solution, sterile.
3. Fill the sterile suspension aseptically into sterile type I glass vials.
4. Keep the suspension homogeneous during transfer and filling operations. Fit the vials with rubber closures and sealed with aluminum seals.

Testing

Noncompendial tests include HPLC potency, nitrogen content, phenol and metacresol by HPLC, insulin by semiautomated Biuret method, endotoxins, zinc by atomic absorption, and pH determination.

Insulin Human Isophane Suspension (NPH)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	U	1	Insulin human, USP, approximately 2% excess	100,000	U
0.012	mg	2	Zinc oxide, USP, to give 0.025 mg/100 U	0.012	g
0.73	mg	3	Liquefied phenol, USP, equivalent to 0.65 mg/mL, calculated at 89% phenol	0.73	g
1.60	mg	4	Metacresol, USP	1.60	g
16.00	mg	5	Glycerin, USP (Parenteral)	16.00	g
0.35	mg	6	Protamine sulfate, USP (purified) to provide 0.025 mg base/100 U insulin; calculated at 77.5% base	0.35	g
3.78	mg	7	Sodium phosphate dibasic, USP	3.78	g
QS	mL	8	Water for injection, USP	QS	
QS	mL	9	Hydrochloric acid, 10% solution, for pH adjustment		
QS	mL	10	Sodium hydroxide, 10% solution, for pH adjustment		

Manufacturing Directions

A typical 5000-L batch will yield 483091 vials. It is prepared from two bulk solutions: an insulin section and a buffer section.

Insulin Section (2500 L)

1. Weigh the required quantity of water for injection (2380 kg) into a stainless steel manufacturing tank.
2. Add accurately weighed quantities of liquefied phenol (1.826 kg), metacresol (4.0 kg), and glycerin (40.0 kg) and mix the solution until homogeneous.
3. Sequentially add accurately weighed quantities of protamine sulfate purified (1.737 g; calculated at 77.5% protamine base; quantity required to yield 0.270 mg of protamine base/100 U of insulin) and insulin human (19.0 kg at the rate of 26.5 U/mg, including 0.7% excess).
4. Dissolve the required amount of zinc oxide (55.6 g) in a measured volume of 10% hydrochloric acid solution (4.5 L) and add to a stainless steel stockpot containing a specified amount of water for injection.
5. Add the contents of the stockpot to the insulin mixture.
6. When the insulin crystals are dissolved, determine the pH of the solution and adjust (7.0–7.5), if necessary, to the proper pH range with 10% hydrochloric acid solution or 10% sodium hydroxide solution.
7. Add additional water for injection to adjust the solution to final weight (QS to 2513 kg = 2500 L).

Buffer Section (2520 L, Includes Extra Amount over Batch Requirement)

1. Weigh the required quantity of water for injection (2450 kg) into a stainless steel manufacturing tank.
2. Add accurately weighed quantities of liquefied phenol (1.840 kg), metacresol (4.032 kg), glycerin (40.32 kg), and sodium phosphate dibasic (19.05 kg) and mix until all crystals are dissolved.
3. Volumetrically measure an amount of 10% hydrochloric acid solution (4.5 L) and add to the solution.
4. Add additional water for injection to adjust the solution to final weight (2538 kg = 2520 L; excess quantity of batch prepared to insure adequate quantity of full insulin solution).
5. Prepare a test sample for pH determination by mixing equal volumes of each bulk solution.
6. Determine pH. If necessary, adjust pH of the buffer section (to 7.0–7.5) with 10% hydrochloric acid solution or 10% sodium hydroxide solution, until the pH of an equal-parts mixture of the two bulk solutions is within proper range (7.0–7.5).
7. Routinely take samples for in-process assays following the sterile filtration process; however, on occasion samples may be taken prior to filtration.
8. Sterilize each of the two solutions by membrane filtration. Collect the two sterile solutions in separate sterile holding tanks.
9. Aseptically fill appropriate amounts of the two sterile solutions (1:1) into sterile type I glass vials. The vials are fitted with rubber closures and sealed with aluminum seals.
10. Maintain the filled vials at controlled room temperature for at least 24 hours to facilitate the crystallization process.
11. Alternatively, mix the two sterile solutions in a sterile filling tank. Maintain the mixture at controlled room temperature for at least 24 hours prior to filling to facilitate the crystallization process.
12. Aseptically take a control sample from the final mixture. The filled vials may be stored in a chill room until ready for finishing.

Testing

Noncompendial analytical methods include nitrogen content of insulin crystals and product by nitrogen analyzer, determination of zinc in insulin by atomic absorption, determination of phenol and metacresol by HPLC, high-molecular-weight protein content of crystals and product by size exclusion HPLC, insulin by Biuret method, and bacterial endotoxin tests.

Insulin Lispro Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	U	1	Insulin lispro[a]	100,000	U
0.28	mg	2	Protamine sulfate	0.28	g
16.00	mg	3	Glycerin	16.00	g
3.78	mg	4	Sodium phosphate dibasic	3.48	g
1.76	mg	5	*M*-Cresol	1.76	g
0.025	mg	6	Zinc ion (as zinc oxide equivalent)	0.025	g
0.715	mg	7	Liquefied phenol	0.715	g
QS	mL	8	Sodium hydroxide, 10% solution, for pH adjustment		
QS	mL	9	Hydrochloric acid, 10% solution, for pH adjustment		
QS	mL	10	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 7.0 to 7.8 with item 8 or 9.
[a] Lys (B28), Pro (B29) human insulin analog.

Insulin Regular

Bill of Materials (Batch Size 2500 L to give 241545 Vials)					
Scale/mL		Item	Material	Qty	UOM
100.00	U	1	Insulin human, USP, 2% excess, 26.5 U/mg	9.519	g
2.50	mg	2	Metacresol, USP	6.25	g
16.00	mg	3	Glycerin, USP	40.00	kg
1.00	mL	4	Water for injection, USP	QS	kg
QS	mL	5	Hydrochloric acid, 10% solution, for pH adjustment	2.215	mL
QS	mL	6	Sodium hydroxide, 10% solution, for pH adjustment	3.30	mL

Note: Adjust the quantity of insulin based on activity.

Manufacturing Directions

1. Put approximately 2400 kg of water for injection into a stainless steel manufacturing tank.
2. Add item 2 and 3 to the tank and mix well until contents are dissolved.
3. While mixing, add item 1. After the crystals are completely wetted, add item 5. When the crystals are dissolved, measure the pH; add item 6 or 5 to adjust the pH to between 7.0 and 7.8.
4. Add item 4 to make up the volume. Measure pH again.
5. Readjust pH with item 5 or 6 to between 7.0 and 7.8.
6. Sterilize the solution by membrane filtration. Sample and hold in sterile holding tank.
7. Fill aseptically into sterile type I glass vials fitted with rubber closure and sealed with aluminum seal.

Testing

Noncompendial analytical methods include nitrogen content of crystals and formulation by nitrogen analyzer, determination of zinc by atomic absorption, high-molecular-weight protein content by size exclusion HPLC, pH determination, and bacterial endotoxin test.

Interferon Injection 1: Interferon Alpha-2a

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3 MM	IU	1	Interferon alpha-2a	3 B	IU
7.21	mg	2	Sodium chloride	7.21	g
0.20	mg	3	Polysorbate 80	0.20	g
10.00	mg	4	Benzyl alcohol	10.00	g
0.77	mg	5	Ammonium acetate	0.77	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: The active concentration may range from 3 to 36 MM with no change in the quantity of other ingredients.

Interferon Injection 1: Interferon Alpha-2a (Prefilled Syringe)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3 MM	IU	1	Interferon alpha-2a	3B	IU
3.60	mg	2	Sodium chloride	3.60	g
0.10	mg	3	Polysorbate 80	0.10	g
5.00	mg	4	Benzyl alcohol	5.00	g
0.385	mg	5	Ammonium acetate	0.385	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: 11.1 mg/0.5 mL.

Interferon Beta-1b Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.30	mg	1	Interferon beta-1b	0.30	g
15.00	mg	2	Albumin human	15.00	g
15.00	mg	3	Dextrose	15.00	g
5.40	mg	4[a]	Sodium chloride	5.40	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] This item is packaged separately as 0.54% solution (2 mL diluent for lyophilized product).

Interferon Beta-1a Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
33.00[a]	mg	1	Interferon beta-1a	33.00	mg
15.00	mg	2	Albumin (human)	15.00	g
5.80	mg	3	Sodium chloride	5.80	g
5.70	mg	4	Sodium phosphate dibasic	5.70	g
1.20	mg	5	Sodium phosphate monobasic	1.20	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] Equivalent to 6.6 million IU.

Interferon Alpha-n3 Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5 MM	U	1	Interferon alpha-n3	5B	U
3.30	mg	2	Liquefied phenol	3.30	g
1.00	mg	3	Albumin (human)	1.00	g
8.00	mg	4	Sodium chloride	8.00	g
1.74	mg	5	Sodium phosphate dibasic	1.74	g
0.20	mg	6	Potassium phosphate monobasic	0.20	g
0.20	mg	7	Potassium chloride	0.20	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

5: Interferon Alphacon-1 Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.03	mg	1	Interferon alphacon-1	0.03	g
5.90	mg	2	Sodium chloride	5.90	g
3.80	mg	3	Sodium phosphate	3.80	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Interferon Gamma-1b Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Interferon gamma-1b[a]	200.00	mg
40.00	mg	2	Mannitol	40.00	g
0.72	mg	3	Sodium succinate	0.72	g
0.10	mg	4	Polysorbate 20	0.10	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] 0.5-mL fill gives 100 mg or 2 million IU.

Interleukin Eye drop

Manufacturing Directions

(per 100 mL) Interleukin-6 0.01 g, sodium chloride 0.9 g, sterilized purified water, QS.

Vitamin C Vaginal Ointment

Manufacturing Directions

A 12.5% by weight vitamin C containing vaginal ointment is produced in a 200 kg batch in the following manner.

1. The following components are melted in an ointment machine (dissolver) at 80°C: white Vaseline (petroleum jelly) 43750 g, cetyl stearyl alcohol (Lanette N) 52500 g, highly liquid paraffin 78750 g.
2. The melt is stirred and homogenized for 20 minutes and cooling is allowed to start. The dissolver is switched off at an internal temperature of 35°C. At an internal temperature of 30°C, 25,000 g of ascorbic acid is added and the dissolver is allowed to run for 15 minutes.
3. The mixture is cold stirred in a partial vacuum and then is introduced into a storage container via a homogenizer.

Interleukin for Injection (IL-2)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.25	mg	1	IL-2	0.25	g
0.70	mg	2	Sodium laurate	0.70	g
10.00	mM	3	Disodium hydrogen phosphate	10.00	M
50.00	mg	4	Mannitol	50.00	g
QS	mL	5	Hydrochloric acid, 1 M, for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take the IL-2 from the column and mix in a suitable container with items 2, 3, 4, and 6. Mix well.
2. Check and adjust pH to 7.5 (7.3–7.6) with item 5.
3. Filter and lyophilize.

Iodine IV Additive

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
118.00	mg	1	Sodium iodide (equivalent to 100 mg iodine)	118.00	mg
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Sodium hydroxide for pH adjustment		

Note: Sterile, nonpyrogenic solution for use as an additive to solutions for total parenteral nutrition (TPN).

Iron Copper Solution Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
30.00	mg	1	Sodium cacodylate (arsenic derivative)	30.00	g
0.522	mg	2	Ferric chloride	0.522	g
0.09	mg	3	Copper gluconate	0.09	g
3.00	mg	4	Thymol, USP	3.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Iron Dextran Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Elemental iron as iron dextran complex	50.00[a]	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5.2 to 6.2 with item 3 or 4.

[a] According to iron activity.

Iron Sucrose Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Element iron (polynuclear iron III) as iron sucrose[a]	20.00	g
60.00	mg	2	Sucrose	60.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: pH 10.5 to 11.1.
[a] Adjust according to available iron. Fill 5 mL into vial.

Isometheptene Hydrochloride Veterinary Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Isometheptene hydrochloride	100.00	g
55.00	mg	2	Hydrochloric acid, 37%	55.00	g
1.80	mg	3	Methyl paraben, USP	1.80	g
0.20	mg	4	Propyl paraben, USP	0.20	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Itraconazole Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Itraconazole, use itraconazole solubilized by hydroxypropyl (beta) cyclodextrin	400.00	mg
3.80	mL	2	Hydrochloric acid	3.00	mL
25.00	mL	3	Propylene glycol	25.00	mL
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: For dilution with 50 mL of 0.9% sodium chloride; each vial contains 200 mg itraconazole.

Ketoprofen Lysine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Citric acid	2.50	g
1.50	mg	2	Sodium hydroxide	1.50	g
80.00	mg	3	(R,S)-Ketoprofen salt of *d,l*-lysine	80.00	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	ft^3	5	Nitrogen gas, NF	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Make this preparation protected from light and continuously under cover of item 5.
2. Take 0.8 L of item 6 and bubble item 5 for 20 minutes protecting from light once the addition of drug begins.
3. Add items 1 and 2, mix, and dissolve.
4. Add item 3 and mix well.
5. Check and adjust pH to 7.0 to 7.5 with item 4. Keep bubbling item 5.
6. Using a pressurized source of item 5, filter through a 0.22-μm cartridge, and collect in a suitable staging vessel protected from exposure to ultraviolet light.
7. Fill type I 2-mL glass ampoule, with pre- and post-item 5 flush.
8. Sterilize.

Ketorolac Tromethamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
30.00	mg	1	Ketorolac tromethamine	30.00	g
100.00	mg	2	Alcohol USP	100.00	g
6.68	mg	3	Sodium chloride[a]	6.68	g
10.00	mg	4	Citric acid	10.00	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a] Used in prefilled syringes; use only item 4 in vials.

Ketorolac Tromethamine Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Ketorolac tromethamine	5.00	g
0.10	mg	2	Benzalkonium chloride	0.10	g
1.00	mg	3	Disodium edetate	1.00	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
0.1	mg	6	Octoxynol 40	0.1	g
QS	mL	7	Sodium chloride[a]	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 7.4.
[a] Adjust osmolality to 290 mOsm/kg.

Labetalol Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Labetalol hydrochloride	5.00	g
45.00	mg	2	Dextrose anhydrous, USP	45.00	g
0.10	mg	3	Disodium edetate	0.10	g
0.80	mg	4	Methyl paraben	0.80	g
0.10	mg	5	Propyl paraben	0.10	g
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Citric acid monohydrate for pH adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.0 to 4.0 with item 6 or 7.

Lactobionic Acid Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
120.00	mg	1	Lactobionic acid, powder	120.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Collect ca. 90% of final volume of item 2 in a clean glass-lined container or 316 stainless steel tank.
2. Add and dissolve item 1.
3. Sample for lactobionic acid concentration, silica content, and volume.
4. Based on step 3, calculate the final volume as follows: final volume = (solution volume × % concentration)/12%. Adjust volume.
5. Filter solution through previously rinsed and approved cellulose pads and papers. Recirculate until clear and essentially free of insoluble material into clean Pyrex tank or portable tank.
6. Sterile filter the solution through a sterile 0.22-μm membrane into a sterile Pyrex bottle.
7. Sample. Keep product refrigerated.

Lamotrigine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Lamotrigine	25.00	g
37.78	mg	2	Mannitol	37.78	g
9.37	mg	3	Methanesulfonic acid	9.375	g
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve mannitol in appropriate amount of water. The amount of mannitol needed is calculated to provide tonicity on reconstitution.
2. The mesylate salt of lamotrigine is formed in situ during the manufacturing process described in European patent 21121 and U.S. patent. no. 4486354 by addition of commercially available methanesulfonic acid.
3. When the appropriate amounts of lamotrigine and methanesulfonic acid are combined, the resulting solution pH ranges from ca. 2.8 to 3.5. Add sodium hydroxide and water to achieve the required pH and volumes as given in the protocol.
4. Adjust the solution pH to a range of 3.3 to 3.5 with sodium hydroxide solution or methane-sulfonic acid solution.
5. The final concentration of the lamotrigine calculated as free base in solution prior to freeze drying may vary from 1 to 50 mg/mL, preferably 25 mg/mL.
6. The solution is chemically and physically stable at room temperature for at least 7 days and may be held in suitable stainless steel/glass manufacturing tank for this period of time, if needed.
7. Sterile filter the solution and fill into appropriate vials to a fill volume of 10 mL.
8. Load the vials into a freeze drier that is pre-cooled to 5°C prior to loading.
9. Freeze the solution to −24°C for 4 to 5 hours. Initiate primary drying by ramping the shelf temperature to 0°C while maintaining the vacuum at 0.5 torr. After the product temperature reaches the shelf temperature, initiate and conduct secondary drying at a product temperature of 35°C for 6 to 8 hours. Maintain the chamber pressure at 0.5 torr during lyophilization.
10. Reconstitution of the lyophilized formulation with 12.5 mL of sterile water for injection provides an isotonic solution containing 20 mg lamotrigine free base/mL.

Lazaroid Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Lazaroid[a]	25.00	g
44.20	mg	2	Citric acid anhydrous, USP	44.20	g
5.88	mg	3	Sodium citrate anhydrous, USP	5.88	g
0.40	mL	4	Propylene glycol	0.40	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a] 2-[[4-(2,6)-bis(1-pyrrolidinyl)-4-pyrimidinyl-1-piperazinyl-16-alpha-methylpregna-1,4,9(11)-triene-3,20-dione mesylate]]; a 5× dose formulation for bolus injection has 100 mg/mL of active drug, and all other components are increased proportionally.

Manufacturing Directions

1. Add and dissolve items 1 and 2 in approximately 0.25 L of item 7.
2. Add and dissolve item 4 and mix well.
3. Check and adjust pH to 2.9 (2.7–3.0) with item 5 or 6.
4. Add item 1 and mix well.
5. Check and adjust pH again as in step 3.
6. Make up volume with item 7.
7. Filter and sterilize by autoclaving.

Lepirudin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Lepirudin	50.00	g
40.00	mg	2	Mannitol	40.00	g
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 7 with item 3.

Leucovorin Calcium Injection (50 mg/5 mL, 10-mL Vial Lyophilized)

Bill of Materials (Batch Size 5 L)					
Scale/mL		Item	Material	Qty	UOM
12.71	mg	1	Leucovorin calcium, $5H_2O$	63.51	g
5.60	mg	2	Sodium chloride	40.00	g
QS	mL	3	Water for injection, USP	QS to 5.00	L
QS	mL	4	Sodium hydroxide, 2%, for pH adjustment		
QS	mL	5	Hydrochloric acid, 2%, for pH adjustment		

Manufacturing Directions

1. Dissolve item 1 in 4 L of item 3 in a suitable vessel. Stir until a clear solution is obtained.
2. Add item 2 with constant agitation until clear solution is obtained.
3. Check pH and adjust to 8.1±0.1 with item 4 or 5.
4. QS to volume with item 3.
5. Sample for testing.
6. After approval, filter solution through a 0.22-μm filter and fill 10-mL flint vial with an 841 gray stopper without coating (applied later).
7. Load product into lyophilizer.
8. Set temperature to −40°C.
9. Product thermocouples should register −40°C or less for at least 4 hours before starting the drying cycle.
10. Start condenser and do not start vacuum until 100 μm or less.
11. Start vacuum to the chamber to achieve at least 100 μm or less.
12. Set to low heat and bring up temperature controller to +15°C. Hold at this temperature for at least 12 hours.
13. Bring up the temperature controller to +28°C. Hold at this temperature for at least 24 hours.
14. Bleed chamber slowly with sterile dry air or N_2 gas.
15. Stopper vials by using the internal stoppering mechanism or stopper the vials with depyrogenated cover in the laminar hood.
16. Withdraw the product from lyophilizer.

Leucovorin Calcium Injection (3 mg/mL, 2-mL Vial)

Bill of Materials (Batch Size 5 L)					
Scale/mL		Item	Material	Qty	UOM
3.81	mg	1	Leucovorin calcium, $5H_2O$	15.97	g
5.6	mg	2	Sodium chloride	28.00	g
9.0	mg	3	Benzyl alcohol, NF	45.00	g
QS	mL	4	Water for injection, USP	QS to 5	L
QS	mL	5	Sodium hydroxide, 2%, for pH adjustment		
QS	mL	6	Hydrochloric acid, 2%, for pH adjustment		

Manufacturing Directions

1. Dissolve item 1 in 4 L of item 4 in a suitable vessel. Stir until a clear solution is obtained.
2. Add item 2 and item 3, one by one, with constant agitation, until a clear solution is obtained.
3. Check pH and adjust to 8.4±0.05 with item 5 or 6.
4. QS to volume with item 4.
5. Sample for testing.
6. After approval, filter solution through 0.22-μm filter and fill a type I 2-mL amber vial, 1888 gray stopper without coating (sterilized after washing in disodium edetate).

Leuprolide Acetate Injection (5 mg/mL Injection)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Leuprolide acetate powder	5.00	g
9.00	mg	2	Benzyl alcohol, NF	9.00	g
QS		3	Sodium chloride, USP		
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Glacial acetic acid, USP	QS	
QS	mL	6	Nitrogen gas, NF	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Warning: Leuprolide is a potent drug and a reproductive hazard. It is biologically active in very small quantities. May cause adverse effects on reproduction. Women of childbearing potential are restricted from working where leuprolide is expected. Use and store under well-ventilated conditions. Avoid direct contact. Wear the appropriate personal protective equipment as required by operating procedures. Periodic medical monitoring (blood test) may be requested to evaluate evidence of exposure.

First aid: Remove contaminated clothing. Wash affected area with plenty of soap and water. Report to employee first aid.

1. Preparation of leuprolide acetate solution. *Caution*: Handle with care. Eye protection required. Wear respirator or equivalent, rubber gloves, hood, coveralls, and shoe coverings when handling powder or preparing solution.
   a. Add benzyl alcohol, sodium chloride, and leuprolide acetate to ca. 900 mL of water for injection with mixing. Mix solution.
   b. Check and adjust pH to 5.7 to 6.3 with 2% acetic acid (made by adding 0.4 mL of glacial acetic acid q.s. to 10 mL water for injection) or 2% sodium hydroxide (prepared by adding 0.4 g QS to 10 mL water for injection).
   c. QS with water for injection to 1 L.
   d. Check and adjust pH again as in step 1b.
   e. Filter solution through a 0.22-μm or finer filter with an appropriate prefilter, if necessary, into a suitable glass or 316 stainless steel container.
   f. Sample for testing; adjust pH or ingredients if outside limits. Fill as soon as possible.
2. Preparation of bottles.
   a. Wash and dry type I 5-mL clear glass bottles and load into appropriate containers for sterilization.
   b. Sterilize by using dry heat at 200°C (−0, +50°C) glass temperature for 225 minutes (−0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of the cycle.
   c. Deliver to the sterile filling area.
3. Preparation of stoppers.
   a. Leach stoppers by boiling for 10 minutes in deionized water.
   b. Wash stoppers using rubber cycle (slow tumbling) with Triton X-100 or similar.
   c. Dry in a fast dryer at 55°C.
   d. Store in a suitable container until ready for use.
   e. Try, inspect, and rinse thoroughly. Wrap tray and identify properly.
   f. Sterilize in a steam autoclave for 121°C for 50 minutes.
4. Sterile filtration and setup.
   a. Connect storage container to a sterilized 0.22-μm or finer filter with an appropriate sterile prefilter.
   b. Filter enough solution into sterile container so as to wet filter.

c. Pressure test filter using N_2 at 40-lb pressure.
d. Filter solution into sterile container.
e. Commence filling.
f. Sample for testing.

5. Filling.
   a. Under aseptic conditions, fill 3.2 mL into each sterilized 5-mL vial.
   b. Sample for testing.
   c. Pressure test filter using N_2 at 40-lb pressure at end of filling run.
   d. Aseptically stopper each vial with a clean, sterile siliconized stopper.
   e. Apply overseal.
   f. Inspect each vial for defects.
   g. Sample for testing.

Leuprolide Acetate Injection: Depot Preparation (3.75 and 7.50 mg for Injecting Every Month)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
Chamber 1					
3.75	mg	1	Leuprolide acetate	3.75	g
0.65	mg	2	Purified gelatin	0.65	g
33.10	mg	3	*dl*-Lactic acid glycolic acids	33.10	g
6.60	mg	4	D-Mannitol	6.60	g
Chamber 2					
5.00	mg	1	Carboxymethylcellulose	5.00	g
50.00	mg	2	D-Mannitol	50.00	g
1.00	mg	3	Polysorbate 80	10.00	g
QS	mL	4	Glacial acetic acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: 3.75 or 7.50 mg active; same inactive ingredients.

Leuprolide Acetate Injection (11.25 and 22.50 mg for Injecting Every 3 Months)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
Chamber 1					
11.25	mg	1	Leuprolide acetate	11.25	g
99.30	mg	2	Polylactic acid	99.30	g
19.45	mg	3	D-Mannitol	19.45	g
Chamber 2					
7.50	mg	1	Carboxymethylcellulose	7.50	g
75.00	mg	2	D-Mannitol	75.00	g
1.50	mg	3	Polysorbate 80	1.50	g
QS	mL	4	Glacial acetic acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: 11.25 or 22.50 mg active; same inactive ingredients.

Leuprolide Acetate Injection (30 mg for Injecting Every 4 Months)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
Chamber 1					
30.00	mg	1	Leuprolide acetate	30.00	g
264.80	mg	2	Polylactic acid	264.80	g
51.90	mg	3	D-Mannitol	51.90	g
Chamber 2					
7.50	mg	1	Carboxymethylcellulose	7.50	g
75.00	mg	2	D-Mannitol	75.00	g
1.50	mg	3	Polysorbate 80	15.00	g
QS	mL	4	Glacial acetic acid for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Leuprolide Acetate Implant

Leuprolide acetate implant is a sterile, nonbiodegradable, osmotically driven miniaturized implant designed to deliver leuprolide acetate for 12 months at a controlled rate. It contains 72 mg of leuprolide acetate (equivalent to 65 mg leuprolide free base) dissolved in 104 mg dimethyl sulfoxide. The 4 mm × 45 mm titanium alloy reservoir houses a polyurethane rate-controlling membrane, an elastomeric piston, and a polyethylene diffusion moderator. The reservoir also contains the osmotic tablets, which are not released with the drug formulation. The osmotic tablets are composed of sodium chloride, sodium carboxymethyl cellulose, povidone, magnesium stearate, and sterile water for injection. Polyethylene glycol fills the space between the osmotic tablets and the reservoir. A minute amount of silicone medical fluid is used during manufacture as a lubricant. The weight of the implant is ca. 1.1 g.

Levorphanol Tartarate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Levorphanol tartarate	2.00	g
1.80	mg	2	Methyl paraben	1.80	g
0.20	mg	3	Propyl paraben	0.20	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 4.3 with item 4.

Levothyroxine Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Levothyroxine Sodium	20.00	mg
1.00	mg	2	Mannitol	1.00	g
0.07	mg	3	Tribasic Sodium Phosphate Anhydrous	0.07	g
QS	mL	4	Sodium Hydroxide for pH adjustment	QS	
QS	mL	5	Water for Injection, USP	QS to 1.00	L

Note: For 500-mg label, use 1.75 mg item 3. Fill 10 mL and lyophilize. Reconstitute with 5 mL of 0.9% sodium chloride injection.

Lidocaine Hydrochloride and Epinephrine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Lidocaine HCl, USP	10.00	g
6.00	mg	2	Sodium chloride, USP	6.00	g
1.00	mg	3	Methyl paraben, USP	1.00	g
0.50	mg	4	Disodium edetate	0.50	g
0.01	mg	5	Epinephrine, USP	0.01	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Glacial acetic acid, USP	QS	
QS	mL	8	Sodium acetate for buffering; see item 7	QS	

Note: Adjust item 1 for different strength.

Lidocaine Hydrochloride and Epinephrine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Lidocaine HCl, USP (lidocaine base 8.8 mg)	10.00	g
6.00	mg	2	Sodium chloride, USP	6.00	g
1.00	mg	3	Methyl paraben, USP	1.00	g
1.50	mg	4	Sodium metabisulfite, NF	1.50	g
0.01	mg	5	Epinephrine, USP	0.01	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Glacial acetic acid for buffering	QS	
QS	mL	8	Sodium acetate for buffering; see item 7	QS	
QS	mL	9	Sodium hydroxide for pH adjustment	QS	

Note: Adjust quantity of item 1 for different strengths.

Lidocaine Hydrochloride and Epinephrine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Lidocaine HCl, USP (lidocaine base 8.8 mg)	10.00	g
6.00	mg	2	Sodium chloride, USP	6.00	g
0.20	mg	3	Citric acid	0.20	g
0.50	mg	4	Sodium metabisulfite, NF	1.50	g
0.01	mg	5	Epinephrine, USP	0.01	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Sodium hydroxide for pH adjustment	QS	
QS	mL	8	Hydrochloric acid for pH adjustment		

Note: For a multiple-dose vial, add 1 mg methyl paraben. Adjust pH to 3.3 to 5.5.

Lidocaine Hydrochloride Injection (1% or 1.5% 20 mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
15.00	mg	1	Lidocaine hydrochloride, USP anhydrous, use lidocaine hydrochloride monohydrate, USP	16.00	g
6.50	mg	2	Sodium chloride, USP	6.50	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: For 1% strength, reduce the quantity accordingly; different fill volumes.

Manufacturing Directions

Note: The solution must be prepared in a glass-lined or a 316 or higher temper-grade stainless steel tank cleaned according to approved SOPs.

1. Preparation.
   a. Add water for injection to tank to ca. 90% of the final volume.
   b. Add and dissolve the lidocaine hydrochloride and the sodium chloride with mixing.
   c. Add water for injection to final volume and mix till ingredients are dissolved and solution is uniform.
   d. Check and record the pH. Adjust if necessary to pH 6.5 (6.2–6.7) with a 10% sodium hydroxide solution or 10% hydrochloric acid solution.
   e. Sample for testing.
   f. Filter solution through a previously rinsed filtration setup, using an approved 0.45-μm micrometer or finer membrane and an approved prefilter. Filter solution into a clean glass-lined or a 316 stainless steel holding tank.
   g. Prepare a 0.45-μm or finer membrane inline filter for the filling line.
2. Filling. Use type I 20-mL or other fill size glass ampoules, USP.
   a. Using the inline filter, fill specified amount into each clean, dry ampoule.
   b. Seal ampoules.
3. Sterilization. Sterilize at 115°C (+3°C, −0°C) and an F_0 range of 8 to 18. Use water spray cooling and terminal air pressure to maintain autoclave pressure.

Lincomycin Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
300.00	mg	1	Lincomycin, use lincomycin hydrochloride monohydrate for injectables (at the rate of 790 μ g/mg)	379.75[a]	g
9.45	mg	2	Benzyl alcohol, NF	9.45	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	mL
QS	mL	4	Sodium hydroxide reagent-grade pellets for pH adjustment	QS	mL
QS	mL	5	Nitrogen gas, NF	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a] Adjust weight of Lincomycin hydrochloride monohydrate to allow for variable potency: (379.746 × 790)/potency = g required for 1 L.

Manufacturing Directions

Caution: Lincomycin may cause an allergic reaction in some individuals. Avoid contact with skin. Wear appropriate personal protection gear.

1. Prepare 2% hydrochloric acid immediately prior to use by adding 0.4 mL of hydrochloric acid to ca. 10 mL of item 6. QS to 20 mL and mix.
2. Prepare 2% sodium hydroxide immediately prior to use by adding 0.4 g of pellets of item 4 into 10 mL of item 6. QS to 20.00 mL and mix.
3. Prepare the drug solution in a glass-lined or 316 or higher temper-grade stainless steel tank. Add ca. 50% of item 6. Add and dissolve item 1 and mix thoroughly.
4. With agitation, add item 2. Rinse residue from container by using item 6 and mix thoroughly until uniform solution is produced.
5. Check and record pH (range 3.0–5.5). Adjust if necessary as in step 2 or 3.
6. Make up volume with item 6. Sample for testing.
7. Filter solution through a previously rinsed filtration setup, using an approved 0.22-μm membrane filter with a 0.45-μm prefilter, into a clean glass-lined of 316 or higher temper-grade stainless steel tank.
8. Prepare type I glass ampoules by washing and drying and sterilizing at 200°C (−0, +50°C) glass temperature for 225 minutes (−0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of cycle.
9. Filter from the storage tank using 0.22-μm filter under aseptic condition 2.2 mL (or such other volumes as labeled into appropriate size ampoule) into ampoules. Seal immediately. Pressure test filter before and after filling. Sample (1 mL = 300 mg).

Liothyronine Sodium Injection (T_3)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Liothyronine sodium	10.00	mg
68.00	mL	2	Alcohol, USP	68.00	mL
0.175	mg	3	Citric acid anhydrous	0.175	mg
2.19	mg	4	Ammonia as ammonium hydroxide	2.19	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Lipid Emulsion 20% for Parenteral Nutrition

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Safflower oil winterized	200.00	g
12.00	mg	2	Egg phosphatides purified	12.00	g
25.00	mg	3	Glycerin, USP	25.00	g
QS	mL	4	Sodium hydroxide, reagent grade, for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Collect a volume of item 5 ca. equal to the final batch size. Heat and protect with item 6.
2. Maintain item 6 atmosphere in all containers and processing.
3. Add and disperse item 2 into a portion of the prepared water with agitation.
4. Add and dissolve item 3 previously filtered by using homogenizer to increase degree of dispersion.
5. Filter aqueous phosphatide dispersion phase.
6. Check pH and adjust accordingly.
7. Heat item 1. Unless previously filtered, filter and add to the aqueous phase with agitation to form a coarse emulsion concentrate.
8. Homogenize the coarse emulsion concentrate.
9. After homogenization, QS to final volume with prepared item 5.
10. Filter emulsion through a filter surface area to provide adequate flow.
11. Collect filtered emulsion with N_2 protection to surge tank.
12. Fill specified amount of emulsion into clean bottle.
13. Flush headspace of each bottle with filtered N_2; apply stopper.
14. Seal with ferrule.
15. Autoclave and then agitate to stabilize emulsion.
16. Visually inspect bottles and sample for testing.

Liver, Iron, and Cyanocobalamin with Procaine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
30.00	mg	1	Cyanocobalamin, USP	30.00	mg
0.10	mg	2	Liver injection (supplies 2 mg of cyanocobalamin activity), 20 mg/mL concentrate	0.10	g
50.00	mg	3	Ferrous gluconate, NF	50.00	g
1.50	mg	4	Riboflavin-5′-phosphate sodium	1.50	g
100.00	mg	5	Niacinamide, USP	100.00	g
16.40	mg	6	Citric acid, USP	16.40	g
23.60	mg	7	Sodium citrate, USP	23.60	g
20.00	mg	8	Procaine hydrochloride, USP	20.00	g
2.50	mg	9	Calcium pantothenate, USP	2.50	g
20.00	mg	10	Benzyl alcohol, NF	20.00	g
QS	mL	11	Water for injection, USP	QS to 1.00	L

Note: Protect from light.

Liver, Iron, and Vitamin B_{12} Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Thiamine HCl, USP	10.00	g
1.00	mg	2	Riboflavin-5′-phosphate sodium	1.00	g
1.00	mg	3	Pyridoxine HCl, USP	1.00	g
100.00	mg	4	Niacinamide, USP	100.00	g
1.00	mg	5	D-Panthenol	1.00	g
15.00	mg	6	Cyanocobalamin, USP	15.00	mg
33.00	mg	7	Ferrous gluconate, NF	33.00	mg
0.10	mL	8	Liver injection (20 mg/mL concentrate), supplies 2 mg of B_{12} activity	100.00	mL
10.00	mg	9	Sodium citrate, USP	10.00	g
1.00	mg	10	Liquefied phenol, USP	1.00	g
15.00	mg	11	Benzyl alcohol, NF	15.00	g
QS	mL	12	Water for injection, USP	QS to 1.00	L

Liver, Iron, and Vitamin B_{12} Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Cyanocobalamin, USP	50.00	mg
25.00	mg	2	Niacinamide, USP	25.00	g
0.50	mg	3	Riboflavin-5′-phosphate sodium	0.50	g
30.00	mg	4	Iron and ammonium citrate	30.00	g
0.10	mL	5	Liver injection (20 mg/mL concentrate), supplies 2 mg of B_{12}	100.00	mL
5.00	mg	6	Liquefied phenol, USP	5.00	g
10.00	mg	7	Benzyl alcohol, NF	10.00	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

Lorazepam Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Lorazepam injection	2.00	g
0.18	mL	2	Polyethylene glycol 400	0.18	L
20.00	mg	3	Benzyl alcohol	20.00	g
QS	mL	4	Propylene glycol	QS to 1.00	L

Note: Increase the active ingredient to 4.00 mg for higher label product.

Magnesium Sulfate 50% Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
500.00	mg	1	Magnesium sulfate, USP	500.00	g
2.00	mg	2	Phenol, USP	2.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manganese Sulfate Injection (5-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.57	mg	1	Manganese sulfate monohydrate	21.95	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Manganese Sulfate Injection (10-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.308	mg	1	Manganese sulfate monohydrate	0.308	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Manganese Sulfate Injection (30-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.308	mg	1	Manganese sulfate monohydrate	4.39	g
0.90	%	2	Benzyl alcohol, NF	0.90	%
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Sulfuric acid for pH adjustment	QS	

Note: pH 4.0 to 7.0. Assay by atomic absorption 85% to 115%. Packaging commodity: Type I glass vials, West Co. 1888 gray stoppers, and West Co. flip-off aluminum seals.

Mechlorethamine Hydrochloride for Injection Trituration

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.10	mg	1	Mechlorethamine hydrochloride	0.10	g
QS	mg	2	Sodium chloride	QS to 1.00	kg

Note: This a triturate of drug with sodium chloride; when 100 mg is reconstituted with 10 mL water for injection, it yields 0.9% sodium chloride at pH 3 to 5 containing 1 mg of drug/mL.

Medroxyprogesterone Acetate Sterile Aqueous Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Medroxyprogesterone acetate (micronized)	200.00	g
0.85	mg	2	Myristyl gamma picolinium chloride	0.85	g
11.00	mg	3	Sodium sulfate	11.00	g
20.30	mg	4	Polyethylene glycol 3350	20.30	g
2.50	mg	5	Polyvinylpyrrolidone K17	2.50	g
0.694	mg	6	Sodium phosphate monobasic hydrate	0.694	g
0.588	mg	7	Sodium phosphate dibasic dodecahydrate	0.588	g
1.50	mg	8	L-Methionine	1.50	g
QS	mL	9	Hydrochloric acid for pH adjustment	QS	
QS	mL	10	Sodium hydroxide for pH adjustment	QS	
QS	mL	11	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable container (stainless steel), dissolve items 2 to 8 with aggressive mixing in item 11.
2. Sterilize the step 1 preparation by autoclaving at 121°C for 15 minutes.
3. Sterilize item 1 separately and add to step 2 under aseptic conditions.
4. Homogenize in a homogenizer.
5. Make up volume with item 11.
6. Check and adjust pH to 6.0 to 7.0 with item 8 or 9.
7. Filter and sterile fill.

Medroxyprogesterone Acetate Sterile Aqueous Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
140.00	mg	1	Medroxyprogesterone acetate (micronized)	200.00	g
1.80	mg	2	Methyl paraben	1.80	g
0.20	mg	3	Propyl paraben	0.20	g
8.00	mg	4	Sodium chloride	8.00	g
28.75	mg	5	Polyethylene glycol 3350	28.75	g
3.00	mg	6	Polysorbate 80	3.00	g
5.00	mg	7	Polyvinylpyrrolidone K17	5.00	g
0.694	mg	8	Sodium phosphate monobasic hydrate	0.694	g
0.588	mg	9	Sodium phosphate dibasic dodecahydrate	0.588	g
1.50	mg	10	L-Methionine	1.50	g
QS	mL	11	Hydrochloric acid for pH adjustment	QS	
QS	mL	12	Sodium hydroxide for pH adjustment	QS	
QS	mL	13	Water for injection, USP	QS to 1.00	L

Note: Use the same method as given previously, except that in step 1, first preheat item 13 to between 70°C and 90°C to dissolve items 2 and 3 and then cool.

Medroxyprogesterone Acetate Sterile Aqueous Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150.00	mg	1	Medroxyprogesterone acetate	150.00	g
28.90	mg	2	Polyethylene glycol 3350	28.90	g
2.41	mg	3	Polysorbate 80	2.41	g
8.68	mg	4	Sodium chloride	8.68	g
1.37	mg	5	Methyl paraben	1.37	g
0.15	mg	6	Propyl paraben	0.15	g
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	mL	8	Hydrochloric acid for pH adjustment	QS	
QS	mL	9	Sodium hydroxide for pH adjustment	QS	

Note: Fill 1 mL into syringe; terminally sterilize.

Medroxyprogesterone and Estradiol Sterile Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Medroxyprogesterone acetate (micronized)	50.00	g
10.00	mg	2	Estradiol cypionate (micronized)	10.00	g
1.80	mg	3	Methyl paraben	1.80	g
0.20	mg	4	Propyl paraben	0.20	g
8.00	mg	5	Sodium chloride	8.00	g
28.75	mg	6	Polyethylene glycol 3350	28.75	g
1.90	mg	7	Polysorbate 80	1.90	g
2.50	mg	8	Polyvinylpyrrolidone K17	2.50	g
0.694	mg	9	Sodium phosphate monobasic hydrate	0.694	g
0.588	mg	10	Sodium phosphate dibasic dodecahydrate	0.588	g
1.50	mg	11	L-Methionine	1.50	g
QS	mL	12	Hydrochloric acid for pH adjustment	QS	
QS	mL	13	Sodium hydroxide for pH adjustment	QS	
QS	mL	14	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable stainless steel container, add item 14 and heat to 70°C to 90°C.
2. Add and dissolve items 3 and 4.
3. Cool to room temperature.
4. Add and dissolve items 5 to 11. Mix well.
5. Check and adjust pH to 6.0 to 7.0 with item 12 or 13.
6. Add items 1 and 2 and make a smooth slurry by using a homogenizer.
7. Filter and sterile fill.

Melphalan Hydrochloride for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Melphalan hydrochloride	5.00	g
2.00	mg	2	Povidone	2.00	g
QS	mL		Water for injection, USP	QS to 1.00	L
Diluent					
0.02	mg	1	Sodium citrate	0.02	g
0.60	mL	2	Propylene glycol	0.60	L
0.052	mL	3	Ethanol (96%)	52.00	mL
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL into vials and lyophilize. Reconstitute with 10 mL of diluent.

Menadione Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Menadione	25.00	g
30.00	mg	2	Benzyl alcohol	30.00	g
QS	mL	3	Sesame oil, USP	QS to 1.00	L

Menadione Sodium Bisulfite Injection Veterinary (50 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Menadione sodium bisulfite	50.00	g
10.00	mg	2	Sodium bisulfite, USP	10.00	g
10.00	mg	3	Benzyl alcohol, NF	10.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium acetate for buffering	QS	
QS	mL	7	Glacial acetic acid for buffering; see item 6	QS	

Menadione Sodium Bisulfite Injection Veterinary (5 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Menadione sodium bisulfite	5.00	g
5.00	mg	2	Sodium chloride, USP	5.00	g
20.00	mg	3	Sodium bisulfite, USP	20.00	g
10.00	mg	4	Benzyl alcohol, NF	10.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium acetate for buffering	QS	
QS	mL	7	Glacial acetic acid for buffering; see item 6	QS	

Menotropins for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
7.50	IU	1	Follicle-stimulating hormone	7,500	IU
7.50	IU	2	Luteinizing hormone	7,500	IU
1.05	mg	3	Lactose hydrous	1.05	g
0.025	mg	4	Monosodium phosphate monohydrate	0.025	g
0.025	mg	5	Disodium phosphate anhydrous	0.025	g
QS	mg	6	Phosphoric acid for pH adjustment	QS	
QS	mL	7	Sodium hydroxide for pH adjustment		
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL into each vial and lyophilize; reconstitute before administration. Menotropins for injection, USP, is a purified preparation of gonadotropins. Menotropins are extracted from the urine of postmenopausal females and possess follicle-stimulating hormone (FSH) and luteinizing hormone (LH) activity. The ratio of FSH bioactivity and LH bioactivity in menotropins is adjusted to approximate unity by the addition of human chorionic gonadotropin purified from the urine of pregnant women.

Meperidine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Meperidine hydrochloride, USP	50.00	g
QS	mL	2	Hydrochloric acid for pH adjustment	QS	
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: Use a clean, glass-lined tank. Protect from light.

1. Preparation.
   a. Add water for injection ca. 65% of the final volume into glass-lined tank protected from light.
   b. Add and dissolve meperidine hydrochloride with mixing.
   c. Check and record pH of the solution; adjust to 4 to 5 with 1 N hydrochloride acid solution.
   d. QS with water for injection to final volume.
   e. Sample for testing.
   f. Sterilize an approved 0.2- or 0.22-μm membrane filter with an approved prefilter.
   g. Filter the solution through the sterilized filter unit into a sterile glass-lined holding container.
2. Preparation of ampoules.
   a. Wash and dry type I 1-mL sulfur-treated ampoules and load into appropriate containers for sterilization.
   b. Sterilize using dry heat at 245°C for at least 3 hours and 25 minutes (or use an equivalent cycle).
   c. Deliver to sterile filling area.
3. Filling.
   a. Connect bulk solution container by using aseptic technique to the filling machines.
   b. Aseptically fill 1.2 mL (range 1.1–1.3 mL) into each clean, sterile ampoule.
   c. Immediately seal each ampoule.
4. Sterilization.
   a. Autoclave at 121°C for 20 minutes.
   b. Sample for testing.

Meperidine Hydrochloride and Promethazine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Meperidine hydrochloride	25.00	g
25.00	mg	2	Promethazine hydrochloride	25.00	g
0.10	mg	3	Edetate sodium	0.10	g
0.04	mg	4	Calcium chloride	0.04	g
0.75	mg	5	Sodium formaldehyde sulfoxylate	0.75	g
0.25	mg	6	Sodium metabisulfite	0.25	g
5.00	mg	7	Phenol liquefied	5.00	g
QS	mg	8	Acetic acid for buffering	QS	
QS	mg	9	Sodium acetate for buffering	QS	
QS	mL	10	Water for injection, USP	QS to 1.00	L

Note: Fill 2- and 10-mL vials.

Mepivacaine Hydrochloride Injection Single-Dose Vials

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Mepivacaine hydrochloride	1.00	g
6.60	mg	2	Sodium chloride	6.60	g
0.30	mg	3	Potassium chloride	0.30	g
0.33	mg	4	Calcium chloride	0.33	g
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: This formula is for 1%, 1.5%, and 2.0% solutions. Reduce quantity of sodium chloride only to 5.6 and 4.6 mg, respectively. Fill volumes are 20 or 30 mL. Adjust pH to 4.5 to 6.8 with item 5 or 6. Autoclave at 15-lb pressure 121°C for 15 minutes. May be reautoclaved.

Mepivacaine Hydrochloride Injection Multidose Vials

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Mepivacaine hydrochloride	1.00	g
7.00	mg	2	Sodium chloride	7.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: This formula is for a 1% (50-mL) vial; for 2% concentration, reduce sodium chloride to 5.0 mg. Adjust pH to 4.5 to 6.8 with item 5 or 6. Autoclave at 15-lb pressure 121°C for 15 minutes. May be reautoclaved.

Meropenem for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Meropenem	100.00	g
9.02	mg	2	Sodium as sodium carbonate (3.92 mEq)	9.02	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: For 1-g strength, fill 10 mL into vials and lyophilize; reconstitute with water for injection, USP. Fill 5 mL and lyophilize for 500-mg strength. pH of freshly constituted solution is between 7.3 and 8.3.

Mesoridazine Besylate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Mesoridazine as mesoridazine besylate	25.00	g
0.50	mg	2	Edetate sodium	0.50	g
QS	lb	3	Carbon dioxide, dried	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Fill under CO_2 environment.

Metaraminol Bitartrate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Metaraminol as equivalent metaraminol bitartrate	10.00	g
4.40	mg	2	Sodium chloride	4.40	g
1.50	mg	3	Methyl paraben	1.50	g
0.20	mg	4	Propyl paraben	0.20	g
2.00	mg	5	Sodium bisulfite	2.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Methandriol Dipropionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Methandriol dipropionate	50.00	g
50.00	mg	2	Benzyl alcohol, NF	50.00	g
QS	mL	3	Sesame oil, USP	QS to 1.00	L

Methocarbamol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Methocarbamol	100.00	g
0.50	mL	2	Polyethylene glycol 300	0.50	L
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.5 to 6.0; fill 10 mL into single-dose vials.

Methohexital Sodium for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
500.00	mg	1	Methohexital sodium	500.00	g
60.00	mg	2	Sodium carbonate anhydrous	60.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: Fill 1 mL to 10 m for 0.5- to 5.0-g strengths and lyophilize. The pH of the 1% solution in water for injection is between 10 and 11; the pH of the 0.2% solution in 5% dextrose is between 9.5 and 10.5.

Methylprednisolone Acetate Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Methylprednisolone acetate, USP	20.00	g
29.60	mg	2	Polyethylene glycol 4000, USP	29.60	g
8.90	mg	3	Sodium chloride, USP	8.90	g
0.20	mg	4	Benzalkonium chloride 50%, USP	0.20	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Glacial acetic acid for buffering	QS	
QS	mL	7	Sodium acetate for buffering; see item 6	QS	

Note: For higher strength, use 40 or 80 mg as item 1.

Methylprednisolone Acetate Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Methylprednisolone acetate	20.00	mg
29.50	mg	2	Polyethylene glycol 3350	29.50	g
1.97	mg	3	Polysorbate 80	1.97	g
6.90	mg	4	Sodium phosphate monobasic	6.90	g
1.44	mg	5	Sodium phosphate dibasic	1.44	g
9.30	mg	6	Benzyl alcohol	9.30	g
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	mL	8	Hydrochloric acid for pH adjustment		
QS	mL	9	Sodium hydroxide for pH adjustment		

Note: For higher strengths, use 40 or 80 mg without adjusting tonicity with sodium chloride. Adjust pH to between 3.5 and 7.0 with item 8 or 9.

Metoclopramide Injection: Preservative Formula

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Metoclopramide HCl, USP; based on assay	5.00	g
7.00	mg	2	Sodium chloride, USP	7.00	g
1.50	mg	3	Sodium metabisulfite, USP	1.50	g
20.00	mg	4	Benzyl alcohol, NF	20.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Nitrogen gas, NF	QS	

Manufacturing Directions

Note: The product is light sensitive. Protect from light throughout.

1. Preparation of water. Check item 5 to be used for solution preparation and verify that it meets the following requirements: conductivity limit of NMT 1.0 mS/cm and pH range of 5.0 to 7.0.
2. Preparation of solution.
   a. Take 900 mL of item 5 in the preparation vessel and bubble item 6 to expel dissolved oxygen gas. Monitor the O_2 sensor display (O_2% limit = NMT 1).
   b. Add and dissolve item 4 and item 2 into step 2a preparation vessel. Mix well with stirring. After that add and dissolve item 1 and make clear solution by mixing.
   c. Add and dissolve items 3 and 2 into step 2b.
   d. Check pH (range 3.5–5.5).
   e. Adjust pH if necessary with 1 N HCl solution or 10% NaOH solution (range 3.5–5.5).
   f. After adjustment of pH, make up volume to 1 L with item 5 and mix during bubbling item 6 until O_2% is less than 1.
   g. Check final pH (range 3.5–5.5).
3. Preparation of prefiltration assembly. Clean and sterilize filtration assembly by autoclaving at 121.5°C for 30 minutes according to the current validated cycle.
4. Prefiltration.
   a. Transfer the solution from the preparation vessel to mobile vessel through filtration assembly containing the 0.45-μm filter cartridge.
   b. After filtration, check the integrity of filter cartridge.
   c. After filtration, transfer the mobile vessel to the solution room.
5. Preparation of ampoules. Use type I 2-mL clear glass ampoules, USP.
   a. Wash the ampoules in the washing machine as per following parameters and their limits:
      DI water pressure: 2 bar min
      WFI pressure: 2 bar min
      Compressed air pressure: 6 bar
      Machine speed: 100%
   b. Sterilize the ampoules by using dry heat.
   c. Set the temperature at 330°C.
6. Final filtration.
   a. Clean and sterilize filling machine parts by autoclaving at 122°C for 30 minutes (or as per latest validation studies).
   b. Before starting the final filtration, check the integrity of filter cartridge.
   c. Aseptically connect the N_2 line through sterile N_2 filter to the inlet of mobile vessel. Check the validity of the N_2 filter.
   d. Aseptically connect one end of previously sterilized filtration assembly with the 0.22-μm pore-size filtration cartridge to the outlet of mobile vessel and the other end to the buffer holding tank.
   e. Filter the solution.
7. Aseptic filling.
   a. Operate the previously sterilized ampoules-filling machine as per machine parameters. Adjust the fill volume to 2.15 mL.
   b. Fill 2.15 mL (range 2.1–2.2 mL) metoclopramide injection from the bulk into each sterile dry clean ampoule and seal it.
8. Terminal sterilization and leak test. Load the inverted ampoules inside the autoclave chamber, run the cycle as per following parameters (as per latest validation studies): Sterilization temperature of 121.1°C, exposure time of 20 minutes.

Metoclopramide Injection: Preservative-Free Formula

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Metoclopramide base as metoclopramide monohydrochloride monohydrate	5.00	mg
8.50	mg	2	Sodium chloride	8.50	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Metolazone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Metolazone	10.00	g
100.00	mg	2	Ethanol, USP, 95%	100.00	g
650.00	mg	3	Propylene glycol	650.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable vessel, add item 3 and begin mixing.
2. Add item 1 with stirring and begin heating vessel to 50°C until dissolved.
3. Cool the solution to 25°C.
4. Add item 2 with stirring.
5. Make up volume with item 4.
6. Filter and sterilize.

Metronidazole Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Metronidazole	5.00	g
8.50	mg	2	Sodium chloride, USP	8.50	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve items 1 and 2 in approximately 0.8 L of item 3 in a stainless steel 316 or higher temper-grade vessel. Perform all processing aseptically and protected from light.
2. Make up volume with item 3.
3. Check pH 5.0 to 6.0; do not adjust.
4. Filter the solution through a 0.22-μm membrane filter and fill immediately into bags at a filling volume of 105 mL. Check filter integrity before and after filling.
5. Seal the PVC bags and autoclave at 115°C for 40 minutes starting from the moment temperature has reached 115°C inside the bag.
6. Individually seal bag into further PVC bag. Sample for complete testing.

Metronidazole Injectable Solution (500 mg/10 mL)

Formulation

I. Metronidazole, 5.0 g.
II. Kollidon 12 PF [1], 25.0 g; propylene glycol [1], 25.0 g; Lutrol E 400 [1], 25.0 g; water for injectables, 20.0 g.
III. Hydrochloric acid 0.1 N, QS.

Manufacturing Directions

Suspend I in the solution II, adjust pH 4.4 with III, and heat until metronidazole is dissolved.

Properties of the Solution

A clear solution was obtained. It can be diluted with water without precipitation.

Remark

To prevent of discoloration of Kollidon in the solution during storage, 0.2% to 0.5% of cysteine could be added as antioxidant.

Metronidazole Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Metronidazole	5.00	g
0.48	mg	2	Sodium phosphate dibasic anhydrous	476.00	mg
0.23	mg	3	Citric acid anhydrous	229.00	mg
7.90	mg	4	Sodium chloride	7.90	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: The solution must be prepared in a 315 or higher temper-grade stainless steel or glass-lined tank cleaned according to approved plant BOPs.

1. Preparation of solution.
   a. Obtain a sample from the water for injection source to be used for rinsing and mixing and certify that it meets the conductivity requirements of NMT 3.0 mS/s and pH range of 5 to 7. Record values.
   b. Test the rinse draining from the tank for conductivity and oxidizable substances prior to batch preparation. Record values (conductivity NMT 3).
   c. Record pH, conductivity, and temperature of water for injection.
   d. Add water for injection to tank to ca. 95% of the final volume.
   e. Add and dissolve the sodium phosphate dibasic, citric acid, and sodium chloride.
   f. Check and record pH (range 5.4–6). *Note*: Solution is buffered to fall into this pH range.
   g. Add and dissolve the metronidazole with mixing.
   h. Check and record pH (range 5.6–6). Solution is buffered to fall into this pH range.
   i. Add water for injection to final volume and mix until ingredients are completely dissolved and solution is uniform.
   j. Send first sample for testing.
   k. Filter solution through a Sparkler or equivalent prefilter and recirculate until clear. Then filter through an approved 0.45-μm or finer membrane connected in series to the prefilter. Recirculate until sparkling clear. *Note*: Perform the bubble point test on the membrane before and after filtration.
2. Filling.
   a. Fill a specified volume into each clean container.
   b. Send a second sample for testing.
3. Sterilization.
   a. Sterilize by using standard autoclave cycle.
   b. Send final sample for testing.

Metronidazole and Dextrose Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Metronidazole, USP, 5% excess	2.10	g
50.00	mg	2	Dextrose anhydrous, 5% excess	52.50	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Use freshly prepared item 3 stored for NMT 24 hours at 80°C. Add items 1 and 2 to item 3 at 60°C and mix for 15 minutes.
2. Filter using at least a 0.45-μm filter before final filtration with a 0.22-μm filter and fill into type I 540-mL glass bottles.
3. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers prewashed and sterilized at 116°C for 30 minutes; use triple aluminum seals and suitable plastic hangers.
4. Sterilize filled bottle by autoclaving at 121°C for 20 minutes. Do not exceed temperature by 3°C or time by 2 minutes either side of the limit. The autoclaving cycle should be fully validated to prevent excess 5-hydroxy methyl furfural test limits of USP.
5. Check pH of solution (4.0–4.3). Before autoclaving, pH is 5.5 to 6.5.

Midazolam Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Midazolam as midazolam hydrochloride equivalent	1.00	g
8.00	mg	2	Sodium chloride	8.00	g
0.10	mg	3	Edetate sodium	0.10	g
10.00	mg	4	Benzyl alcohol	10.00	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 2.9 to 3.2 with items 5 and 6. The same formula is used for 5-mg strength.

Milrinone Lactate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.20	mg	1	Milrinone as milrinone lactate equivalent	0.20	g
49.40	mg	2	Dextrose anhydrous, USP	49.40	g
QS	mg	3	Lactic acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.2 to 4.0 with item 3 or 4. The nominal concentration of lactic acid is 0.282 mg/mL.

Mineral Complex Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
6.43	mg	1	Sodium chloride, USP	6.43	g
0.176	mg	2	Calcium chloride dihydrate, USP	0.176	g
3.253	mg	3	Magnesium chloride hexahydrate, USP	3.253	g
1.193	mg	4	Potassium chloride granules, USP	1.193	g
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add ca. 95% of the final volume of water for 5. injection into a glass-lined or 316 or higher temper-grade stainless steel tank.
2. Bubble N_2 gas through the water and maintain N_2 gas protection throughout the remainder of the solution preparation.
3. Add and dissolve sodium chloride, calcium chloride, magnesium chloride, and potassium chloride while mixing.
4. QS with water for injection to final volume and mix until solution is uniform.
5. Check and record pH. Adjust with hydrochloric acid or sodium hydroxide if needed.
6. Filter solution with a prefilter.
7. Filter solution through a 0.45-μm membrane filter.
8. Fill correct volume into each flexible container.
9. Seal, overwrap, and autoclave.
10. Inspect and finish.
11. Sample for testing.

Miconazole Injectable Solution (1%)

Formulation

1. Miconazole, 1.0 g; Cremophor EL [1], 12.0 g.
2. Parabens, QS; water for injectables, add 100 mL.

Manufacturing Directions

Heat mixture I to approximately 65 °C, stir well, and add slowly the hot solution II.

After the ampoules have been heat-sterilized, they should be shaken for a short time, while they are still hot, to eliminate any separation of the phases that may have occurred. Sterilization can also be performed by membrane filtration under pressure.

Mitoxantrone for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Mitoxantrone base as mitoxantrone hydrochloride equivalent	2.00	g
8.00	mg	2	Sodium chloride	8.00	g
0.05	mg	3	Sodium acetate	0.05	g
0.46	mg	4	Glacial acetic acid	0.46	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: pH 4.0 to 4.5; must be diluted prior to administration.

Morphine Sulfate Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Morphine sulfate	10.00	g
8.00	mg	2	Sodium chloride	8.00	g
QS	mL	3	Sodium hydroxide for pH adjustment		
QS	mL	4	Sulfuric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 4.5 with item 3 or 4. Sterile fill; do not heat-sterilize. A 10-mL fill provides a 100-mg dose for infusion; for 500-mg strength use 6.25 mg/mL of sodium chloride instead and label quantity of 8.00 mg/mL.

Morphine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Morphine sulfate, USP, pentahydrate	25.00	g
QS		2	Nitrogen gas, NF	QS	
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Precaution: Prepare solution in a clean glass-lined tank or stainless steel container. This product requires N_2 gas and light protection during solution preparation. This product is a narcotic drug.

1. Preparation.
   a. Add water for injection to ca. 90% of the final volume into a glass-lined or stainless steel container; protect from light. Heat to 70°C (65–75°C). Pass bubble-filtered sterile N_2 gas for 10 minutes. Cool the water to 25°C (range 22–30°C).
   b. Add and dissolve morphine with mixing. Check and record pH (2.7–5.8). QS with water to final volume and mix thoroughly. Sample for testing.
   c. Sterilize an approved 0.2- or 0.22-μm membrane filter with an approved prefilter. Filter the solution by using N_2 pressure through the sterilized filter unit into a sterile glass-lined, light-protected container blanketed with N_2.
2. Preparation of ampoules. Use type I amber sulfur-treated ampoules. Wash, dry, and load into appropriate containers for sterilization. Use dry heat at 245°C to 330°C for 2 hours and 45 minutes to 3 hours and 30 minutes or equivalent cycle. Deliver to sterile filling area.
3. Filling. Connect bulk solution container with an aseptic technique to the filling machines. Aseptically fill each clean, sterile ampoule. Flush headspace with sterile filtered N_2. Immediately seal. This product is not terminally sterilized.

Moxidectin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.50	mg	1	Moxidectin	10.50	g
100.00	mg	2	Sucrose monolaurate	100.00	g
200.00	mg	3	Ethanol, USP	200.00	g
678.50	mg	4	Propylene glycol[a]	670.50	g

[a] Or QS to 1 L.

Manufacturing Directions

1. In a suitable vessel, add item 3 at room temperature and add to it item 1, stir, and mix.
2. In a separate vessel, add item 4 and dissolve in it item 2. Mix vigorously to dissolve.
3. Add solution of step 1 into solution of step 2 and mix vigorously.
4. Filter and sterilize.

Multiple Electrolytes and Dextrose Injection (Elliott's B Solution)

Bill of Materials (Batch Size 10.5 L)					
Scale/mL		Item	Material	Qty	UOM
7.50	mg	1	Sodium chloride, USP	76.65	g
1.90	mg	2	Sodium bicarbonate, USP	19.95	g
0.80	mg	3	Dextrose hydrous, USP	8.40	g
0.30	mg	4	Magnesium sulfate, USP	3.15	g
0.30	mg	5	Potassium chloride, USP	2.10	g
0.20	mg	6	Calcium chloride-$2H_2O$, USP	2.10	g
0.20	mg	7	Sodium phosphate dibasic.$7H_2O$	2.10	g
0.10	mg	8	Phenolsulfonphthalein, USP	1.05	mg
QS	mL	9	Water for injection, USP	10.50	L
QS	—	10	Carbon dioxide, NF, to adjust pH	QS	—

Manufacturing Directions

1. Dissolve 42 mg of item 8 in 1 L of item 9; warm gently if necessary to approximately 40°C to make a stock solution.
2. Place 9 L of item 9 into a suitable mixing tank. Add items 2, 7, 1, 6, 4, 5, and 3, in order, one by one with constant stirring; allow each ingredient to dissolve completely before adding the next one.
3. Pipe 25 mL of the stock solution in step 1 to mixing tank and mix well. Check pH, QS the volume with item 9, keep a cover with item 10, and flush with item 10 to adjust the pH to 6.2 to 6.4.
4. Sample, filter through 0.22-μm filter, and transfer to clean vessel and fill. *Caution*: The solution should be filtered and filled as soon as possible after compounding because the pH may not be stable.
5. Rinse stoppers with purified water and autoclave in a solution of EDTA (62.5 g in 2.5 L) at 121°C for 1 hour; rinse at least 3 times with purified water.

Muromonab-CD3 Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Muromonab-CD3	1.00	g
0.45	mg	2	Sodium phosphate monobasic	0.45	g
1.80	mg	3	Sodium phosphate dibasic	1.80	g
0.80	mg	4	Sodium chloride	0.80	g
0.20	mg	5	Polysorbate 80	0.20	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill 5 mL into each vial, pH 6.5 to 7.5; buffered preparation. The proper name, Muromonab-CD3, is derived from the descriptive term *murine monoclonal antibody*. The CD3 designation identifies the specificity of the antibody as the Cell Differentiation (CD) cluster 3 defined by the First International Workshop on Human Leukocyte Differentiation Antigens.

Nalbuphine Hydrochloride

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Nalbuphine hydrochloride	10.00	g
2.00	mg	2	Sodium chloride	2.00	g
9.40	mg	3	Sodium citrate	9.40	g
12.60	mg	4	Citric acid	12.60	g
1.80	mg	5	Methyl paraben	1.80	g
0.20	mg	6	Propyl paraben	0.20	g
QS	mL	7	Hydrochloric acid for pH adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Note: pH adjusted to 3.5 to 3.7 with item 7. A 20-mg/mL strength has the same formula.

Naloxone Hydrochloride Injection (1 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Naloxone hydrochloride	1.00	g
8.35	mg	2	Sodium chloride	8.35	g
1.80	mg	3	Methyl paraben	1.80	g
0.20	mg	4	Propyl paraben	0.20	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.0 to 4.0 with item 5. Also available as paraben-free formula.

Naloxone Hydrochloride Injection (0.04 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.04	mg	1	Naloxone hydrochloride	0.04	g
8.60	mg	2	Sodium chloride	8.60	g
1.80	mg	3	Methyl paraben	1.80	g
0.20	mg	4	Propyl paraben	0.20	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.0 to 4.0 with item 5.

Naloxone Hydrochloride Injection (0.02 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.02	mg	1	Naloxone hydrochloride	0.02	g
9.00	mg	2	Sodium chloride	9.00	g
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 3.0 to 4.0 with item 3.

Nandrolone Decanoate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Nandrolone decanoate, USP, 5% excess	105.00	g
100.00	mg	2	Benzyl alcohol, NF, 5% excess	105.00	g
QS	mL	3	Sesame oil, USP	QS to 1.00	L

Manufacturing Directions

Note: Use clean, dry equipment for compounding and filling the product.

1. Heat approximately 0.8 L of item 3 to approximately 40°C. Use this preheated oil for the compounding of product.
2. Add item 1 to step 1; agitate until dissolved. Add a small amount of sesame oil, if necessary.
3. Add item 2 to the mixing tank and continue stirring.
4. QS to volume with sesame oil.
5. Filter through a 0.22-μm membrane filter into a sterile reservoir for filling.
6. Fill into type I 2-mL amber vials (presterilized at 330°C for at least 240 minutes) and 1888 gray stopper without coating and appropriate aluminum seal.

Nandrolone Phenylpropionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Nandrolone phenylpropionate	25.00	g
0.40	mL	2	Ethyl oleate	0.40	L
0.60	mL	3	Arachis oil	0.60	L

Manufacturing Directions

1. Place items 2 and 3 in a suitable stainless steel 316 or higher temper-grade vessel, mix and filter through an appropriate system, and sterilize by dry heat at 160°C for 2 hours; allow to cool to 80°C.
2. In a separate vessel, add item 1 and portions of step 1 to dissolve item 1 completely. Add oil mixture from step 1 to make up the volume.
3. Filter through a presterilized assembly and fill 1.2 mL into type I flint ampoules.

Naphazoline Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
17.71	mg	1	Acid boric granular	17.71	g
1.50	mg	2	Hydroxypropyl methylcellulose 4000, cps	1.50	g
0.36	mg	3	Borax, sodium borate	0.36	g
1.00	mg	4	Edetate sodium	1.00	g
0.114	mg	5	Naphazoline hydrochloride, 5% excess	0.12	g
0.586	mL	6	Benzalkonium chloride, 17%, 7% excess	0.63	mL
QS	mL	7	Water for injection, USP	QS to 0.95	L

Manufacturing Directions

Use a thoroughly cleaned and rinsed steam-jacketed, glass-lined, or stainless steel tank (No. 304 or better) equipped with a speed-controlled agitator. Tank should have a cover. Foaming occurs due to benzalkonium chloride, which concentrates in foam; processing and filling systems should be designed to minimize foaming and allow rapid dissipation of foaming.

1. Bulk solution.
   a. Charge 80% of final volume of water into mixing tank.
   b. If using methylcellulose, heat deionized water to 90°C. While agitating, add and disperse methylcellulose by slowly sprinkling onto the surface of solution; mix to avoid excessive foaming. Allow 15 minutes for hydration of methylcellulose before discontinuing heating and allowing to cool to 40°C.
   c. While agitating, add and dissolve disodium edetate, benzalkonium chloride, boric acid, and sodium borate; continue cooling to 30°C (25–30°C); discontinue agitation and QS to 950 mL with deionized water. Start agitator and mix for at least 15 minutes at 30°C. Discontinue agitation and cooling. Sample.
2. Naphazoline hydrochloride concentrate solution. Dissolve naphazoline hydrochloride in 50 mL of deionized water, and sterile filter solution through a previously sterilized Millipore® filter unit containing a 0.22-μm membrane. Hold naphazoline solution under aseptic conditions for addition to bulk solution (after it has been autoclaved and cooled).
3. Prefiltration. Methylcellulose solutions filter at a slow rate. Recirculate solution until clear and transfer to holding or sterilization.
4. Sterilization and filling. Use either heat sterilization or sterile filtration. In heat sterilization, sterilize at 112°C to 115°C for 60 minutes, cool the solution to 25°C to 30°C, aseptically add the sterile naphazoline solution, and mix well. Set up a previously sterilized filter and transfer line with 10-μm stainless steel filter. Aseptically fill sterile solution into sterilized containers and apply sterile closure components. Sample. In sterile filtration, use Pall cartridge with Sartorius cartridge. Prepare and steam-sterilize the recommended filter units and aseptically fill the sterilize solution to which naphazoline solution has been added into each sterilized container and apply sterile closure. Sample.

Natamycin Ophthalmic Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Natamycin	50.00	g
0.20	mg	2	Benzalkonium chloride	0.20	g
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill into 15-mL glass bottles with dropper assembly.

Natural Estrogenic Substances Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.50	mg	1	Estrone, NF	1.50	g
0.50	mg	2	Estrogenic substances; items 1 and 2 combined, 2 mg	0.50	g
1.00	mg	3	Carboxymethylcellulose sodium, USP	1.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
1.00	mg	5	Sodium phosphate, USP	1.00	g
1:10	M	6	Benzalkonium, 50%, USP	1:10	M
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	mL	8	Acetic acid for buffering	QS	
QS	mL	9	Sodium acetate for buffering; see item 8	QS	

Note: For 5-mg strength, adjust fill volume.

Nedocromil Sodium Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Nedocromil sodium	20.00	g
0.10	mg	2	Benzalkonium chloride	0.10	g
0.50	mg	3	Edetate sodium	0.50	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: pH 4 to 5.5; fill into 5-mL natural LDPE round eye drop bottle with controlled dropper tip and a natural polypropylene cap.

Neomycin and Prednisolone Acetate Ophthalmic Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
5.50	mg	1	Borosilicate beads		
247.50	g	2	Prednisolone acetate, USP (10% overage)		
0.0066	mL	3	Water purified (distilled), USP	300.00	mL
0.0055	mL	4	P VA micronizing diluent	250.00	mL
0.0177	mL	5	Water purified (distilled), USP, ca.	800.00	mL
Part II					
0.3333	mL	6	Water purified (distilled), USP, ca.	15.00	L
14.00[a]	mg	7	Polyvinyl alcohol, 20–90	941.30	g
0.0003[a]	mL	8	Polysorbate 80, NF (use 10% solution)	141.00	mL
Part III					
0.8222	mL	9	Water purified (distilled), USP, ca.	37.00	L
0.01	mL	10	Propylene glycol, USP	675.00	mL
8.33	mg	11	Sodium acetate trihydrate, USP	562.30	g
3.85[b]	mg	12	Neomycin sulfate, USP (10% overage)	259.90[c]	g
11,500	U	13	Polymyxin B sulfate, USP (15% overage)	92.37[d]	g
Part IV					
0.0044	mL	14	Water purified (distilled), USP, ca.	200.00	mL
0.01	mg	15	Thimerosal, USP[e]	0.675	g
QS	mL	16	Water purified (distilled), USP, ca.; QS add parts II, III, and IV	60.00	L
QS	mL	17	Sterile filtrate QS parts II, III, IV	40.00	L
Part V					
0.0811	mL	18	Water purified (distilled), USP	3.65	L

[a] Includes amount contained in polyvinyl alcohol micronizing diluent. Polyvinyl alcohol micronizing diluent contains 1.0% polyvinyl alcohol 20–90 and 1.65% polysorbate 80, NF.
[b] Equivalent to 3.85 mg/mL neomycin base.
[c] The amount of neomycin sulfate to be added must be calculated on the basis of the manufacturer's assay value of the raw material lot used as per the following formula: 259.9 g neomycin base ∞ 1000 mg/mg/manufacturer's assay value (mg/mg) = g of neomycin sulfate required.
[d] The amount of Polymyxin B sulfate to be added must be calculated on the basis of the manufacturer's assay value of the raw material lot used as per the following formula: 776250000 U Polymyxin B sulfate/manufacturer's assay value (U/mg $\times$ 1000 mg/g = g of Polymyxin B sulfate required. (Assuming assay = 8403 U/mg.)T
[e] The amount of thimerosal to be added must be calculated on the basis of the manufacturer's assay value of the raw material lot used as per the following formula: 0.675 g $\times$ 100.0%/assay value(%) = g thimerosal required.

Manufacturing Directions

Caution: Hazardous handling of prednisolone and neomycin; observe protection and precaution. Protect the preparation from light after adding neomycin and Polymyxin B.

Part I

1. Add item 2 into a 2-L grinding jar filled to approximately half with glass beads; add 300 mL of item 5 to it and then 250 mL of item 4.
2. Seal the jar with a Teflon stopper and mix until the steroid has been wetted; remove the stopper and wrap the mount of jar with a double layer of aluminum foil and a double layer of parchment paper and secure it with steel wires.
3. Sterilize the jar by autoclaving for at least 2 hours and 30 minutes at 121°C; remove the jar from the autoclave and allow it to cool to room temperature.
4. Transfer 800 mL of item 5 into a 1-L flask; wrap the mouth of the flask with a double layer of aluminum foil and a double layer of parchment paper and secure the two rubber bands.
5. Sterilize item 5 by autoclaving for 30 minutes minimum at 121°C; remove the flask from the autoclave and allow it to cool to room temperature.
6. Wrap a Teflon stopper that will fit the mouth of the grinding jar with two layers of aluminum foil; sterilize the Teflon stopper by autoclaving for at least 30 minutes at 121°C.
7. Aseptically (under a laminar flow hood, with appropriate gowning) add as much of the 800 mL of sterile item 5 as it takes to fill the grinding jar to the neck. Seal the grinding jar with the sterilized Teflon stopper, cover the Teflon stopper with double layers of aluminum and double

layers of parchment paper, and secure the parchment paper and aluminum foil with two steel wires.
8. Place the grinding jar on the mill and grind until the particle size is approved by QC.

Part II
1. Measure out ca. 20 L of item 6 into a container suitable for heating. Begin mixing with a suitable mixer. Heat the item 5 to 85°C to 90°C.
2. Measure out 15 L of heated item 6 into a 20-L container; begin mixing with a propeller mixer.
3. Add item 7 slowly to the vortex. Avoid formation of excessive foam. Mix for at least 90 minutes until it is completely dissolved (mixing time not less than 90 minutes).
4. Add item 8, 10% solution, and mix well; cool to room temperature.

Part III
1. Measure out ca. 37 L of item 9 into a mixing tank suitably calibrated for a final QS of 60 L; begin mixing.
2. Add items 10, 11, 12, and 13, in order, allowing each to mix thoroughly or dissolve completely before adding the next.
3. Add part II to the mixing tank containing part III while mixing part III.
4. Use 3 to 4 L of item 9 to rinse the part II container, add the rinsings to the mixing tank, mix thoroughly.

Part IV
1. Weigh out item 15 and carefully transfer it to a suitable flask.
2. Add 200 mL of item 14 and mix until item 15 is dissolved.
3. Add part IV to combined parts II and III and mix thoroughly.
4. Rinse the part IV flask with ca. 200 mL of item 16 and add the rinsings to the mixing tank.
5. Allow any foam to dissipate and QS the combined solution of parts II, III, and IV (product base) to 60 L with item 16; mix thoroughly for at least 15 minutes.
6. Take a 60-mL sample of combined parts II, III, and IV product base for bulk assay.

Sterile Filtration
Note: Sterile filter 40-L of combined parts II, III, and IV base, using an approved 0.2-μm filter.

1. Sterilize for 1 hour (range 45–60 minutes) at 121°C (−0, +5°C) in an autoclave at 15 psi in a 100-L stainless steel pressure vessel. Transfer to solution preparation area.
2. Mix the product for at least 10 minutes before filtration.
3. Connect the sterilized filter and sterile filter with the aid of N_2 pressure (15–30 lb) into the sterilized 100-L stainless steel pressure vessel. *Note*: Before sterile filtration to the 100-L pressure vessel, perform the bubble point test at NLT 40 psi and on a 0.22-Lim in-line gas filter at 18 psi.
4. After completion of product filtration, flush the sterilizing filter with at least 10 L of water purified (distilled).
5. After filtration, decontaminate the outer surface of the bulk holding the pressure vessel and then transfer to filling cubicle; discard NLT 10 L through the sterilized filter prior to connecting on the sterile filling lead line.
6. QA sample for bulk assay. Discard any remaining base portion, after keeping 40 L of the combined parts II, III, and IV.

Sterilization
Sterilize filling unit, 20-L surge bottle, P2 sintered glass filter, and uniforms at 121°C (−0°, +2°C) and 15 psi for 1 hour.

Part V
1. Measure out and transfer item 18 into a suitable glass bottle. Seal the mouth of the bottle with two layers of aluminum foil and two layers of parchment paper; secure the aluminum foil and parchment paper with two rubber bands.
2. Sterilize item 18 by autoclaving for at least 60 minutes at 121°C. Remove the bottle from the autoclave and allow it to cool to room temperature.

Mixing Procedure
Note: Perform all mixing of steroid under aseptic conditions. Product is light sensitive.

1. Grind the steroid (part I) for at least 6 hours before mixing.
2. Aseptically receive 40.0 L of sterile filtered product base (combined parts II, III, and IV) into a sterilized glass bottle calibrated at 40.0 and 45.0 L.
3. Place the glass bottle containing the product base (combined parts II, III, and IV) on a magnetic mixing table.
4. Place the bottle and magnetic mixer in front of a laminar air flow hood.
5. Aseptically add a sterilized magnetic stirring bar to the glass bottle containing the product base. Adjust the mixing speed such that a 10.5-in. deep vortex is formed.
6. Aseptically pour the ground prednisolone acetate, part I, from the grinding jar through a sterilized polyethylene Buchner funnel into the bottle containing the product base. Rinse the grinding jar and the funnel with the sterilized water purified (distilled) (part V).
7. Add the rinsings to the bottle containing parts II, III, and I V. The volume of the suspension in the bottle should now be 45 L. Remove the Buchner funnel and insert a sterilized closing stopper into the mouth of the bottle containing combined parts I to V.
8. Allow the product to mix with a 0.5-in deep vortex for at least 2 hours. Continue mixing at this setting.

Homogenization Procedure
Homogenize the product suspension in a sterilized homogenizer. Filter the suspension through filter into an empty 45-L sterilized glass bottle located in the filling room. Aseptically add a sterilized magnetic stirring bar to the empty 45-L sterilized glass bottle located in the filling room. Place the empty 45-L sterilized glass bottle onto a magnetic mixing table. Adjust the homogenizer controls while cycling the suspension from the bottle through the sterilized homogenizer back to the bottle.

Sterile Filling
1. Transfer the radiation-sterilized bottles, plugs, and caps to the filling cubicle after swabbing their outer polyethylene packing with filtered methylated spirit and keep under the laminar flow hood.
2. Transfer the sterilized assembly line to the filling room; wear surgical gloves and uniforms. Aseptically connect the sterilized filling tubing and N_2 line from the 100-L pressure vessel to the surge bottle.
3. Aseptically fill 5.4 mL of sterile solution through P2 sintered glass into the sterilized container by using the automatic filling, plugging, and sealing machine and apply sterile closure components (plugs and caps). *Note*: While filtering, do not exceed to N_2 pressure of 5 to 10 lb.
4. Perform the bubble point test on a 0.22-μm inline gas filter before and after filtration at 18 psi.

Neomycin Sulfate–Polymyxin B Sulfate for Irrigation

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Neomycin base	40.00	g
200,000	U	2	Polymyxin B sulfate	2 MM	U
10.00	mg	3	Methyl paraben	10.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Fill 1 mL per ampoule.

Neostigmine Methylsulfate Injection Single-Dose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	mg	1	Neostigmine methylsulfate	0.50	g
1.80	mg	2	Methyl paraben	1.80	g
0.20	mg	3	Propyl paraben	0.20	g
QS	mL	4	Sodium hydroxide for pH adjustment		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to ca. 5.9 with item 4.

Neostigmine Methylsulfate Injection Multidose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.50	mg	1	Neostigmine methylsulfate	0.50	g
1.80	mg	2	Glacial acetic acid	1.80	g
0.20	mg	3	Sodium acetate	0.20	g
4.50	mg	4	Phenol liquefied	4.50	g
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to ca. 5.9 with item 5.

Nesiritide for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.15	mg	1	Nesiritide, 5% excess	0.158	g
2.00	mg	2	Mannitol	2.00	g
0.21	mg	3	Citric acid monohydrate	0.21	g
0.294	mg	4	Sodium citrate dihydrate	0.294	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL into each vial and lyophilize.

Netilmicin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Netilmicin, use netilmicin sulfate	12.00	g
4.00	mg	2	Sodium sulfite	4.00	g
1.30	mg	3	Methyl paraben	1.30	g
0.20	mg	4	Propyl paraben	0.20	g
5.40	mg	5	Sodium chloride	5.40	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 0.9 L of item 6 into a jacketed stainless steel vessel; heat it to 70°C to 90°C.
2. Add and dissolve items 3 and 4 to complete solution.
3. Cool to room temperature.
4. Add item 2 and dissolve.
5. Add item 5 and dissolve.
6. Add item 1 and dissolve.
7. Check pH to 6.7 to 6.9; do not adjust.
8. Filter and sterilize.

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Netilmicin, use netilmicin sulfate	3.00	g
1.20	mg	2	Sodium sulfite	1.20	g
2.10	mg	3	Sodium metabisulfite	2.10	g
1.30	mg	4	Methyl paraben	1.30	g
0.20	mg	5	Propyl paraben	0.20	g
2.60	mg	6	Sodium sulfate	2.60	g
0.10	mg	7	Disodium edetate	0.10	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

Niacinamide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Niacinamide, USP	100.00	g
5.00	mg	2	Liquefied phenol, USP	5.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Hydrochloric acid for pH adjustment	QS	

Nicardipine Hydrochloride for Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Nicardipine hydrochloride	2.50	g
48.00	mg	2	Sorbitol	48.00	g
0.525	mg	3	Citric acid monohydrate	0.525	g
0.09	mg	4	Sodium hydroxide	0.09	g
QS	mg	5	Citric acid monohydrate for pH adjustment	QS	g
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to around 3.5 with item 5 or 6. Fill into 10-mL ampoules for infusion after dilution.

Nicardipine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Nicardipine hydrochloride	1.00	g
48.90	mg	2	Sorbitol	48.90	g
0.09	mg	3	Sodium hydroxide	0.09	g
0.525	mg	4	Citric acid monohydrate	0.525	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Nikethamide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Nikethamide	250.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Place item 2 in a suitable stainless steel vessel, add item 1, and dissolve.
2. Check pH to 7.2 (7.0–7.3); do not adjust.
3. Filter the solution in step 1 into a staging vessel, using a 0.45-μm prefilter and 0.22-μm filter.
4. Fill 2 mL presterilized (e.g., 200°C for 4 hours) type I flint ampoules.
5. Autoclave at 121°C for 30 minutes.
6. Sample for clarity and sterility.

Nimesulide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Nimesulide	5.00	g
20.00	mg	2	Benzyl alcohol	20.00	g
10.00	mg	3	Lecithin (Lipoid E-80®)	10.00	g
100.00	mg	4	Dimethylacetamide	100.00	g
20.00	mL	5	Water for injection	20.00	mL
QS	mL	6	Propylene glycol	QS to 1.00	L

Nimodipine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.20	mg	1	Nimodipine	0.20	g
200.00	mg	2	Ethanol USP, 95%	200.00	g
170.00	mg	3	Polyethylene glycol 400	170.00	g
2.00	mg	4	Tertiary sodium citrate	2.00	g
0.30	mg	5	Citric acid	0.30	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Nystatin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Nystatin	50.00	g
50.00	mg	2	Pluronic F-68®	50.00	g
50.00	mg	3	Dimethylsulfoxide	50.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: The concentration of nystatin can be varied; the concentration of Pluronic and DMSO should be proportional to it. Store at 0°C. Lyophilized powder for reconstitution.

Octreotide Acetate Injection Single-Dose Ampoule

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Octreotide as octreotide acetate	50.00	mg
3.40	mg	2	Lactic acid	3.40	g
45.00	mg	3	Mannitol	45.00	g
QS	mg	4	Sodium carbonate for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to between 3.9 and 4.7 with item 4; a 1-mg/mL concentration is also available.

Octreotide Acetate Injection Multidose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Octreotide as octreotide acetate	50.00	mg
3.40	mg	2	Lactic acid	3.40	g
45.00	mg	3	Mannitol	45.00	g
5.00	mg	4	Phenol liquefied	5.00	g
QS	mg	5	Sodium carbonate for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to between 3.9 and 4.7 with item 5; a 1-mg/mL concentration is also available.

Octreotide Acetate Injection Depot

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Octreotide base as octreotide acetate[a]	11.20	mg
188.80	mg	2	DL-Lactic and glycolic acid copolymer	188.80	g
41.00	mg	3	Mannitol	41.00	g
Diluent					
5.00	mg	1	Carboxymethylcellulose sodium	5.00	g
6.00	mg	2	Mannitol	6.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

[a] Equivalent to labeled quantity of 10, 20, or 30 mg octreotide base. Fill powder into 5-mL vial; provide 2 mL of diluent.

Ofloxacin Otic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
3.00	mg	1	Ofloxacin	3.00	g
0.025	mg	2	Benzalkonium chloride	0.025	g
9.00	mg	3	Sodium chloride	9.00	g
QS	mL	4	Hydrochloric acid for pH adjustment		
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 6.0 to7.0 with item 4 or 5. Fill 5 mL or 10 mL into plastic dropper bottle.

Ondansetron Hydrochloride Injection Single-Dose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Ondansetron as ondansetron hydrochloride dihydrate equivalent	2.00	g
9.00	mg	2	Sodium chloride	9.00	g
0.50	mg	3	Citric acid monohydrate	0.50	g
0.25	mg	4	Sodium citrate dihydrate	0.25	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 2 mL into each vial. pH 3.3 to 4.0.

Ondansetron Hydrochloride Injection Multidose Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Ondansetron as ondansetron hydrochloride dihydrate equivalent	2.00	g
8.30	mg	2	Sodium chloride	8.30	g
0.50	mg	3	Citric acid monohydrate	0.50	g
0.25	mg	4	Sodium citrate dihydrate	0.25	g
1.20	mg	5	Methyl paraben	1.20	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill 20 mL into each vial. pH 3.3 to 4.0.

Ondansetron Hydrochloride Injection Premixed for Infusion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.64	mg	1	Ondansetron as ondansetron hydrochloride dihydrate equivalent	0.64	g
50.00	mg	2	Dextrose	50.00	g
0.52	mg	3	Citric acid monohydrate	0.50	g
0.23	mg	4	Sodium citrate dihydrate		
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 50 mL into each flexible plastic container specially formulated, nonplasticized, thermoplastic copolyster; pH 3.3 to 4.0.

Oprelvekin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Oprelvekin (interleukin IL-11)[a]	1.00	g
4.60	mg	2	Glycine	4.60	g
0.32	mg	3	Sodium phosphate dibasic heptahydrate	0.32	g
0.11	mg	4	Sodium phosphate monobasic monohydrate	0.11	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] Specific activity ca. 8×10^6 U/mg; adjust for activity. Fill 5 mL into each 5-mL vial and lyophilize. On reconstitution with 5 mL water for injection, the pH is around 7.0.

Orphenadrine Citrate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
30.00	mg	1	Orphenadrine citrate, NF	30.00	g
1.00	mg	2	Sodium bisulfite, USP	1.00	g
2.90	mg	3	Sodium chloride, USP	2.90	g
0.10	mg	4	Benzethonium chloride, NF	0.10	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	

Oxacarbazepine-10 Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Oxacarbazepine-10	2.50	g
47.50	mg	2	Dextrose anhydrous, USP	47.50	g
QS	ft^3	3	Nitrogen gas, NF	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. In a suitable vessel, take approximately 0.9 L of item 4. Bubble with item 3 for 20 minutes.
2. Heat to 60° to 80°C and add item 1, mix, and dissolve.
3. Cool to room temperature.
4. Add item 2, mix, and dissolve.
5. Filter through a 0.22-μm membrane filter and fill into type I glass vials.
6. Sterilize by autoclaving at 121°C for 15 minutes.

Oxazepine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	2-Chloro-11-(4-methyl-1-piperazinyl)-dibenz[b,f][1,4] oxazepine base	63.00	g
0.70	mL	2	Propylene glycol	2.10	L
QS	mL	3	Hydrochloric acid, 10%, for pH adjustment, ca.	51.00	mL
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Add and dissolve item 1 into item 2.
2. Add 800 mL of item 4 and mix well.
3. Check and adjust pH to 6.1 to 6.3 with item 3 and heating to 60°C.
4. Make up volume with item 4.
5. Sterile filter through a 293-mm Selas filter or equivalent with a 0.22-μm membrane.
6. Fill into glass ampoules or vials, 2.0 mL (each unit containing 40 mg of item 1).

Oxendolone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Oxendolone	100.00	g
5.00	mg	2	Sodium carboxymethylcellulose	5.00	g
80.00	mg	3	Sorbitol, NF, crystalline powder nonpyrogenic	80.00	g
10.00	mg	4	Benzyl alcohol, NF	10.00	g
1.40	mg	5	Methyl paraben, NF	1.40	g
0.14	mg	6	Propyl paraben, NF	0.14	g
2.00	mg	7	Polysorbate 80, NF	2.00	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Preparation of sterile bulk suspension.
   a. Take sufficient quantity of item 8 and heat to 80°C; add and dissolve items 5 and 6 and cool to room temperature.
   b. Add item 2 slowly with gentle stirring until smoothly dispersed.
   c. Add item 3 and stir to dissolve.
   d. In a separate container, heat sufficient quantity of item 8 to 50°C and add item 1 and disperse evenly; cool to room temperature and add items 4 and 7 and mix gently to avoid air entrapment.
   e. Add the two suspensions above and mix for 2 to 3 minutes.
   f. Add item 3, stir, and make up the volume.
2. Preparation of vials. Use type I 5-mL borosilicate vials.
   a. Wash and dry vials and load into suitable containers for sterilization.
   b. Sterilize by using dry heat at 200°C (–0, +500°C) vial temperature for 225 minutes (–0, +360 minutes) while maintaining the oven temperature at 225°C (±10°C) for the duration of the cycle.
   c. Deliver to the sterile filling area.
3. Preparation of stoppers. Use type isobutylene isoprene rubber-Daikyo F713 stoppers.
   a. Wash by using the rubber cycle (slow tumbling) with Triton X-100 detergent.
   b. Dry in dryer at 55°C.
   c. Rack, inspect, and wrap the stoppers for autoclaving.
   d. Sterilize in an autoclave for 1 hour at 121°C and vacuum dry with heat for a minimum of 4 hours at a temperature not exceeding 90°C.
   e. Deliver to the sterile filling area.
4. Filling.
   a. Using aseptic technique, connect bulk suspension container to a suitable filling machine.
   b. With continuous gentle stirring of bulk suspension, aseptically fill 2.2 mL of suspension into each clean, sterile vial.
   c. Insert a sterile rubber stopper into each filled vial and apply overcap.
   d. Remove from sterile area and pack into bulk container and label each container with product lot number.
   e. Sample for testing.

Oxymorphone Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Oxymorphone hydrochloride	1.00	g
8.00	mg	2	Sodium chloride	8.00	g
1.80	mg	3	Methyl paraben	1.80	g
0.20	mg	4	Propyl paraben	0.20	g
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill into vials; delete items 3 and 4 for ampoule filling.

Oxytetracycline Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Oxytetracycline, use oxytetracycline dihydrate	65.00	g
3.34	mg	2	Sodium formaldehyde sulfoxylate	3.34	g
0.20	mg	3	Propyl gallate	0.20	g
11.00	mg	4	Monothioglycerol	11.00	g
0.64	mL	5	Propylene glycol	0.64	L
0.005	mL	6	Propylene glycol	5.00	mL
0.05	mL	7	Propylene glycol	50.00	mL
0.026	mL	8	Propylene glycol, QS to ca.	26.00	mL
0.029	mL	9	Monoethanolamine	29.00	mL
25.00	mg	10	Magnesium chloride	25.00	g
10.00	mg	11	Citric acid	10.00	g
20.00	mg	12	Lidocaine HCl	20.00	g
0.114	mL	13	Water for injection, USP	114.00	mL
0.025	mL	14	Water for injection, USP	25.00	mL
0.002	mL	15	Water for injection, USP	2.00	mL
0.008	mL	16	Water for injection, USP	8.00	mL
QS		17	Nitrogen gas, NF		

Manufacturing Directions

Note: Use glass-lined container. Provide N_2 cover throughout. Be careful about the order of steps and intermediate times required.

1. Put item 13 into a suitable vessel and bubble item 17 for 20 minutes.
2. Add item 2 to step 1 and dissolve by stirring.
3. In a separate container, dissolve item 3 in item 6 and mix to step 2.
4. Add item 4 slowly over a 5-minutes period. Ensure complete dissolution.
5. Concurrently with step 4, add item 1 and stir to dissolve.
6. Take item 5 in a separate tank and keep under cover of item 17; maintain at 15°C by circulating chilled water through walled stainless steel vessel.
7. Dissolve item 10 into item 14 and add to step 6.
8. Transfer step 2 solution to step 6 and mix vigorously.
9. Dissolve item 12 into item 7 and add to step 6; wait for 10 minutes.
10. Dissolve item 11 into item 15 and add to step 6. Check pH; it should be around 7.0
11. Add item 9 to step 6 to get a final pH of 8.5 to 8.6. Use item 16 for washings.
12. Make up volume with item 8.
13. Filter the solution under pressure of item 17 using a 0.45-μm prefilter and 0.22-μm filter into a staging glass tank.
14. Fill aseptically into type I 30-mL flint glass vials.

Oxytetracycline Injectable Solution for IM + IV Veterinary Application (500 mg/10 mL)

Formulation

I. Oxytetracycline hydrochloride, 5.7 g;.
II. Kollidon 17 PF [1], 10.0 g; reducing agent, 0.5 g; (e.g. Rongalite® C, BASF); water for injectables, add 100 mL.
III. Magnesium oxide, 0.46 g.
IV. Ethanolamine to adjust pH 8.8.

Manufacturing Directions

Suspend III in solution II, pass continuously nitrogen through the solution to avoid oxidation, and add slowly I to the well-stirred solution. Adjust the pH with IV.

Properties of the solution

Yellow, clear solution.

Remarks

The absence of oxygen during manufacturing and in the final packaging and a good quality of oxytetracycline HCl are essential to avoid the oxidation (= dark solution).

The function of Kollidon 17 PF not only is the solubilization of oxytetracycline but also the reduction of its local toxicity.

The reducing agent must be selected in accordance with the legislation of the corresponding country.

Oxytetracycline Sustained-Release Injectable for IM Veterinary Application (2.2 g/10 mL)

(According to U.S. Patent 4.018.889 (1976)

Formulation

Oxytetracycline, 22.65 g; magnesium oxide, 1.92 g; Soluphor P [1], 40.00 g; Kollidon 17 PF [1], 5.00 g; sodium formaldehyde sulfoxylate, 0.44 g; 2-aminoethanol, 3.84 g; water of injectables, QS, add 100.00 mL.

Manufacturing Directions

Mix the water and the Soluphor P and dissolve the Kollidon 17 PF in the mixture. Heat the solution to 75°C. Add the sodium formaldehyde sulfoxylate and stir until dissolved. After the magnesium oxide has been suspended, slowly stir in the oxytetracycline until a clear solution is obtained. After the solution has cooled, set to pH 8.5 with aminoethanol.

Remarks

The quality of the oxytetracycline and the complete absence of oxygen during the manufacturing and packaging of the solution is essential to obtain a acceptable chemical stability and no dark color.

The reducing agent, sodium formaldehyde sulfoxylate (rongalite, C, BASF), must be selected in accordance with the legislation of the corresponding country.

Oxytocin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Sodium acetate trihydrate USP	2.00	g
5.10	mg	2	Sodium chloride, USP	5.10	g
10.00	U	3	Oxytocin acetate powder (300 U/mg)	33.333[a]	mg
5.00	mg	4	Chlorobutanol, NF, anhydrous crystals	5.00	g
2.20	mg	5	Glacial acetic acid, USP, for pH adjustment	2.20	g
QS	mL	6	Nitrogen gas, NF	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a] Adjust according to potency.

Manufacturing Directions

Note: Oxytocin is a potent drug, which can be absorbed by the nasal and buccal administration route. It is particularly hazardous for women, especially during the last trimester of pregnancy. Prepare solution in a clean glass-lined tank or a 316 stainless steel tank, cleaned according to approved SOPs.

1. Preparation of water. Collect ca. 90% to 95% of final volume of water for injection in a suitable tank. Determine pH (range 5.5–6.5). Sample for testing.
2. Preparation of solution.
   a. Bubble sterile-filtered N_2 into water in the tank; continue bubbling throughout the preparation.
   b. Add sodium acetate, acetic acid glacial, sodium chloride, and chlorobutanol, in order, with mixing. Check and record pH of the solution. Adjust to pH 3.9 to 3.95 by adding acetic acid. Adjust pH with acetic acid.
   c. While bubbling N_2 gas, add the oxytocin acetate. Mix well. Adjust pH to 3.9 to 3.95 with 1 N acetic acid freshly prepared by 6.0 mL glacial acetic acid and 94 mL water for injection.
3. Preparation of sterile apparatus.
   a. Prepare a 0.2-μm filter and sterilize in autoclave at 121°C for 30 to 35 minutes slow exhaust.
   b. Sterilize all Pyrex bottle fittings in an autoclave at 121°C for 30 to 35 minutes.
   c. Sterilize a sufficient number of Pyrex bottles with dry heat (oven) at 245°C to 330°C for 2 hours and 445 minutes to 3 hours and 30 minutes.
   d. Aseptically filter through a 0.2-μm membrane assembly with an approved filter in an N_2 atmosphere.
4. Preparation of ampoules. Wash and dry ampoules and load into appropriate containers for sterilization. Sterilize by using a dry-heat oven at 245°C to 330°C for 2 hours and 45 minutes to 3 hours and 30 minutes. May use equivalent cycle to assure sterility, pyrogen-free ampoules. Deliver to sterile filling area.
5. Filling.
   a. Connect bulk solution container by using aseptic technique to the filling machines. Fill aseptically specified amount in clean, dry sterile ampoule.
   b. Displace headspace air with sterile N_2 aseptically and immediately seal each ampoule. Sample for testing. Do not autoclave.

Oxytocin Injection, USP (20 U/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	U	1	Oxytocin, USP	20,000	U
5.00	mg	2	Chlorobutanol anhydrous, USP	5.00	g
0.25	%	3	Acetic acid	0.25	%
QS	mL	4	Water for injection, USP	QS to 1.00	L

Paclitaxel Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
6.00	mg	1	Paclitaxel	6.00	g
527.00	mg	2	Cremophor® EL purified (polyoxyetylated castor oil)[a]	527.00	g
0.497	mL	3	Dehydrated alcohol[b]	497.00	mL

[a] Paclitaxel is dissolved in an organic solvent as the primary vehicle, that is, dimethylacetamide (DMA) or dimethylsulfoxide (DMSO), and then followed with a secondary solvent, such as polyethyleneglycol 400 (PEG), to stabilize the drug in solution for subsequent (final) dilution in an aqueous solvent. A preferred final solvent is an aqueous lipid emulsion such as emulsified soybean oil (e.g., Intralipid® or Liposyn®, Soyacal®, or Travemulsion®).
[b] Paclitaxel injection without Cremophor: 49.7% v/v final preparation. Fill 5, 16.7, or 50 mL into each vial.

Palivizumab for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Palivizumab	100.00	g
47.00	mM	2	Histidine	47.00	mM
3.00	mM	3	Glycine	3.00	mM
56.00	mg	4	Mannitol	56.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 1 mL and lyophilize; dilute concentrations for higher volume fill for lyophilization.

Pancuronium Bromide Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.20	mg	1	Sodium acetate anhydrous, USP	1.20	g
3.20	mL	2	Glacial acetic acid, USP, for pH adjustment	3.20	mL
QS	mL	3	Glacial acetic acid, USP, for tonicity adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
10.00	mg	5	Benzyl alcohol, NF	10.00	g
2.00	mg	6	Pancuronium bromide	10.00	g
QS	mg	7	Sodium chloride, USP, for tonicity adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Prepare the solution in a glass-lined or 316 stainless steel tank.
2. Add water for injection to ca. 95% of the final volume into tank. If necessary, cool the water to within the temperature range of 20°C to 30°C.
3. Add and dissolve the sodium acetate with mixing.
4. Check and record the pH. Adjust to pH 4.0 (range 3.9–4.1) with the slow addition of either glacial acetic acid or 10% sodium hydroxide.
5. With mixing, add benzyl alcohol. Mix until the solution is uniform.
6. With mixing, add and dissolve sodium chloride to adjust tonicity.
7. Using extreme care in handling, add and dissolve the pancuronium bromide with mixing.
8. QS to final volume with water for injection.
9. Check pH. Readjust to 4.0 (range 3.9–4.1), with either glacial acetic acid or 10% sodium hydroxide, if necessary.
10. Aseptically filter the solution through a 0.22-μm (or finer) membrane.
11. Aseptically fill solution into ampoules.
12. Inspect and label container.
13. Sample for testing.

Parenteral Nutrition Fat Emulsion

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Safflower oil, winterized	50.00	g
50.00	mg	2	Soybean oil, winterized	50.00	g
9.00	mg	3	Egg phosphate, purified, reduced electrolytes	9.00[a]	g
25.00	mg	4	Glycerin, USP	25.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Nitrogen gas, NF	QS	
QS	mL	7	Sodium hydroxide for pH adjustment	QS	

[a] Range 9.0 to 12.0 g.

Manufacturing Directions

1. Take the amount of item 5 that is equal to the final volume, heat to 70°C to 90°C, and protect with item 6. Maintain this atmosphere throughout processing.
2. Add and disperse item 3 into a portion of item 5 in step 1 with agitation, keeping temperature at 50°C to 90°C.
3. Add and dissolve item 4 previously filtered through a 0.8-μm membrane filter, using a homogenizer to increase degree of dispersion.
4. Filter the dispersion through a cellulose acetate (Millipore®) 0.45-μm or equivalent membrane.
5. Check pH and adjust to 8.5 to 9.5 with item 7 and maintain this pH throughout the process.
6. Filter oils (items 1 and 2) through a 0.45-μm filter and heat to 65°C to 95°C and add to the aqueous phase with agitation to form a coarse emulsion.
7. Homogenize in a homogenizer at a pressure of 5000 psi (range 4000–8000 psi) with a minimum of 10 passes or equivalent.
8. Check pH and adjust again to 8.5 to 9.5.
9. Filter emulsion through a 0.8-μm cellulose acetate filter (Millipore) into a holding tank.
10. Homogenize again with at least three passes at the above specification, and make up volume with item 5. Check and adjust pH again.
11. Fill by using a displacement filler into syringes maintained to reduce foaming; add rubber plunger, add cap, and autoclave. Alternative filling is in a bottle.
12. Sample.

Paricalcitol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	μg	1	Paricalcitol	5.00	mg
0.30	mL	2	Propylene glycol	0.30	L
0.20	mL	3	Alcohol	0.20	L
QS	mL	4	Water for injection, USP	QS to 1.00	L

Pegademase Bovine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	U	1	Pegademase bovine	250,000	U
1.20	mg	2	Sodium phosphate monobasic	1.20	g
5.58	mg	3	Sodium phosphate dibasic	5.58	g
8.50	mg	4	Sodium chloride	8.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: One unit of activity is defined as the amount of ADA that converts 1 μM of adenosine to inosine per minute at 25°C and pH 7.3. Fill 1.5 mL into each ampoule for single use.

Pegaspargase Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
750.00	IU	1	PEG-L-Asparaginase[a]	750,000	IU
5.58	mg	2	Sodium phosphate dibasic	5.58	g
1.20	mg	3	Sodium phosphate monobasic	1.20	g
8.50	mg	4	Sodium chloride	8.50	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] 750 IU±20%. Fill 5 mL per vial.

Peginterferon Alpha-2b for Injection

Bill of Materials (Batch Size 1000 vials L)					
Scale/mL		Item	Material	Qty	UOM
74.00	mg	1	Peginterferon alpha-2b	74.00	mg
1.11	mg	2	Dibasic sodium phosphate anhydrous	1.11	g
1.11	mg	3	Monobasic sodium phosphate dihydrate	1.11	g
59.20	mg	4	Sucrose	59.20	g
0.074	mg	5	Polysorbate 80	0.074	g

Note: Fill into 2-mL vials; reconstitute with 0.7 mL of sterile water for injection; other strengths include 118.4, 177.6, and 222 μg per vial.

Penicillin G Benzathine and Penicillin G Procaine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150,000	U	1	Penicillin G as the benzathine salt	150 MM	U
150,000	U	2	Penicillin G as the procaine salt	150 MM	U
0.012	mg	3	Citric acid	0.012	g
0.006	mg	4	Sodium citrate	0.006	g
5.00	mg	5	Lecithin	5.00	g
5.50	mg	6	Carboxymethylcellulose	5.50	g
5.50	mg	7	Povidone	5.50	g
1.00	mg	8	Methyl paraben	1.00	g
0.10	mg	9	Propyl paraben	0.10	g
QS	mL	10	Water for injection, USP	QS to 1.00	L

Penicillin G Benzathine Injectable Suspension

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
600,000	U	1	Penicillin G as the benzathine salt	600 MM	U
3.00	mg	2	Polyvinylpyrrolidone	3.00	g
6.00	mg	3	Sodium citrate	6.00	g
0.01	mg	4	Lecithin	0.01	g
3.00	mg	5	Carboxymethylcellulose	3.00	g
1.00	mg	6	Methyl paraben	1.00	g
0.10	mg	7	Propyl paraben	0.10	g
QS	mL	8	Water for injection, USP	QS to 1.00	L

Pentobarbital Sodium Solution Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Pentobarbital sodium	50.00	g
0.40	mL	2	Propylene glycol	0.40	L
0.10	mL	3	Alcohol, USP	0.10	L
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to ca. 9.5 with item 4 or 5. Other strengths, 1- and 2.5-g/vial in multidose vials. Do not use if any precipitate appears.

Pentostatin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Pentostatin	10.00	g
50.00	mg	2	Mannitol	50.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 1 mL per vial and lyophilize; for higher fill volume, adjust levels accordingly. Adjust pH to 7.0 to 8.5 with item 3 or 4.

Pentylenetetrazol Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Pentylenetetrazol	100.00	g
1.80	mg	2	Methyl paraben, USP	1.80	g
0.20	mg	3	Propyl paraben, USP	0.20	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Sodium hydroxide for pH adjustment	QS	

Pheniramine Maleate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
22.50	mg	1	Pheniramine maleate	22.50	g
QS	mL	2	Sodium hydroxide for pH adjustment		
QS	mL	3	Hydrochloric acid for pH adjustment		
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve item 1 in item 4 in a suitable 316 or higher temper-grade stainless steel vessel.
2. Check pH and adjust to between 4.5 and 5.0 with item 2 or 3.
3. Filter solution through presterilized assembly by using a 0.45-μm prefilter and a 0.22-μm filter into a sterilized staging vessel.
4. Fill 2.15 mL into presterilized type I amber ampoules (presterilized at 200°C for 4 hours).
5. Autoclave filled ampoules at 116°C for 30 minutes.
6. Sample for assay, sterility, and clarity testing.

Phenol Saline Diluent

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
9.00	mg	1	Sodium chloride, USP	9.00	g
4.00	mg	2	Liquefied phenol, USP	4.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Phenylbutazone and Dipyrone Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
150.00	mg	1	Phenylbutazone	150.00	g
150.00	mg	2	Dipyrone	150.00	g
20.00	mg	3	Lidocaine	20.00	g
20.00	mg	4	Sodium hydroxide, USP	20.00	g
2.00	mg	5	Sodium metabisulfite	2.00	g
1.00	mg	6	Disodium edetate	1.00	g
0.25	mL	7	Propylene glycol	0.25	L
QS	mL	8	Water for injection, USP	QS to 1.00	L
QS	mL	9	Sodium hydroxide for pH adjustment	QS	
QS		10	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Dissolve item 4 in ca. 0.2 L of item 8. Add item 1 with stirring.
2. Check and adjust pH to 13 to 14 with item 9; continue stirring.
3. Dissolve item 3 in item 7 in a separate vessel and stir to a clear solution.
4. Add step 3 to step 2.
5. Dissolve item 2 in 0.2 L (or a suitable amount) of item 8 and add to step 4.
6. Dissolve item 5 and 6 in small amount of item 9 and add to above solution. Make up the volume with item 9.
7. Check and adjust pH to 10 (9.5–10.5) with item 9.
8. Filter through a presterilized filtration assembly by using a 0.45-μm prefilter and a 0.22-μm filter into a staging sterilized vessel.
9. Fill 3 mL solution into type I amber ampoules with pre- and postflush with item 10; presterilize ampoules at 200°C for 4 hours.
10. Autoclave at 121°C for 30 minutes.
11. Sample for testing assay, clarity, and sterility.

Phenylbutazone Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
200	mg	1	Phenylbutazone, USP (use sodium salt in equivalent quantity)	200.00	g
15.00	mg	2	Benzyl alcohol, NF	15.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	

Phenylephrine and Zinc Sulfate Ophthalmic Drops

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Water purified (distilled), USP	10.00	L
14.00	mg	2	Polyvinyl alcohol, 20–90	0.63	kg
Part II					
		3	Water purified (distilled), USP	30.00	L
2.00	mg	4	Sodium citrate dihydrate, USP	90.00	g
1.10	mg	5	Sodium metabisulfite	49.50	g
7.10	mg	6	Sodium chloride, USP	319.50	g
1.32	mg	7	Phenylephrine hydrochloride, USP (10% overage)	59.40	g
2.75	mg	8	Zinc sulfate, USP (10% overage)	123.75	g
0.533	mg	9	Sodium hydroxide, NF	23.99	g
QS	mL	10	1 N Sodium hydroxide, NF[a]	QS	mL
Part III					
		11	Water purified (distilled), USP	100.00	mL
0.05	mg	12	Thimerosal, USP	2.25[b]	g
QS	mL	13	Water purified (distilled), USP	QS to 45.00	L

[a]For pH adjustment only.
[b]The amount of thimerosal to be added must be calculated on the basis of the assay value of the raw material lot used according to the following formula: 2.25 g × 100.0%/assay value (%) = g thimerosal required.

Manufacturing Directions

Part I

1. Measure out ca. 10 L of item 1 into a jacketed stainless steel pressure vessel. Begin mixing with a suitable mixer and heat it to 85°C to 90°C.
2. When the temperature reaches 85°C to 90°C, turn off the heat source. Begin mixing item 1 with a propeller mixer.
3. Add item 2 slowly to the vortex. Avoid formation of excessive foam. Mix for at least 90 minutes until it is completely dissolved. Cool with force cooling to room temperature.

Part II

1. Measure out ca. 30 L of item 3 into a mixing tank suitably calibrated for a final QS of 45 L. Begin mixing.
2. Add items 4 to 9, in order, allowing each to dissolve completely before adding the next. Mix well.
3. Sample for pH (range 6.8–7.0). If necessary, adjust the pH to 6.8 to 7.0 with item 10.
4. Add part I to part II while mixing part II. Use 2.5 to 4.0 L of water purified (distilled) to rinse the part I container, pump, and hoses. Add the rinsings to the mixing tank.

Part III

1. Dissolve item 12 in ca. 100 mL of item 11. Add part III to combined parts I and II and mix thoroughly.
2. Rinse the flask containing item 12 with ca. 100 mL of item 13 and add the rinsings to the batch.
3. Allow any foam to dissipate and QS the batch to 45 L with item 13. Sample.
4. Mix thoroughly for at least 15 minutes.
5. Before filtration, mix the product for at least 10 minutes.
6. Sterile-filter with the aid of N_2 pressure (15–30 lb). Before sterile filtration, perform bubble point test at NLT 40 psi. Sample.
7. Aseptically fill sterile solution into sterilized containers. Sample.

Phenylpropanolamine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
75.00	mg	1	Phenylpropanolamine hydrochloride	75.00	g
5.00	mg	2	Chlorobutanol anhydrous, USP	5.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Phenytoin Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
100.00	mg	1	Polyvinylpyrrolidone, USP	100.00	g
1.00	mL	2	Sodium hydroxide, 1 N solution	10.00	mL
50.00	mg	3	Phenytoin sodium[a]	50.00	mg
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	ft^3	6	Nitrogen gas, NF	QS	

[a]Adjusted to 100% purity assay basis.

Manufacturing Directions

1. Put 0.75 L of item 5 into a jacketed stainless steel vessel; heat it to 40°C to 45°C. Provide item 6 cover throughout.
2. Add item 1 with vigorous mixing until completely dissolved.
3. Cool to room temperature.
4. Add item 2 in small portions and mix well.
5. Add item 3 and dissolve.
6. Check and adjust pH to 12.1 to 12.3 with item 4.
7. Make up volume to 0.98 L with item 5.
8. Check and adjust pH again as in step 6 to 12.2.
9. Make up volume with item 5.
10. Filter with Pall membrane in a Millipore® assembly presterilized under N_2 pressure.
11. Fill under item 6 pre- and postflush into type I glass ampoules aseptically.

Phytonadione (Vitamin K_1) Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
10.00	mg	1	Phytonadione, USP (vitamin K)	10.00	g
200.00	mg	2	Polysorbate 20, NF (sp. gr. 1.08)	200.00	g
500.00	mg	3	Glycerin, USP (sp. gr. 1.249)	500.00	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide 10% for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Weigh item 2 into a clean compounding tank and bring temperature to approximately 45°C (not to exceed 50°C). Take a small portion of polysorbate 20 out and put it in a smaller container. Keep N_2 blanket over the contents of the vessel.
2. Weigh phytonadione under subdued light into another vessel. Pour warm polysorbate 20 from the compounding tank. Mix and pour into the compounding tank and give two more rinses with warm polysorbate 20.
3. Stir to a homogenous mixture.
4. Add approximately 600 mL of water for injection to the compounding tank and mix thoroughly by stirring.
5. Add glycerin to the compounding tank. Mix thoroughly.
6. Check pH, and if necessary adjust with item 5 to between 6.0 and 7.0. Do not adjust pH if it is already within this range.
7. Bring to final volume with water for injection and mix well.
8. Withdraw a 10-mL sample for testing.
9. If approved, filter batch through a sterile 0.22-μm filter into a receiving vessel in the clean room. Keep an N_2 blanket over contents of the receiving vessel.
10. Fill with a postfill flush of N_2. Use type I flint vials sterilized and red uncoated stoppers.

Phytonadione (Vitamin K_1) Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
9.00	mg	1	Benzyl alcohol, NF	9.00	g
41.21	mg	2	Dextrose monohydrate, USP, use dextrose, Powder anhydrous, USP	37.50	g
2.10	mg	3	Phytonadione, USP, 5% excess	2.10	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
70.00	mg	5	Polysorbate 80, NF	70.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Preparation.
   a. Add water for injection to ca. 75% of the final volume into glass-lined, light-protected tank.
   b. Add and dissolve dextrose. Add in portions of benzyl alcohol. Mix in another container polysorbate 80 and phytonadione. Add the dextrose solution.
   c. Check and adjust pH to 6.5 (range 6–7) with 1 N sodium hydroxide solution. Record volumes of each used.
   d. QS with water for injection to final volume.
   e. Sample for testing.
   f. Sterilize an approved 0.2- or 0.22-μm membrane filter with an approved prefilter.
   g. Filter the solution through the sterilized filter unit into a sterile, glass-lined holding container.
2. Preparation of ampoules.
   a. Wash and dry type 1 1-mL sulfur-treated ampoules and load into appropriate containers for sterilization.
   b. Sterilize using dry heat at 245°C for at least 3 hours and 25 minutes or an equivalent cycle to ensure sterile, pyrogen-free bottles.
   c. Deliver to the sterile filling area.
3. Filling.
   a. Connect bulk solution container by aseptic technique to the filling machines.
   b. Aseptically fill 0.65 mL (range 0.6–0.7 mL) into each clean, sterile ampoule.
   c. Immediately seal each ampoule.
   d. Sample for testing.
   e. Finishing. Sample for testing.

Phytonadione Injection—Aqueous Colloidal Solution of Vitamin K_1

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
10.00	mg	1	Phytonadione	10.00	g
70.00	mg	2	Polyoxyethylated fatty acid derivative	70.00	g
37.50	mg	3	Dextrose	37.50	g
9.00	mg	4	Benzyl alcohol	9.00	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium hydroxide for pH adjustment		
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5 to 7; lower strength of 2 mg/mL.

Piperacillin Sodium and Tazobactam Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
40.00	mg	1	Piperacillin as piperacillin sodium	40.00	g
10.00	mg	2	Tazobactam	10.00	g
20.00	mg	3	Dextrose hydrous, USP	20.00	g
2.00	mg	4	Sodium citrate dihydrate	2.00	g
QS	mL	5	Hydrochloric acid for pH adjustment		
QS	mL	6	Sodium bicarbonate for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Fill 50 mL into a PL2040 plastic container; keep frozen until administered. Adjust pH to 4.5 to 6.8 with item 5 or 6. Other strengths: 3.375 g/50 mL (item 3, 350 mg and item 4, 150 mg per bag) and 4.50 g/100 mL (item 3, 2 g and item 4, 300 mg per bag).

Plicamycin for Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
0.25	mg	1	Plicamycin	0.25	g
10.00	mg	2	Mannitol	10.00	g
QS	mg	3	Disodium phosphate to adjust pH	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL and lyophilize. Adjust pH to 7 with item 3.

Polyvinyl Alcohol Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
14.00	mg	1	Polyvinyl alcohol	14.00	g
6.00	mg	2	Povidone, USP (*K* value 29–32)	6.00	g
2.00	mg	3	Potassium chloride granules, USP	2.00	g
4.33	mg	4	Sodium chloride, USP	4.33	g
0.50	mg	5	Sodium bicarbonate, USP	0.50	g
0.009	mg	6	Sodium citrate, USP, dihydrate powder	9.00	mg
0.65	mg	7	Dextrose anhydrous, USP, powder	0.65	g
0.50	mg	8	Disodium edetate, USP	0.50	g
5.33	mg	9	Sodium phosphate dibasic, USP, granules	5.33	g
1.05	mg	10	Sodium phosphate monobasic, USP, monohydrate	1.05	g
0.13	mg	11	Sodium hydroxide	0.13	g
QS	mg	12	Sodium hydroxide	QS	
0.10	mg	13	Benzalkonium chloride, use benzalkonium chloride solution, USP, 17% (with 7% excess)	0.63	mL
QS	mL	14	Water purified (deionized), USP		

Manufacturing Directions

1. Use steam-jacketed, glass-lined, or 316 or higher temper-grade stainless steel tank equipped with agitator. Wear suitable mask when handling item 1.
2. Put 0.4 L of item 14 into the mixing tank, maintaining the temperature at 20°C to 30°C. Add item 1 with mixing. Rinse the tank walls and agitator shaft with 35 mL of item 14. Continue mixing for 10 minutes. Raise the temperature to 82°C to 85°C and hold at this temperature for 30 to 45 minutes. (Do not exceed 85°C.) Continue mixing and cool to 25°C to 35°C.
3. Put 0.3 L of item 14 into another mixing tank at 20°C to 30°C and add item 2 slowly with mixing, using rinsing of tank and shaft to 0.4-L total. (Adding item 2 too rapidly will cause clumping that may be difficult to disperse.)
4. Slowly add items 3 to 10.
5. In a separate container, dissolve item 11 in ca. 3 mL of item 14 with mixing (ca. 5% solution).
   Slowly add while mixing this solution to solution in step 5 (approximately 0.2 mL/min; if added too rapidly, Povidone may precipitate out). Continue mixing with rinsing tank for another 30 minutes.
6. When solution in step 2 has cooled to 20°C to 30°C, transfer solution in step 3 into it slowly and rinse the tank. (Avoid foaming by keeping transfer line below the surface of solution.)
7. Continue mixing and bring to volume with item 14 to 0.98 L.
8. Check and record pH (7.4–7.5); adjust pH with 1% of item 12 solution by slow addition.
9. While mixing, add item 13 slowly and mix for at least 30 minutes.
10. Make up volume to 1 L.
11. Check and record pH (7.3–7.5); again adjust as above if necessary.
12. Prepare and sterilize a nylon filter Pall 0.2 μm and aseptically fill the sterile solution into sterilized container and apply sterile closure components.
13. Sample for testing.

Potassium Estrone Sulfate Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
4.00	mg	1	Potassium estrone sulfate	4.00	g
8.00	mg	2	Sodium phosphate, USP	8.00	g
15.00	mg	3	Benzyl alcohol, NF	15.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	

Potassium Estrone Sulfate Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
1.00	mg	1	Potassium estrone sulfate	1.00	g
2.00	mg	2	Estrone, NF	2.00	g
1.00	mg	3	Carboxymethylcellulose sodium, USP	1.00	g
1:10	M	4	Benzalkonium chloride, 50%, USP	1:10	M
1.00	mg	5	Polysorbate 80, USP	1.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Potassium Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale		Item	Material	Qty	UOM
224.00	mg	1	Potassium phosphate monobasic, NF	224.00	g
236.00	mg	2	Potassium phosphate dibasic anhydrous, USP	236.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: Use clean glass-lined tank.

1. Preparation.
   a. Add water for injection to ca. 80% into tank and heat to 70°C (65–75°C). Add and dissolve potassium phosphate monobasic with mixing, add and dissolve potassium phosphate dibasic with mixing, and cool to 25°C (20–30°C). QS with water to 1 L and mix until completely dissolved. Sample. Allow to stand overnight and filter (do not recirculate) by using an approved 0.22-μm membrane filter with an approved prefilter into a glass-lined tank.
   b. Prepare for sterilization a 0.22-μm membrane filtration setup.
2. Preparation of bottles. Use type I or type II 20-mL bottles.
   a. Wash and dry bottles and sterilize using dry heat at 200°C (–0, +50°C) glass temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of cycle.
   b. Deliver to sterile filling area.
3. Preparation of stoppers.
   a. Leach stoppers by boiling for 10 minutes in deionized water. Wash stoppers by using the rubber cycle (slow tumbling) with Triton X-100.
   b. Dry in fast dryer at 55°C. Store in a suitable container until ready for use.
   c. Tray, inspect, and rinse thoroughly. Wrap, try and identify properly, and sterilize in a steam autoclave at 121°C for 60 minutes.
4. Filling.
   a. Connect the bulk solution container, previously prepared sterile filter, and sterile surge bottle to filler by aseptic technique.
   b. Aseptically fill 15.5 mL (15.2–15.8 mL) of solution into each clean, dry sterile bottle. Stopper aseptically, apply seal, and inspect. Sample.

Prednisolone and Neomycin Ophthalmic Suspension

Bill of Materials (Batch Size 45 L)					
Scale		Item	Material	Qty	UOM
Part I					
5.50	mg	1	Borosilicate beads prednisolone acetate, USP (10% overage)	247.50	g
0.0066	mL	2	Water purified (distilled), USP	300.00	mL
0.0055	mL	3	PVA micronizing diluent	250.00	mL
0.0177	mL	4	Water purified (distilled), USP, ca.	800.00	mL
Part II					
0.3333	mL	5	Water purified (distilled), USP, ca.	15.00	L
14.00[a]	mg	6	Polyvinyl alcohol 20–90	941.30	g
0.0003[a]	mL	7	Polysorbate 80, NF (use 10% solution)	141.00	mL
Part III					
0.8222	mL	8	Water purified (distilled), USP, ca.	37.00	L
0.01	mL	9	Propylene glycol, USP	675.00	mL
8.33	mg	10	Sodium acetate trihydrate, USP	562.30	g
3.8500[b]	mg	11	Neomycin sulfate, USP (10% overage)	259.90[c]	g
11,500	U	12	Polymyxin B sulfate, USP (15% overage)	92.37[d]	g
Part IV					
0.0044	mL	13	Water purified (distilled) USP, ca.	200.00	mL
0.01	mg	14	Thimerosal USP[e]	0.675	g
QS	mL	15	Water purified (distilled) USP, approx; QS add parts II, III, and IV	60.00	L
QS	mL	16	Sterile filtrate QS parts II, III, IV	40.00	L
Part V					
0.0811	mL	17	Water purified (distilled) USP	3.65	L

[a] Includes amount contained in polyvinyl alcohol micronizing diluent. Polyvinyl alcohol micronizing diluent contains 1.0% polyvinyl alcohol 20–90 and 1.65% polysorbate 80, NF.
[b] Equivalent to 3.85 mg/mL neomycin base.
[c] The amount of neomycin sulfate to be added must be calculated on the basis of the manufacturer's assay value of the raw material lot used according to the following formula: 259.9 g neomycin base $\times$ 1000 mg/mg/manufacturer's assay value (μg/mg) = g of neomycin sulfate required.
[d] The amount of Polymyxin B sulfate to be added must be calculated on the basis of the manufacturer's assay value of the raw material lot used according to the following formula: 776250000 U Polymyxin B sulfate/manufacturer's assay value (U/mg $\times$ 1000 mg/g) = g of Polymyxin B sulfate required. (Standard 8403 U/mg.)
[e] The amount of thimerosal to be added must be calculated on the basis of the manufacturer's assay value of the raw material lot used according to the following formula: 0.675 g $\times$ 100.0%/assay value (%) = g thimerosal required.

Manufacturing Directions

Part I

1. Add item 1 into a 2-L grinding jar filled approximately half with glass beads. Add 300 mL of item 4 to it and then 250 mL of item 3.
2. Seal the jar with a Teflon stopper and mix until the steroid has been wetted. Remove the stopper and wrap the mount of jar with a double layer of aluminum foil and a double layer of parchment paper, and secure it with steel wires.
3. Sterilize the jar by autoclaving for at least 2 hours and 30 minutes at 121°C. Remove the jar from the autoclave and allow it to cool to room temperature.
4. Transfer 800 mL of item 4 into a 1-L flask. Wrap the mouth of the flask with a double layer of aluminum foil and a double layer of parchment paper and secure with two rubber bands.
5. Sterilize item 4 by autoclaving for 30 minutes minimum at 121°C. Remove the flask from the autoclave and allow it to cool to room temperature.
6. Wrap a Teflon stopper that will fit the mouth of the grinding jar with two layers of aluminum foil. Sterilize the Teflon stopper by autoclaving for at least 30 minutes at 121°C.
7. Aseptically (under a laminar flow hood, with appropriate gowning) add as much of the 800 mL of sterile item 4 as it takes to fill the grinding jar to the neck. Seal the grinding jar with the sterilized Teflon stopper. Cover the Teflon stopper with double layers of aluminum and double layer of parchment paper. Secure the parchment paper and aluminum foil with two steel wires.
8. Place the grinding jar on the mill and grind until the particle size is approved by QC.

Part II

1. Measure out ca. 20 L of item 5 into a container suitable for heating. Begin mixing with a suitable mixer. Heat the item 4 to 85°C to 90°C.
2. Measure out 15 L of heated item 5 into a 20-L container. Begin mixing using a propeller mixer.
3. Add item 6 slowly to the vortex. Avoid formation of excessive foam. Mix for at least 90 minutes until it is completely dissolved. (Mixing time is not less than 90 minutes.)
4. Add item 7, 10% solution, and mix well. Cool to room temperature.

Part III

1. Measure out ca. 37 L of item 8 into a mixing tank and begin mixing.
2. Add items 9, 10, 11, and 12, in order, allowing each to mix thoroughly or dissolve completely before adding the next.
3. Add part II to the mixing tank containing part III while mixing part III.
4. Use 3 to 4 L of item 8 to rinse the part II container. Add the rinsings to the mixing tank and mix thoroughly.

Part IV

1. Weigh out item 14 and carefully transfer it to a suitable flask.
2. Add 200 mL of item 13 and mix until item 14 is dissolved.
3. Add part IV to combined parts II and III and mix thoroughly.
4. Rinse the part IV flask with ca. 200 mL of item 15 and add the rinsings to the mixing tank.
5. Allow any foam to dissipate and QS the combined solution of parts II, III, and IV (product base) to 60 L with item 15. Mix thoroughly for at least 15 minutes. Sample.
6. Mix the product for at least 10 minutes before filtration.
7. Connect the sterilized filter and sterile filter with the aid of N_2 pressure (15–30 lb) into a sterilized 100-L stainless steel pressure vessel. Perform the bubble point test at NLT 40 psi and on a 0.22-μm inline gas filter at 18 psi. Sample.

Part V

1. Measure out and transfer item 17 into a suitable glass bottle. Seal the mouth of the bottle with two layers of aluminum foil and two layers of parchment paper and secure with two rubber bands.
2. Sterilize item 17 by autoclaving for at least 60 minutes at 121°C. Remove the bottle from the autoclave and allow it to cool to room temperature.

Mixing Procedure

1. Grind the steroid (part I) for at least 6 hours before mixing.
2. Aseptically receive 40 L of the sterile-filtered product base (combined parts II, III, and IV) into a sterilized glass bottle calibrated at 40 and 45 L.
3. Place the glass bottle containing the product base (combined parts II, III, and IV) on a magnetic mixing table. Place the bottle and magnetic mixer in front of a laminar air flow hood.
4. Aseptically add a sterilized magnetic stirring bar to the glass bottle containing the product base. Adjust the mixing speed such that a 0.5-in deep vortex is formed.
5. Aseptically pour the ground prednisolone acetate, part I, from the grinding jar through a sterilized funnel into the bottle containing the product base. Rinse the grinding jar and the funnel with the sterilized water purified (distilled; part V).
6. Add the rinsings to the bottle containing parts II, III, and IV. The volume of the suspension in the bottle should now be 45 L. Allow the product to mix with a 0.5-in deep vortex for at least 2 hours. Continue mixing at this setting.
7. Homogenize the product suspension with a sterilized homogenizer.
8. Allow the product to mix in the receiving bottle after completion of homogenization for at least 2 hours. Sample. If bulk assay results are acceptable, fill the product.
9. Aseptically fill sterile solution through P2 sintered glass into sterilized containers. Perform bubble point test on 0.22-μm inline gas filter before and after filtration at 18 psi.

Prednisolone Injection: Acetate/Phosphate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
80.00	mg	1	Prednisolone acetate, USP	80.00	g
20.00	mg	2	Prednisolone sodium phosphate, USP	20.00	g
25.00	mg	3	Niacinamide, USP	25.00	g
6.50	mg	4	Sodium chloride, USP	6.50	g
2.00	mg	5	Pectin, NF	2.00	g
1:10	M	6	Benzalkonium chloride, 50%, USP	1:10	M
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	mL	8	Glacial acetic acid for buffering		
QS	mL	9	Acetic acid for buffering; see item 8		

Acetate Suspension Injection (50 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Prednisolone acetate, USP	50.00	g
0.25	%	2	Pectin, NF	0.25	%
0.65	%	3	Sodium chloride, USP	0.65	%
0.01	%	4	Benzalkonium chloride, 50%, USP	0.01	%
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Glacial acetic acid for buffering		
QS	mL	7	Acetic acid for buffering; see item 6		

Acetate Suspension Injection (10 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Prednisolone acetate, USP	10.00	g
2.00	mg	2	Polysorbate 80, USP	2.00	g
1.00	mg	3	Carboxymethylcellulose sodium, USP	1.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
0.90	%	5	Benzyl alcohol, NF	0.90	%
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Glacial acetic acid for buffering		
QS	mL	8	Acetic acid for buffering; see item 7		

Prednisolone Acetate Suspension with Niacinamide Injection (20 mg/mL)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Prednisolone sodium phosphate, USP, equivalent to prednisolone phosphate	20.00	g
25.00	mg	2	Niacinamide, USP	25.00	g
1.00	mg	3	Sodium bisulfite, USP	1.00	g
5.00	mg	4	Liquefied phenol, USP	5.00	g
0.50	mg	5	Disodium edetate	0.50	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Sodium hydroxide for pH adjustment		

Prednisolone Ophthalmic Drops

Bill of Materials (Batch Size 45 L)					
Scale/mL		Item	Material	Qty	UOM
Part I					
		1	Borosilicate beads		
1.32	mg	2	Prednisolone acetate, USP, 10% overage	59.40	g
		3	Water purified (distilled), USP	221.70	mL
		4	Hydroxypropylmethyl cellulose micronizing diluent[a]	250.00	mL
0.000063	mL	5	Polysorbate 80, NF (use 10% solution)	28.30	mL
Part II					
		6	Water purified (distilled), USP	10.00	L
1.20[a]		7	Hydroxypropylmethyl cellulose F-4M	74.40	g
Part III					
		8	Water purified (distilled), USP	40.00	L
10.00		9	Boric acid, NF	635.30	g
3.00		10	Sodium citrate dihydrate, USP	190.60	g
0.548		11	Sodium metabisulfite	34.80	g
2.61[a]		12	Sodium chloride, USP	162.60	g
0.127		13	Disodium edetate, USP	8.07	g
0.04		14	Benzalkonium chloride, NF (use 10% solution)	25.40[b]	mL
		15	5 N hydrochloric acid, NF[c]	QS	mL
		16	1 N sodium hydroxide[c]	QS	mL
		17	Water purified (distilled), USP, QS add part II and part III	60.00	L
		18	Sterile filtrate, QS parts II and III	42.50	L
Part IV					
		19	Water purified (distilled), USP	2.00	L

[a] Includes amount contained in hydroxypropyl methylcellulose micronizing diluent. It contains 0.5% hydroxypropylmethyl cellulose F-4M and 0.9% sodium chloride.
[b] The amount of benzalkonium chloride, 10% solution, to be added must be calculated on the basis of the assay value of the raw material lot used according to the following formula: 25.4 mL × 10.0%/assay value (%) = mL benzalkonium chloride, 10% solution, required.
[c] For pH adjustment.

Manufacturing Directions

Part I

1. Weigh out and add item 2 to 1-L grinding jar containing ca. 50% to 55% glass beads.
2. Wrap the mouth of the grinding jar with two layers of aluminium foil and two layers of parchment paper, and secure them with two steel wires.
3. Sterilize the grinding jar by autoclaving for at least 3 hours at 121°C.
4. Remove the grinding jar from the autoclave and allow it to cool to room temperature.
5. Measure out and add items 3, 4, and 5 to a 1000-mL Erlenmeyer flask.
6. Wrap the mouth of the flask with two layers of aluminum foil and two layers of parchment paper and secure them with two steel wires. Sterilize the flask contents by autoclaving for at least 30 minutes at 121°C.
7. Remove the flask from the autoclave and allow it to cool to room temperature. Wrap a Teflon stopper that fits the mouth of the grinding jar with two layers of aluminum foil. Sterilize the Teflon stopper by autoclaving for at least 30 minutes at 121°C.
8. In the laminar flow hood, wearing sterile mask, gloves, and gown, aseptically transfer the sterilized solution of items 3, 4, and 5 into the grinding jar containing the sterilized item 2 and glass beads.
9. Aseptically seal the grinding jar with the sterilized Teflon stopper. Cover the Teflon stopper with two layers of aluminum foil and two layers of parchment paper and secure with two rubber bands.
10. Place the grinding jar on the mill and grind until the particle size is approved or for 7 days.

Part II

1. Measure out ca. 10 L of item 6 into a jacketed kettle for heating. Begin mixing with a suitable mixer. Heat it to 80°C to 90°C.
2. Measure out ca. 3 L of heated item 6 into a 6 L container. Begin mixing with a propeller mixer.
3. Add item 7 slowly to the vortex. Mix until it is thoroughly dispersed. Transfer the dispersion to a glass bottle and

rinse the container thoroughly with 2 to 3 L of hot item 6. Add the rinsings to the glass bottle.
4. Place the glass bottle into the water sink. Begin mixing with a suitable propeller mixer. Add item 6 to the bottle to bring the volume to 10 L.
5. Fill the water sink with cold industrial water. Cool the dispersion to less than 30°C. Cover the mouth of the bottle with two layers of aluminium foil. Place the bottle in the refrigerator.
6. Chill for at least 12 hours at 15°C or less until item 7 is completely hydrated.

Part III
1. Measure out ca. 40 L of item 8 into a mixing tank and begin mixing. Add items 9 to 14, in order, allowing each to mix thoroughly before adding the next. Avoid excess foam formation.
2. Add part II to the mixing tank containing part III while mixing part III. Rinse the pressure vessel from part II with 3 to 4 L of item 17. Add the rinsings to the mixing tank. Sample for pH (range 5.6–5.8). If necessary, adjust the pH with item 15 or 16.
3. Allow any foam to dissipate and QS the combined solution of parts II and III to 60 L with item 17. Mix combined parts II and III thoroughly for at least 15 minutes. Sample.
4. Sterile filter 42.5 L of combined parts II and III through a 0.2-μm filter. Discard any remaining combined parts II and III.

Part IV
1. Transfer item 18 into a suitable glass bottle. Seal the mouth of the bottle with two layers of aluminum foil paper and two layers of parchment paper and secure.
2. Sterilize it by autoclaving for at least 60 minutes at 121°C. Remove the bottle from the autoclave and allow it to cool to room temperature.

Sterile Filtration
Sterilize for 1 hour (range 45–60 minutes) at 121°C (–0, +5°C) in an autoclave at 15 psi the filter and 100-L stainless steel pressure vessel. Prior to this, perform the bubble point test at NLT 46 psi. Sample.

Mixing Procedure
1. Grind the steroid (part I) for at least 6 hours before mixing. Aseptically receive 42.5 L of sterile-filtered combined parts II and III into a sterilized glass bottle.
2. Place the pressure vessel containing the combined parts II and III on a magnetic mixing table. Place the magnetic mixer in front of a laminar air flow hood. Aseptically add a sterilized magnetic stirring bar to this pressure vessel. Adjust the mixing speed such that a 0.5-in deep vortex is formed.
3. Aseptically pour part I from the grinding jar through a sterilized polyethylene Buchner funnel into the bottle containing the combined parts II and III. Rinse with the sterilized water purified (part IV). Add the rinsings to the bottle containing parts I, II, and III. The volume of the suspension in the bottle should now be 45 L.
4. Allow the product to mix with a 0.5-in deep vortex for at least 2 hours.

Homogenization
Homogenize the suspension in a sterilized homogenizer. Filter and aseptically fill sterile solution through P2 sintered glass into sterilized containers.

Procaine Penicillin Injectable Suspension (300 mg/mL)

Formulation
1. Procaine penicillin G, 30.0 g.
2. Kollidon 17 PF [1], 0.4 g; carboxymethyl cellulose, 0.15 g; sodium citrate, 0.57 g; antioxidant QS; preservative, QS; water of injectables, add 100 mL.

Manufacturing Directions
1. Suspend procaine penicillin G in the well-stirred solution II.
2. To prevent of discoloration of the dissolved Kollidon during storage, 0.2% to 0.5% of cysteine could be added as antioxidant.

Procaine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Procaine HCl, USP	10.00	g
2.00	mg	2	Sodium bisulfite, USP	2.00	g
5.50	mg	3	Sodium chloride, USP	5.50	g
2.50	mg	4	Chlorobutanol anhydrous, USP	2.50	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Glacial acetic acid for buffering	QS	
QS	mL	7	Sodium acetate for buffering; see item 6	QS	

Note: For a 2% strength, reduce the quantity of sodium chloride (item 3) to 3.5 mg/mL

Prochlorperazine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Prochlorperazine as prochlorperazine edisylate equivalent	5.00	g
5.00	mg	2	Sodium biphosphate	5.00	g
12.00	mg	3	Sodium tartarate	12.00	g
0.90	mg	4	Sodium saccharin	0.75	g
7.50	mg	5	Benzyl alcohol	0.75	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Progesterone and Tocopheryl Acetate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
15.00	mg	1	Progesterone, 5% excess	15.73	g
30.00	mg	2	Tocopheryl acetate (vitamin E)	30.00	g
33.00	mg	3	Ethyl oleate	33.00	g
0.10	mg	4	Butylated hydroxy toluene	100.00	mg
QS		5	Arachis oil refined	QS to 1.00	L
QS		6	Nitrogen gas, NF	QS	

Manufacturing Directions

Note: All equipment must be thoroughly dried and free of any moisture.

1. Put 1 L of item 5 into a suitable container and heat to 150°C and maintain for 1 hour. Cool to 60°C to 70°C.
2. Dissolve item 1 in approximately 0.6 L of oil from step 1.
3. Dissolve item 2 in approximately 0.25 L of oil from step 1. Add to step 2 at room temperature.
4. Add item 4 to above solution. Make up volume with oil from step 1 at room temperature.
5. Filter through appropriate presterilized filter. Use only polyethylene tubing for filling assembly.
6. Fill 1.15 mL into type I amber ampoule under cover of item 6 dried by passing through calcium chloride and phenol traps.

Progesterone Injection Repository Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Progesterone, USP	50.00	g
120.00	mg	2	Ethyl alcohol, USP	120.00	g
150.00	mg	3	Benzyl alcohol, NF	150.00	g
QS	mg	4	Propylene glycol, USP	QS to 1.00	L

Promazine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Promazine HCl, USP	50.00	g
3.00	mg	2	Sodium chloride, USP	3.00	g
2.00	mg	3	Ascorbic acid, USP, ampoule grade	2.00	g
2.00	mg	4	Sodium metabisulfite, NF	2.00	g
QS	mL	5	Nitrogen gas, NF	QS	
QS		6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: This product requires N_2 gas and light protection during solution preparation. Store between 15°C and 30°C. Prepare solution in a clean glass-lined tank.

1. Preparation.
   a. Add water for injection to ca. 90% of the final volume into a glass-lined tank protected from light.
   b. Bubble filter N_2 gas into water for injection for 10 minutes.
   c. Add and dissolve sodium chloride, ascorbic acid, sodium metabisulfite, and promazine with mixing.
   d. Check and record pH (range 4.5–5.1). Adjust to 4.8 with 5 N sodium hydroxide solution. Record amount used.
   e. QS with water for injection to final volume.
   f. Sample for testing.
   g. Sterilize an approved 0.2- or 0.22-μm filter unit in a sterile, glass-lined holding container.
2. Preparation of ampoules. Use type I 1-mL sulfur-treated glass ampoules.
   a. Wash and dry ampoules and load into appropriate containers for sterilization.
   b. Sterilize using dry heat at 245°C for at least 3 hours and 25 minutes or an equivalent cycle.
   c. Deliver to the sterile filling area.
3. Filling.
   a. Connect bulk solution container by aseptic technique to the filling machines.
   b. Aseptically fill 1.2 mL (range 1.1–1.3 mL) into each clean, sterile ampoule.
   c. Flush the headspace of each ampoule with sterile-filtered N_2 gas.
   d. Immediately seal each ampoule.
4. Sterilization.
   a. Sterilize in an autoclave at 122°C for 12 minutes.
   b. Sample for testing.

Promethazine Hydrochloride Injection Vial

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Promethazine hydrochloride	25.00	g
0.25	mg	2	Sodium metabisulfite	0.25	g
5.00	mg	3	Phenol liquefied	5.00	g
QS	mg	4	Acetic acid	QS	
QS	mg	5	Sodium acetate	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	ft^3	7	Nitrogen gas	QS	

Note: Adjust pH to 4.0 to 5.5 with item 4 or 5. Same composition for a 50 mg/mL dose. Light sensitive, process under cover. Provide item 7 cover throughout and fill with pre- and postflush of item 7.

Promethazine Hydrochloride Injection Cartridge Unit

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Promethazine hydrochloride	25.00	g
0.10	mg	2	Edetate sodium	0.10	g
5.00	mg	3	Phenol liquefied	5.00	g
5.00	mg	4	Monothioglycerol	5.00	g
0.04	mg	5	Calcium chloride	0.04	g
QS	mg	6	Acetic acid	QS	
QS	mg	7	Sodium acetate	QS	
QS	mL	8	Water for injection, USP	QS to 1.00	L
QS	ft^3	9	Nitrogen gas	QS	

Note: Adjust pH to 4.0 to 5.5 with item 4 or 5. Same composition for a 50 mg/mL dose. Light sensitive, process under cover. Provide item 9 cover throughout and fill with pre- and postflush of item 9.

Propanidid Injectable Solution (50 mg/mL)

Formulation

1. Propanidid, 5.0 g; Cremophor EL [1], 20.0 g.
2. Preservatives, QS; water for injectables, add 100 mL.

Manufacturing Directions

Mix propanidid with warm Cremophor EL (60°C) and add slowly the warm solution II. The sterilization can be done by filtration or heat.

Properties of the solution

A clear, colorless solution was obtained.

Remarks

- To reduce the viscosity and the side effects, Cremophor EL could be substituted by Solutol HS 15 [1].
- In Germany, Cremophor EL must be declared on the package of injectables.
- During the heat sterilization, a separation of two layers can be observed. Shaking of the ampoules during cooling gives homogeneous, clear solutions.

Propofol Emulsion Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Propofol	10.00	g
45.00	mg	2	Soybean oil refined	45.00	g
5.00	mg	3	Egg lecithin	5.00	g
22.50	mg	4	Glycerin	22.50	g
QS	mL	5	Sodium hydroxide for pH adjustment		
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	ft^3	7	Nitrogen gas NF	QS	

Manufacturing Directions

1. Put 0.9 L of item 6 into a jacketed stainless steel vessel and heat to 40°C. Maintain throughout manufacturing a blanket cover of item 7.
2. Add and dissolve items 3 and 4 and mix well until a uniform dispersion is obtained.
3. In a separate vessel, add item 2, heat to 40°C, and add and dissolve item 1 to complete solution.
4. Add step 3 into step 2 at 40°C. Mix well.
5. Check and adjust pH to 5.0 to 7.5 with item 5.
6. Homogenize emulsion in a homogenizer until globules are less than 1 μm.
7. Check and adjust pH again as in step 5.
8. Filter and fill under item 7 cover.

Pyridoxine and Thiamine Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine HCl, USP	100.00	g
100.00	mg	2	Pyridoxine HCl, USP	100.00	g
1.00	mg	3	Sodium formaldehyde sulfoxylate, NF	1.00	g
15.00	mg	4	Benzyl alcohol, NF	15.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	

Pyridoxine Hydrochloride Injection (100 mg/mL, 30-mL vial)

Bill of Materials (Batch Size 30 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Pyridoxine HCl, USP, 10% excess	110.00	g
15.00	mg	2	Benzyl alcohol, NF	15.00	g
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Measure ca. one-third of the final volume of water for injection into an appropriate clean and identified mixing tank.
2. Add item 1 into the mixing tank and stir until a clear solution is obtained.
3. Add item 2 with constant stirring into the mixing tank.
4. Bring the final volume with item 5 and check pH.
5. Adjust pH between 2.0 and 3.8, if necessary.
6. Sample to test for pH and assay.
7. Filter through a sterile 0.45-μm prefilter and a 0.22-μm membrane filter. Check the integrity test of sterile filter and note results.
8. Aseptically fill sterile vials.
9. Autoclave at 121°C for 20 minutes.
10. Sample for full testing.

Pyridoxine Hydrochloride Injection (100 mg/mL, 1-mL Ampoule)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Pyridoxine HCl, USP, 10% excess	110.00	g
QS	mL	2	Sodium hydroxide for pH adjustment	QS	
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Preparation.
   a. Add water for injection to ca. 80% of the final volume into a glass-lined tank protected from light.
   b. Add and dissolve pyridoxine hydrochloride with mixing.
   c. Record and adjust pH to 3 (range 2.7–3.3) with 5 N sodium hydroxide solution.
   d. QS with water for injection to final volume.
   e. Sample for testing.
   f. Sterilize and approved 0.22-μm membrane filter with an approved prefilter.
   g. Filter the solution through the sterilized filter unit into a sterile, glass-lined holding container.
2. Preparation of ampoules.
   a. Wash and dry type 1 1-mL sulfur-treated ampoules and load into appropriate containers for sterilization.
   b. Sterilize by using dry heat at 245°C for at least 3 hours and 25 minutes or an equivalent cycle to assure sterile, pyrogen-free bottles.
   c. Deliver to the sterile filling area.
3. Filling.
   a. Connect bulk solution container by aseptic technique to the filling machines.
   b. Aseptically fill 1.2 mL (range 1.1–1.3 mL) into each clean, sterile ampoule.
   c. Immediately seal each ampoule.
4. Sterilization.
   a. Autoclave at 121°C for 20 minutes.
   b. Sample for testing.

Pyrilamine Maleate and Ephedrine Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Pyrilamine maleate, NF	25.00	g
10.00	mg	2	Ephedrine HCl, NF	10.00	g
3.00	mg	3	Chlorobutanol anhydrous, USP	3.00	g
QS		4	Water for injection	QS	

Quinidine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
QS		1	Nitrogen gas, NF	QS	
877.13	mg	2	Propylene glycol, USP (QS to 1 L), ca.	877.13	g
190.00	mg	3	Quinidine sulfate, USP	190.00	g

Manufacturing Directions

Precaution: Prepare solution in a clean glass-lined tank. The product requires N_2 gas and light protection during solution preparation.

1. Preparation.
   a. Add propylene glycol into a glass-lined tank protected from light. Bubble N_2 gas into tank for 10 minutes.
   b. Add and dissolve quinidine sulfate with mixing.
   c. Check and record pH.
   d. QS with propylene glycol for injection to final volume.
   e. Sample.
   f. Sterilize an approved 0.2- or 0.22-μm membrane filter with an approved prefilter (0.45 μm).
   g. Filter the solution through the sterilized filter unit into a sterile, glass-lined holding container.
2. Preparation of ampoules. Use type 1 1-mL sulfur-treated ampoules.
   a. Wash and dry ampoule and load into appropriate containers for sterilization.
   b. Sterilize using dry heat at 245°C for at least 3 hours and 25 minutes (or equivalent cycle that ensures sterile, pyrogen-free bottles).
   c. Deliver to the sterile filling area.
3. Filling.
   a. Connect bulk solution container by aseptic technique to the filling machines.
   b. Aseptically fill 1.2 mL (range 1.1–1.3 mL) into each clean, sterile ampoule.
   c. Flush the headspace of each ampoule with sterile filtered N_2 gas. Immediately seal each ampoule.

Quinolone Lyophilized Injections

A variety of quinolone antibiotics can be prepared in a lyophilized form by a simple procedure wherein, as an example, 10 g of powdered antibiotic is dissolved in 50 mL of 1 M lactic acid, the pH adjusted to 4.5 with 1 N sodium hydroxide solution and diluted with distilled water for injection to 100 mL. This solution is filtered through a membrane filter (pore size 0.22 μm) and each 2 mL of the filtrate filled into clean and sterilized vials. These vials are cooled to –42°C and dried under vacuum. The temperature of the shelf is –20°C during the initial stage (up to 22 hours) of drying. Under vacuum, the temperature is elevated to 20°C and kept for 24 hours and further elevated to 40°C and kept for 6 hours to give a freeze-dried preparation.

Quinolone–Calcium Lactate Complex for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
30.00	mg	1	Quinolone antibiotic	30.00	g
12.00	mg	2	L-(+)-Lactic acid	12.00	g
1.90	mg	3	Calcium hydroxide	1.90	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: The complex is produced by dissolving the antibacterial compound in an aqueous lactic acid solution, preferably L-(+)-lactic acid solution, neutralizing the resulting solution with calcium hydroxide in a quantity that is selected so that any precipitation of the antibacterial compound from the solution is avoided and yet on IV injection, venous irritation by the neutralized solution is either absent or is minimized. Adjust the quantity of antibiotic according to amount of moisture in it.

Manufacturing Directions

1. Dissolve item 2 in ca. 0.9 L of item 4 in a suitable container and mix well.
2. Add item 1 with mixing until all the drug particles are dissolved.
3. Add item 3 with mixing.
4. Check pH (ca. 4.6–4.9); adjust pH with calcium hydroxide or lactic acid if necessary.
5. Sterilize the solution by filtering through a previously sterilized 0.22-μm membrane filter or equivalent using 5 for positive pressure.
6. Discard 100 mL of solution to flush the system. Aseptically fill 10.05 to 10.1 mL of the solution into previously sterilized and depyrogenated vials. Stopper loosely with slotted closures and lyophilize. Stopper and cap the lyophilized vials.

Ranitidine Injection Ampoule

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Ranitidine, use ranitidine HCl, 10% excess	27.50	g
2.40	mg	2	Sodium phosphate dibasic anhydrous, use as sodium phosphate dibasic.12 H_2O	2.40	g
0.96	mg	3	Potassium phosphate monobasic	0.96	g
5.00	mg	4	Liquefied phenol, NF	5.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Nitrogen gas, NF	QS	

Note: Quantity of ranitidine and sodium phosphate dibasic to be adjusted for assay on dry basis and to take into account moisture content.

Manufacturing Directions

1. Check item 5 that it does not have conductivity more than 1.0 μS/cm, pH range should be 5.0 to 7.0.
2. Put 0.9 L of item 5 into a suitable preparation vessel and bubble N_2 gas to expel dissolved oxygen. Monitor oxygen level.
3. Add and dissolve sodium phosphate dibasic, potassium phosphate monobasic, and phenol into solution in step 2. Mix well to make clear solution.
4. Add item 1 into the solution in step 3 and mix by stirring to make clear solution. Protect solution from light from this step on.
5. Check pH (range 6.87–7.2).
6. Make up volume and mix during bubbling N_2 gas until oxygen is undetectable.
7. Sample for testing.
8. Prepare filtration assembly and use silicone hoses and filter cartridges dedicated to product.
9. Transfer the solution from the preparation vessel to holding tank by passing through 0.45-μm cartridge.
10. Sterilize ampoules. Check integrity of final filtration filter of 0.22-μm filter.
11. Fill 2.1 to 2.2 mL into ampoules and seal. Perform leak test and optical check.
12. Sample for testing.

Ranitidine Injection Ampoule (50-mL Flexible Plastic Container)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Ranitidine hydrochloride	5.00	g
4.50	mg	2	Sodium chloride	4.50	g
0.30	mg	3	Citric acid	0.30	g
1.80	mg	4	Dibasic sodium phosphate	1.80	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 50 mL into nonplasticized, thermoplastic copolyster (CR3) container; pH 6.7 to 7.3.

Reteplase Recombinant for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
18.10	mg	1	Reteplase	18.10	g
8.32	mg	2	Tranexamic acid	8.32	g
136.24	mg	3	Dipotassium hydrogen phosphate	136.24	g
51.27	mg	4	Phosphoric acid	51.27	g
364.00	mg	5	Sucrose	364.00	g
5.20	mg	6	Polysorbate 80	5.20	g

Note: Reconstitute lyophilized product with water for injection.

Retinol (Vitamin A) Injection

Bill of Materials (Batch Size 2 L)					
Scale/mL		Item	Material	Qty	UOM
5000	IU	1	Vitamin A (retinol in polysorbate 20)[a]	1000,000	IU
500.00	mg	2	Glycerin, USP	1000.00	g
150.00	mg	3	Polysorbate 20, NF[b]	300.00	g
QS	mL	4	Water for injection, USP	QS to 2.00	L
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS		6	Nitrogen gas, NF	QS	

[a]1000000 IU/(potency/g of raw material).
[b]This is the total amount of polysorbate 20 required for the batch. Because Vitamin A raw material used is provided in polysorbate 20, make adjustment for the contribution from the raw material.

Manufacturing Directions

1. Put item 3 into clean compounding tank of suitable size and place it on a hot plate. Heat it to approximately 40°C but do not exceed 60°C. Keep an N_2 blanket over the tank contents during all remaining compounding steps.
2. With constant stirring, add item 1 to the warm polysorbate 20 solution. Use a rubber policeman to transfer all item 1 to the tank. Keep stirring till a clear solution is obtained.
3. Stop heating the compounding tank. While agitating, add, in portions, glycerin to the compounding tank. Rinse the vessel containing item 1 raw material with glycerin and add the rinses to the compounding tank.
4. Add approximately 500 mL item 4 to the tank. Stir to a complete solution.
5. Check pH (6.0–7.0); adjust if necessary with 10% item 5. (Item 5 also contains 0.0027% butylated hydroxytoluene and 0.0006% butylated hydroxyanisole.)
6. Bring the final volume with item 4.
7. Sample for testing.
8. On approval of laboratory, filter through a 0.22-μm filter into a light-protected receiving container in the clean room. Keep N_2 blanket over the solution in the receiving container.
9. Fill with an N_2 postfill flush. Use type I amber vials and 1109 red with Y-40 coating stoppers.

Rh_o (D) Immune Globulin (Human) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Rh_o (D) gamma globulin[a]	50.00	g
2.90	mg	2	Sodium chloride	2.90	g
0.10	mg	3	Polysorbate 80	0.10	g
15.00	mg	4	Glycine	15.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

[a] Small amounts of IgA, typically less than 15 μg per dose, are present. pH 6.20 to 6.55. Package in latex-free delivery system.

Ringer Lactate Solution Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.0024	mL	1	Lactic acid (min. assay 88%)	2.40	mL
1.16	mg	2	Sodium hydroxide, 8% excess	1.25	g
0.00063	mL	3	Hydrochloric acid dilute (10%)	0.70	mL
6.00	mg	4	Sodium chloride, 3% excess	6.20	g
0.40	mg	5	Potassium chloride, 5% excess	0.42	g
0.27	mg	6	Calcium chloride dihydrate, 8% excess	0.291	g
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Dissolve item 4 in 50 mL of item 7 and add item 1 with stirring.
2. Autoclave the solution in step 1 at 115°C for 60 minutes. Allow to cool and check pH.
3. Add item 3 slowly to reduce the pH to between 6.8 and 7.0. (Approximately full quantity of item 3 will be consumed.)
4. Dissolve items 4, 5, and 6 in 0.5 L of item 7 in a separate vessel with stirring at 60°C.
5. Add solution in step 4 to solution in step 3. Stir vigorously and make up the volume.
6. Check pH to between 5.0 and 7.0. Do not adjust pH.
7. Filter using at least a 0.45-μm filter before final filtration with a 0.22-μm filter and fill into 540-mL type I glass bottles.
8. Fill 540-mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl gray rubber stoppers prewashed and sterilized at 116°C for 30 minutes; use triple aluminum seals and suitable plastic hangers.
9. Sterilize filled bottle by autoclaving at 121°C for 20 minutes.

Rituximab Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Rituximab	10.00	g
0.90	%	2	Sodium chloride, USP	0.90	%
7.35	mg	3	Sodium citrate dihydrate	7.35	g
0.70	mg	4	Polysorbate 80 (Tween®)	0.70	g
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	ft^3	8	Nitrogen gas, NF	QS	

Description

The rituximab antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is an IgG_1 kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. It has an approximate molecular weight of 145 kDa. Rituximab has a binding affinity for the CD20 antigen of ca. 8.0 nM. The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese hamster ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The anti-CD20 antibody is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures.

Manufacturing Directions

1. Take 0.9 L of item 7 and purge with item 8 for 20 minutes.
2. Add items 2 and 3 and mix well.
3. Add item 4 gently to avoid frothing.
4. Add item 1 and mix well.
5. Check and adjust pH to 6.5 (range 6.3–6.6) with item 5 or 6.
6. Filter and aseptically fill either 10 mL (100 mg) or 50 mL (500 mg).

Rubella Virus Vaccine Live

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2000	TCID[a]	1	Rubella virus vaccine live wistar RA 27/3 strain	2000,000	TCID
29.00	mg	2	Sorbitol	29.00	g
3.80	mg	3	Sodium phosphate	3.80	g
3.80	mg	4	Sodium chloride	3.80	g
29.00	mg	5	Gelatin hydrolyzed	29.00	g
0.60	mg	6	Albumin (human)	0.60	g
50.00	mg	7	Neomycin	50.00	mg
QS	mL	8	Water for injection, USP	QS to 1.00	L

[a]Tissue culture infectious doses; dose = 0.5 mL; contains fetal bovine serum <1 ppm.

Salbutamol Aerosol for Inhalation

Bill of Materials (Batch Size 1000 U)					
Scale/mL		Item	Material	Qty	UOM
1.173	mg	1	Salbutamol, 10% manufacturing excess	26.40	g
0.1176	mg	2	Oleic acid, 10% manufacturing excess	2.64	g
277.61	mg	3	Trichloromonofluoromethane	5664.00	g
721.09	mg	4	Dichlorodifluoromethane	1470.00	g

Manufacturing Directions

Caution: Salbutamol is a low-dose bronchodilator. Operators should wear full protective clothing including suitable hat, face mask, and gloves during all stages of manufacture. It is a suspension-based aerosol and not a solution.

1. Preparation of suspension.
   a. Filter ca. 5 kg of trichloromonofluoromethane and oleic acid through a suitable 0.2-μm filter into a stainless steel concentrate container.
   b. Slowly add the salbutamol to the solution in step 1a and mix for approximately 15 minutes.
   c. Filter most of the remaining trichloromonofluoromethane through a suitable 0.2-μm filter into the suspension-holding tank.
   d. Add the slurry from step 1b to the holding tank. Rinse the concentrate container with filtered trichloromonofluoromethane and add the rinses to the holding tank. Make up the final mass of 5.693 kg with filtered trichloromonofluoromethane. Mix for further 5 minutes. Sample (to determine nonvolatile matter, range 0.49–0.53 w/w).
2. Filling. Packing commodity details

Valve, aerosol, 65 μL, Valois DF50 or valve, aerosol, 65 μL Bespak BK 356
Vial, aluminum, NS4, 12.5-mL fill, 20-mm opening
Mouthpiece adaptor
Cap for mouthpiece adaptor

   a. Fill 5.7 g of suspension into a clean aluminum vial and immediately crimp on the metering valve.
   b. Pressure-fill, through metering valve, sufficient dichlorodifluoromethane to produce a final fill weight of 20.4 g. Check-weigh each aerosol to ensure that the fill weight is in the range of 20 to 20.8 g. *Note*: At the start of the manufacture, fill three vials and apply non-metering valves. Pressure-test these vials with a special gauge adaptor to ensure that the correct propellant mix is being used. The internal pressure measured at 22°C should be 50 to 60 psi.
   c. Store the filled aerosols for a period of 2 weeks and again check-weigh as in step 2b. Test each aerosol by actuation to ensure correct operation.
   d. Pack the filled aerosol units into suitable cardboard cartons. Each carton should be filled with ca. 500 U. Sample.

Sisomicin Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Sisomicin, use sisomicin sulfate	62.00	mg
3.00	mg	2	Sodium metabisulfite	3.00	g
3.60	mg	3	Sodium chloride	3.60	g
0.80	mg	4	Methyl paraben	0.80	g
0.10	mg	5	Propyl paraben	0.10	g
0.10	mg	6	Disodium edetate	0.10	g
QS	mL	7	Water for injection, USP	QS to 1.00	L
QS	ft^3	8	Nitrogen gas, NF	QS	

Manufacturing Directions

1. Put ca. 0.7 L of item 7 into a suitable stainless steel-jacketed vessel and heat to approximately 70°C.
2. Charge the items 4 and 5 to the heated water and dissolve with agitation.
3. When completely dissolved, cool the contents of the tank to 25°C to 30°C.
4. Sparge the solution with item 8 and keep covered with item 8 cover during subsequent processing.
5. Charge and dissolve items 6, 3, 2, and 6.
6. Charge and dissolve item 1.
7. Bring the batch volume up to 51 L with item 7 and agitate until homogenous.
8. Check pH to 5.1 to 5.3; do not adjust.
9. Under sterile conditions, filter the solution through a suitable bacteria-retentive filter (0.22 μm) collecting the filtrate in a filling tank.
10. Fill the product aseptically into sterile, pyrogen-free, multiple-dose vials, ampoules, or syringes and seal.

Sobrerol Injectable Solution (75 mg/5 mL)

Formulation

Sobrerol, 1.5 g; Kollidon 17 PF [1], 6.0 g; water for injectables, 100.0 mL.

Manufacturing Directions

Dissolve sobrerol slowly in the well-stirred solution of Kollidon 17 PF. The sterilization can be done by filtration through a 0.2-μm filter.

Properties

Preservatives could be added if it is needed. To prevent of discoloration of Kollidon in the solution during storage, 0.1% to 0.5% of cysteine could be added as antioxidant.

Sodium Bicarbonate and Disodium Edetate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Sodium bicarbonate, USP	40.00	g
2.00	mg	2	Disodium edetate anhydrous, use disodium edetate, USP, dihydrate	2.214	g
QS		3	Nitrogen gas, NF	QS	
QS		4	Carbon dioxide gas technical	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: CO_2 gas is used to maintain the bicarbonate equilibrium in solution and to avoid the formation of carbonate. Do not fill solution below room temperature as this will form excessive internal pressure after filling and sealing. Prepare the solution in a glass-lined or 316 or higher temper-grade stainless steel tank, cleaned according to approved SOPs.

1. Preparation.
   a. Add water for injection to ca. 90% of the final volume into the tank.
   b. Bubble CO_2 gas into the water for injection and continue CO_2 gassing throughout the process.
   c. Add and dissolve the sodium bicarbonate and the disodium edetate with mixing.
   d. QS with water for injection to final volume and mix for not less than 15 minutes and until solution is uniform.
   e. Cool solution to 23°C (range 18–23°C).
   f. Filter solution through a previously rinsed filter press and recirculate for at least 30 minutes and until solution is clear.
   g. Filter solution through a previously rinsed filtration setup connected in series to the press, using an approved 0.45-μm or finer membrane. Collect solution in clean tank and protect with CO_2 gas by bubbling and flushing headspace.
   h. Check and record pH (range 7.7–7.9). If pH is more than 7.9, add more CO_2 gas until pH falls within the range. If pH is less than 7.9, add N_2 gas until the pH rises to within the range.
   i. Samples for testing.
   j. Store at room temperature if filled within 24 hours. If held longer, store in refrigerator.

   Note: Must allow to warm to room temperature before filling (range 18–23°C).
   k. Prepare for the filling line a sterile 0.22-μm membrane filtration setup.
2. Preparation of bottles. Use type I glass bottles.
   a. Wash and dry bottles and load into appropriate container for sterilization.
   b. Sterilize by using dry heat at 200°C (–0, +50°C) glass temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of cycle.
   c. Deliver to the sterile filling area.
3. Preparation of stoppers. Use West or Faultless stoppers.
   a. Leach stoppers by boiling for 10 minutes in deionized water.
   b. Wash stoppers in a washer by using a rubber cycle (slow tumbling) with 10 mL of Triton X-100.
   c. Dry in a fast dryer at 55°C.
   d. Store in suitable containers until ready for use.
   e. Tray and inspect and rinse thoroughly. Wrap trays and identify properly.
   f. Sterilize in a steam autoclave at 121°C for 60 minutes.
   g. Deliver to the sterile filling area.
4. Filling. *Note*: Check pH frequently and keep in range of 7.7 to 7.9 by increasing or decreasing CO_2 flow.
   a. Aseptically connect tank, sterile filtration setup, and sterile surge bottle. Protect surge bottle headspace with filtered CO_2 gas.
   b. Aseptically fill specified amount into each clean, sterile bottle.
   c. Flush headspace with sterile CO_2 gas; apply closure and seal.
   d. Sample for testing.

Sodium Bicarbonate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
86.52	mg	1	Sodium bicarbonate, USP	86.62	g
QS	mL	2	Nitrogen gas, NF	QS	
QS	mL	3	Carbon dioxide gas technical	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: CO_2 gas is used to maintain the bicarbonate equilibrium in solution and to avoid the formation of carbonate. Do not fill solution below room temperature as this will form excessive internal pressure after filling and sealing. Prepare the solution in a glass-lined or a 316 or higher-temper-grade stainless steel tank cleaned according to approved SOPs.

1. Preparation.
   a. Add water for injection to ca. 90% of the final volume into the tank.
   b. Heat the water for injection to 35°C (30–38°C) and bubble CO_2 gas into the water for injection for 30 minutes.
   c. Add and dissolve the sodium bicarbonate with mixing.
   d. Cool solution to 25°C (range 20–30°C).
   e. QS with water for injection to final volume and mix for not less than 15 minutes and until solution is uniform.
   f. Check and record pH (range 7.7–7.9). If pH is more than 7.9, add more CO_2 gas until pH falls within the range. If pH is less than 7.9, add N_2 gas until the pH rises to within the range.
   g. Filter solution through a previously rinsed filtration setup connected in series to the press, using an approved 0.45-μm or finer membrane. Collect solution in clean tank and protect with CO_2 gas by bubbling and flushing headspace.
   h. Sample for testing.
   i. Prepare for the filling line a sterile 0.22-μm membrane filtration setup.
2. Preparation of bottles. Use type I 50-mL glass bottles.
   a. Wash and dry bottles and load into appropriate container for sterilization.
   b. Sterilize using dry heat at 200°C (–0, +50°C) glass temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of cycle.
   c. Deliver to the sterile filling area.
3. Preparation of stoppers. Use West or Faultless stoppers, butyl rubber.
   a. Leach stoppers by boiling for 10 minutes in deionized water.
   b. Wash stoppers in a washer by using a rubber cycle (slow tumbling) with 10 mL of Triton X-100.
   c. Dry in a fast dryer at 55°C.
   d. Store in suitable containers until ready for use.
   e. Tray and inspect and rinse thoroughly. Wrap trays and identify properly.
   f. Sterilize in a steam autoclave at 121°C for 60 minutes.
   g. Deliver to the sterile filling area.
4. Filling. *Note*: Check pH frequently and keep in range of 7.7 to 7.9 by increasing or decreasing CO_2 flow.
   a. Aseptically connect tank, sterile filtration setup, and sterile surge bottle. Protect surge bottle headspace with filtered CO_2 gas.
   b. Aseptically fill 52.0 mL into each clean, sterile bottle.
   c. Flush headspace with sterile CO_2 gas, apply closure, and seal.
   d. Sample for testing.

Sodium Chloride Bacteriostatic Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
9.00	mg	1	Sodium chloride, USP	9.00	g
20.00	mg	2	Benzyl alcohol, NF	20.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Sodium Chloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
9.00	mg	1	Sodium chloride, NF, injectable grade, 4% overage	9.33	g
0.50	mg	2	Activated charcoal, NF	0.50	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Use freshly prepared item 3 stored for NMT 24 hours at 80°C. Add item 1 to item 3 at 60°C and mix for 15 minutes.
2. Add item 2 and mix vigorously for 15 minutes.
3. Filter the mixture in step 2 through a presterilized filter assembled suitable for retaining charcoal and to yield a clean solution.
4. Filter using at least a 0.45-μm filter before final filtration with a 0.22-μm filter and fill into 540-mL type I glass bottles (alkalinity-free test required to prevent precipitation on storage).
5. Fill 540 mL while maintaining solution at 45°C to 50°C and seal immediately by using butyl grey rubber stoppers prewashed and sterilized at 116°C for 30 minutes. Use triple aluminum seals and suitable plastic hangers.
6. Sterilized filled bottle by autoclaving at 121°C for 20 minutes. Do not exceed temperature by 3°C or time by 2 minutes either side of the limit.
7. Check pH of solution (range 4.0–4.3). Before autoclaving, pH is 5.5 to 6.5.

Sodium Ferric Gluconate Complex in Sucrose Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
12.50	mg	1	Elemental iron as sodium salt of a ferric ion carbohydrate complex-equivalent amount	12.50	mg
19.50	mg	2	Sucrose	195.00	g
9.00	mg	3	Benzyl alcohol	9.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L

Note: Fill 5 mL per ampoule for 62.50 mg iron; adjust the amount of item 1 based on molecular weight and iron content; pH 7.7 to 9.7.

Sodium Hyaluronate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Sodium hyaluronate	10.00	g
8.50	mg	2	Sodium chloride	8.50	g
0.28	mg	3	Disodium hydrogen phosphate dihydrate	0.28	g
0.04	mg	4	Sodium dihydrogen phosphate hydrate	0.04	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill into syringe and terminally sterilize and aseptically package.

Sodium Lactate Compound (Hartmann's) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.27	mg	1	Calcium chloride dihydrate	0.27	g
0.40	mg	2	Potassium chloride	0.40	g
6.00	mg	3	Sodium chloride	6.00	g
3.17	mg	4	Sodium lactate, use sodium lactate 60% solution	3.17	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Hydrochloric acid dilute	QS	mL

Manufacturing Directions

1. Add and dissolve 70% of items 5 (specific conductivity NMT 1.4 mS/cm), 3, 2, and 1 and 60% of item 4.
2. Make up volume and mix well until solution is uniform.
3. Check pH and adjust to 5.4 to 5.6, if necessary, with item 6.
4. Filter through a 0.45-μm membrane. Perform the bubble point test before and after filling.
5. Fill 545 or 1065 mL into 500- or 1-L blow-fill seal containers.
6. Sterilize the product by using recirculated hot water and air overpressure. Perform complete sterilization within 12 hours of addition of first ingredient.

Sodium Thiosulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
250.00	mg	1	Sodium thiosulfate pentahydrate, 10% excess	275.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Hydrochloric acid for pH adjustment	QS	

Manufacturing Directions

1. Boil item 2 in a clean, marked vessel.
2. Transfer 175 mL of item 2 into a clean, marked compounding vessel.
3. Add required quantity of item 1 into the compound vessel containing 175 mL of water. Stir thoroughly until a clear solution is obtained.
4. QS with item 2 and mix thoroughly. Sample for testing.
5. Sterile-filter through a 0.22-μm filter using a 0.45-μm prefilter and fill into type I 30-mL flint vials with 1888 gray Teflon-coated stoppers.

Somatropin (rDNA Origin) Injection (4- or 8-mg Vials, ca. 12 or 24 IU)

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	Somatropin	4.00	g
8.80	mg	2	Glycine	8.00	g
1.30	mg	3	Disodium phosphate dihydrate	1.30	g
1.10	mg	4	Sodium dihydrogen phosphate dihydrate	1.10	g
44.00	mg	5	Mannitol	44.00	g

Note: Lyophilize in water for injection. Same formulation for 8-mg vial. Diluent is water for injection containing 1.5% benzyl alcohol.

Somatropin (rDNA Origin) Injection (5 mg/1.5 mL, 10 mg/1.5 mL, or 15 mg/1.5 mL Cartridge)

Bill of Materials (Batch Size 1.5 L)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Somatropin	5.00	g
1.00	mg	2	Histidine	1.00	g
4.50	mg	3	Poloxamer 188	4.50	g
4.50	mg	4	Phenol liquefied	4.50	g
60.00	mg	5	Mannitol	60.00	g
QS	mL	6	Hydrochloric acid for pH adjustment	QS	
QS	mL	7	Sodium hydroxide for pH adjustment	QS	
QS	mL	8	Water for injection, USP	QS to 1.50	L

Note: Same formulation for 10-mg dose; for 15-mg dose increase histidine to 1.7 mg and reduce mannitol to 58 mg. Each cartridge contains 1.5 mL.

Sterile Water for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
QS	mL	1	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Precaution: Freshly distill water for injection and do not use more than 24 hours after distillation. Store all bulk water in a refrigerator to minimize possibility of bacterial growth and in tightly closed containers to avoid absorption of CO_2 and other gases.

Note: Prepare the solution in a glass-lined or a 316 or higher temper-grade stainless steel.

1. Preparation.
   a. Add water for injection to final volume in tank.
   b. Filter solution through a previously rinsed filtration setup, using an approved 0.45-μm or finer membrane and an approved prefilter.
   c. Sample for testing.
2. Filling. Use type I 10-mL glass ampoules, USP.
   a. With a 0.22-μm membrane filtration setup, fill 10.5 mL of water for injection into each clean, dry ampoule.
   b. Seal.
3. Sterilization.
   a. Sterilize in a steam autoclave at 115°C and an F_0 range of 8 to 18. Use water spray cooling and terminal air overpressure if available.
   b. Inspect.
   c. Sample for testing.

Streptomycin Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
400.00	mg	1	Streptomycin sulfate	400.00	g
12.00	mg	2	Sodium citrate dihydrate	12.00	g
2.50	mg	3	Phenol liquefied	2.50	g
2.00	mg	4	Sodium metabisulfite	2.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: pH 5.0 to 8.0; fill 2.5 mL.

Succinylcholine Chloride Injection: Lyophilized

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Succinylcholine chloride, USP, anhydrous	44.00[a]	g
0.90	mg	2	Methyl paraben, NF	1.60[a]	g
0.10	mg	3	Propyl paraben, NF	0.20[a]	g
QS	mg	4	Sodium hydroxide, reagent-grade pellets, for pH adjustment	QS	
QS	mL	5	Hydrochloric acid, reagent-grade bottle, for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

[a]100% excess to satisfy label claim when 2.55 mL of solution is reconstituted into 5.10 mL/vial.

Manufacturing Directions

Precautions: Drug is extremely poisonous. Do not inhale powder or allow chemical or its solution to come in contact with skin. Wear a mask and goggles when handling powder. Persons with abrasions about hands or exposed portions of skin cannot work with this product. Operators are warned against rubbing the face around the eyes because of the solubility in eye fluid. Solution is sensitive to heat. Store the bulk solution prior to filling in a refrigerator at 2°C to 8°C. Prepare solution in a glass-lined or a 316 or higher temper-grade stainless steel tank cleaned according to approved plant BOPs.

1. Preparation.
   a. Dissolve items 2 and 3 in ca. 85% of the final volume. Heat to 95°C to 100°C.
   b. Cool solution to 25°C to 30°C. Add and dissolve the item 1.
   c. Check pH (range 4.2–4.5). If necessary, adjust pH upward with 1 N sodium hydroxide or downward with 1 N hydrochloric acid to pH 4.2. *Note*: Prepare a 1 N sodium hydroxide solution by dissolving 40 g of sodium hydroxide per liter of water for injection.
   d. Add water for injection to final volume and mix well.
   e. Filter solution through a previously rinsed filtration setup, using an approved 0.45-μm or finer membrane and an approved prefilter. Filter into clean glass bottles or a holding tank.
   f. Sample for testing.
   g. Store bulk solution in refrigerator at 2°C to 8°C until ready to fill.
   h. Prepare for the filling line a sterile 0.22-μm membrane filtration setup.
2. Preparation of bottles. Use type I or type II 5-mL glass bottles.
   a. Wash and dry bottles and load in appropriate containers for sterilization.
   b. Sterilize by using dry heat at 200°C (–0, +50°C) bottle temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (+10°C) for the duration of the cycle.
   c. Deliver to the sterile filling area.
3. Preparation of stoppers. Use West or Faultless stoppers.
   a. Leach stoppers by boiling for 10 minutes in deionized water.
   b. Wash stoppers in washer.
   c. Dry in a fast dryer at 55°C.
   d. Store in a suitable container until ready for use.
   e. Tray and inspect and rinse thoroughly. Wrap trays and identify.
   f. Sterilize in a steam autoclave at 121°C for 60 minutes.
   g. Deliver to the sterile filling area.
4. Filling.
   a. Connect tank, sterile filtration setup, and sterile surge bottle by aseptic technique.
   b. Aseptically fill 2.55 mL of solution into each sterile bottle.
   c. Sample for testing.
   d. Place filled bottles into sterile metal trays and cover with sterile covers.
   e. Place trays in close cabinet truck until ready for freezing (must be frozen within 8 hours).
   f. Freeze at –50°C for 4.5 hours and lyophilize for 60 hours to less than 10% moisture. (Do not allow temperature to go more than 45°C.)
   g. On completion of lyophilization, immediately stopper aseptically.
   h. Sample for testing.
   i. Cap bottles with aluminum seals.
5. Finishing. Sample for final testing.

Succinylcholine Chloride Injection: Ampoule

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Succinylcholine chloride, USP	50.00	g
QS	mL	2	Sodium hydroxide for pH adjustment	QS	
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Caution: Extremely poisonous drug. Take all precautions against exposure. Solution sensitive to heat; keep bulk refrigerated. Prepare solution in a glass-lined or stainless steel tank.

1. Add 0.9 L of item 4 into tank. Add and dissolve item 1 with mixing. Mix well.
2. Make up volume with item 4.
3. Check and adjust pH 3.0 to 4.5; adjust with item 2 or 3, if necessary.
4. Circulate solution through a filter press precoated with activated carbon.
5. Check pH and adjust as in step 3, if necessary.
6. Filter solution by using a 0.45-μm prefilter and a 0.22-μm membrane filter into a sterile surge bottle.
7. Aseptically fill 10.2 mL (10-mL claim).
8. Sample for final testing.

Succinylcholine Chloride Injection: Veterinary Nonsterile

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20	mg	1	Succinylcholine chloride, USP	20.00	g
0.35	mg	2	Methyl paraben, USP	0.35	
0.175	mg	3	Propyl paraben, USP	0.175	mg
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Hydrochloric acid for pH adjustment	QS	

Sulfadimethoxine Veterinary Injectable Solution (2.5% = 250 mg/10 mL)

Formulation

I. Sulfadimethoxine, 5 g; ethanol 96%, 40 mL; propylene glycol [1], 40 mL.
II. Kollidon 12 PF [1], 70 g; antioxidant, QS; water for injectables, QS, add 200 mL.

Manufacturing Directions

Mix solution I slowly with solution II at 60°C and cool.

Sulfadoxine + Trimethoprim Veterinary Injectable Solution (1000 mg + 200 mg/10 mL)

Formulation

Sulfadoxine, 2.0 g; trimethoprim. 10.0 g; Soluphor P [1], 56.0 g; water for injectables, 29.0 g; sodium hydroxide, QS.

Manufacturing Directions

Dissolve sulfadoxine and trimethoprim in Soluphor P, add the water, and set to pH 8.5 with sodium hydroxide.

Sulfadoxine solution (2% = 20 mg/mL)

Formulation

I. Sulfadoxine, 2.0 g; Lutrol E 400 [1], 68.0 g.
II. Preservative, QS; water, 30.0 g.

Manufacturing Directions

Prepare solution I at 60°C. Heat the solution II to the same temperature and mix slowly with solution I.

Sulfamoxole + Trimethoprim Veterinary Injectable Solution (400 mg + 80 mg/10 mL)

Formulation

Sulfamoxole, 4.0 g; trimethoprim, 0.8 g; Kollidon 12 PF [1], 30.0 g; paraben, 0.2 g; sodium sulfite or cysteine, 0.4 g; propylene glycol [1], 10.0 g; water for injectables, 44.6 g; ethanol, 10.0 g.

Manufacturing Directions

Dissolve Kollidon, paraben, sodium sulfite (or cysteine) in the mixture of water und propylene glycol, heat, add the active ingredients and stir until they are dissolved. Add ethanol, cool, and sterilize.

Sulfathiazole veterinary injectable and oral solutions (0.8% = 8 mg/mL)

Formulations

Injectable oral solutions.

Manufacturing Directions

Dissolve Kollidon and sulfathiazole at 70°C in water and cool slowly to room temperature.

Sterilization of the injectable solution can be done by filtration through a 0.2-μm filter.

Sumatriptan Succinate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
12.00	mg	1	Sumatriptan base as succinate salt equivalent	16.75	g
7.00	mg	2	Sodium chloride	7.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Note: Fill 0.5 mL; pH 4.2 to 5.3.

Tenecteplase for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
50.00	mg	1	Tenecteplase, 5% excess	52.50	g
0.55	g	2	L-Arginine	0.55	kg
0.17	g	3	Phosphoric acid	0.17	kg
4.30	mg	4	Polysorbate 80	4.30	g

Note: Dissolve in water for injection and lyophilize appropriate volume. Product under partial vacuum.

Testosterone Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Testosterone, NF	25.00	g
1.00	mg	2	Carboxymethylcellulose sodium, USP	1.00	g
1.00	mg	3	Sodium phosphate, USP	1.00	g
9.00	mg	4	Sodium chloride, USP	9.00	g
1:10	M	5	Benzalkonium chloride 50%, USP	1:10	M
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Use different fill volumes for different strengths.

Testosterone Cypionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Testosterone cypionate, USP	100.00	g
9.00	mg	2	Benzyl alcohol, NF	9.00	g
200.00	mg	3	Benzyl benzoate, USP	200.00	g
QS	mg	4	Cottonseed oil, USP	QS to 1.00	L

Note: Use different amounts of item 1 for different strengths.

Testosterone Enanthate–Estradiol Valerate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
90.00	mg	1	Testosterone enanthate, USP	90.00	g
4.00	mg	2	Estradiol valerate, USP	4.00	g
20.00	mg	3	Benzyl alcohol, NF	20.00	g
QS	mg	4	Sesame oil, USP	QS to 1.00	L

Note: Use same formulation for 180-mg dose.

Testosterone Enanthate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
200.00	mg	1	Testosterone enanthate	200.00	g
5.00	mg	2	Chlorobutanol	5.00	g
QS	mg	3	Sesame oil purified	QS to 1.00	L

Note: Fill 5 mL into each syringe; terminally sterilized.

Testosterone Repository Veterinary Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Testosterone propionate, USP	25.00	g
150.00	mg	2	Benzyl alcohol, NF	150.00	g
150.00	mg	3	Ethyl alcohol, USP	150.00	g
450.00	mg	4	Propylene glycol, USP	450.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Testosterone Propionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Testosterone propionate, USP	25.00	g
20.00	mg	2	Benzyl alcohol, NF	20.00	g
QS	mg	3	Sesame oil, USP	QS to 1.00	L

Note: Fill 2 mL for 50-mg strength.

Testosterone Propionate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Testosterone propionate, USP	100.00	g
60.00	mg	2	Ethanol, USP	60.00	g
20.00	mg	3	Benzyl alcohol, NF	20.00	g
QS	mg	4	Sesame oil, USP	QS to 1.00	L

Tetrahydrozoline Ophthalmic Drops

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
17.20	mg	1	Boric acid	17.20	g
1.50	mg	2	Hydroxypropylmethylcellulose 2910, 4000 cps	1.50	g
0.40	mg	3	Borax (sodium borate) powder	1.00	g
0.50	mg	4	Tetrahydrozoline hydrochloride	0.50	g
0.585	mL	5	Benzalkonium chloride solution 17%, 7% excess	0.63	mL
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: Use thoroughly cleaned and rinsed steam-jacketed, glass-lined tank or stainless steel tank (No. 304 or better) equipped with a speed-controlled agitator; tank should have a cover. Foaming occurs because of benzalkonium chloride, which concentrates in foam. Processing and filling systems should be designed to minimize foaming and allow rapid dissipation of foaming.

1. Bulk solution.
   a. Charge 80% of final volume of water into mixing tank.
   b. If using methylcellulose, heat deionized water to 90°C. While agitating, add and disperse methylcellulose by slowly sprinkling onto the surface of solution. Mix to avoid excessive foaming. Allow 15 minutes for hydration of methylcellulose before discontinuing heating and allowing to cool to 40°C.
   c. While agitating, add and dissolve disodium edetate, benzalkonium chloride, boric acid, sodium borate, and tetrahydrozoline and continue cooling to 25°C. Discontinue agitation and QS to 1 L with deionized water. Sample.
2. Prefiltration. Methylcellulose solutions filter at a slow rate. Recirculate solution until clear and transfer to holding or sterilization.
3. Sterilization and filling. Use either heat sterilization or sterile filtration. In heat sterilization, sterilize at 112°C to 115°C for 60 minutes. Cool the solution to 25°C to 30°C and aseptically add the sterile naphazoline solution and mix well. Set up a previously sterilized filter and transfer line with a 10-μm stainless steel FulFlo filter or equivalent. Aseptically fill sterile solution into sterilized containers and apply sterile closure components. Sample. In sterile filtration, use appropriate Pall cartridge with Sartorius cartridge. Prepare and steam-sterilize the recommended filter units, aseptically fill the sterilize solution into each sterilized container, and apply sterile closure. Sample.

Theophylline Injectable Solution (4% = 200 mg/5 mL)

Formulation

Theophylline (Knoll), 2 g; Kollidon 12 PF [1], 15 g; propylene glycol [1], 10 g; preservative, QS; antioxidant, QS; water for injectables, add 50 g.

Manufacturing Directions

Dissolve Kollidon 12 PF and the preservative/antioxidant in water and add theophylline to the well-stirred solution.

Theophylline and Dextrose Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.40	mg	1	Theophylline powder, USP	0.40	g
50.00	mg	2	Dextrose monohydrate, USP	50.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS		4	Nitrogen gas, NF	QS	

Note: The amount of theophylline (item 1) to be changed for 0.8, 1.6, 2.0, and 4.0 mg/mL labeled quantity; the amount of item 2 does not change. The product is intended for IV infusion and packaged in containers of different sizes.

Manufacturing Directions

1. Add ca. 95% of the final volume of item 3 into a glass-lined or 316 or higher temper-grade stainless steel tank.
2. Bubble N_2 gas through the water and maintain N_2 gas protection throughout the remainder of the solution preparation.
3. Add and dissolve item 1 with mixing.
4. Add and dissolve item 2 with mixing.
5. QS with item 3 to the final volume and mix until the solution is uniform.
6. Filter solution with a prefilter.
7. Filter solution through a 0.45-μm or finer membrane filter.
8. Fill correct volume with 3% overage into each flexible container.
9. Seal, overwrap, and autoclave 121°C for 30 minutes.
10. Sample for final testing.

Thiamine Hydrochloride Injection: Unbuffered

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine hydrochloride, USP, 5% excess	105.00	g
5.00	mg	2	Chlorobutanol	5.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Measure ca. 0.7 L of the final volume of item 3 into an appropriate clean and identified tank.
2. Add item 1 into the mixing tank and mix until a clear solution is obtained.
3. Add item 2 into the mixing tank and mix until a clear solution is obtained.
4. Bring the final volume with item 3.
5. Check pH to 2.5 to 4.5.
6. Sample for testing.
7. Sterile-filter through a 0.22-μm membrane disc filter with a 0.45-μm prefilter into an appropriate container.
8. Sterilize 30-mL flint vials at 220°C for 240 minutes; use gray stoppers.

In the next four formulations, a 5% to 10% stability excess can be added.

Thiamine Hydrochloride Injection: with Citric Acid and Gelatin

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Thiamine HCl, USP	25.00	g
0.25	mg	2	Citric acid, USP	0.25	g
40.00	mg	3	Gelatin, USP	40.00	g
15.00	mg	4	Benzyl alcohol	15.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	

Thiamine Hydrochloride Injection: Buffered

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Thiamine HCl, USP	25.00	g
52.50	mg	2	L-Glutamic acid (Buffer)	52.50	mg
5.00	mg	3	Chlorobutanol anhydrous, USP	5.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Sodium hydroxide for pH adjustment	QS	

Thiamine Hydrochloride Injection: with Sodium Formaldehyde Sulfoxylate

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Thiamine HCl, USP	100.00	g
1.00	mg	2	Sodium formaldehyde sulfoxylate, NF	1.00	g
15.00	mg	3	Benzyl alcohol, NF	15.00	g
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	mL	5	Sodium hydroxide for pH adjustment	QS	

Thiamine Hydrochloride Injection: Buffered and Gelatin

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Thiamine HCl	25.00	g
52.50	mg	2	L-Glutamic acid	52.50	mg
40.00	mg	3	Gelatin, USP	40.00	g
5.00	mg	4	Chlorobutanol anhydrous	5.00	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Thiopental Sodium for Injection

Bill of Materials (Batch Size 1000 Ampoules)					
Scale/mL		Item	Material	Qty	UOM
500.0	mg	1	Thiopental sodium, sodium carbonate mixture FMU sterilized	500.00	g
QS	mL	2	Nitrogen gas, NF	QS	

Manufacturing Directions

Caution: Use of CO_2 in place of N_2 may cause precipitation that may not be detectable; use of N_2 is thus preferred. Deliver item 1 in air-tight, sterile glass containers only. Pentothal sodium is sensitive to moisture and CO_2. This powder is sterile and must be handled aseptically in a dry, dust-free atmosphere. Minimize the time between filling and sealing the primary container. Relative humidity (RH) should preferably be less than 25% at 27°C; however, actual RH requirements will depend on the type of filling equipment and other process parameters. RH up to 45% at 25°C may be used. Avoid inhaling vapors. Protect bulk material from prolonged exposure to CO_2 and humidity. Aseptically flush exposed bulk containers with sterile N_2 gas and release.

1. Preparation.
   a. Record details of the drug used.
   b. Wipe outer surface of each bottle with 3A alcohol and deliver immediately to sterile area.
   c. Sample for testing.
2. Preparation of ampoules. Use type I, II, or III glass ampoules.
   a. Wash and dry ampoule and load into appropriate containers for sterilization.
   b. Sterilize by using dry heat at 200°C (–0, +50°C) ampoule temperature for 225 minutes (–0, +360 minutes). Maintain oven temperature at 225°C (±10°C) for the duration of the cycle. *Note*: This cycle or a cycle providing equivalent heat input may be used.
   c. Deliver to sterile filling area.
3. Filling.
   a. Sterile-fill 500 mg of powder into each clean, dry sterile ampoule. Seal ampoule. Remove from sterile area and pack into bulk containers, labeling each container with product lot number.
   b. Sample for testing.
   c. Sterile-fill powder equivalent to 0.5 g at a factor of 1.0 into each clean, dry sterile ampoule.
   d. Seal ampoule.

Thiotepa for Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
15.00	mg	1	Thiotepa	15.00	g
0.03	mg	2	Sodium carbonate	2.00	g

Note: Dissolve in adequate amount of water for injection and lyophilize; reconstituted solution has pH of 6.5 to 8.1. Drug unstable in alkaline media.

Thiothixene Hydrochloride Injection

Bill of Materials (Batch Size 1000 Vials)					
Scale/mL		Item	Material	Qty	UOM
5.00	mg	1	Thiothixene hydrochloride, 10% excess	5.50	g
59.60	mg	2	Mannitol	65.00	g
2.20	mL	3	Water for injection	2.20	mL

Note: Reconstitute with 2.2 mL of water for injection to give above concentration.

Thyrotropin-Alpha for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.10	mg	1	Thyrotropin alpha	1.10	g
36.00	mg	2	Mannitol	36.00	g
5.10	mg	3	Sodium phosphate	5.10	g
2.40	mg	4	Sodium chloride	2.40	g
1.20	mL	5	Water for injection, USP	QS to 1.20	L

Note: Reconstituted lyophilized solution has pH around 7.0 and concentration of item 1 is 0.90 mg/mL.

Timolol Ophthalmic Solution

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Timolol as timolol hemihydrate	2.56	g
QS	mg	2	Monosodium phosphate dihydrate to adjust pH	QS	
QS	mg	3	Disodium phosphate dihydrate to adjust pH	QS	
0.10	mg	4	Benzalkonium chloride	0.10	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 6.5 to 7.5 with item 2 or 3. For 0.5% label use twice the amount of item 1.

Tinzaparin Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40,000	IU	1	Tinzaparin sodium	40 MM	IU
10.00	mg	2	Benzyl alcohol	10.00	g
3.10	mg	3	Sodium metabisulfite	3.10	g
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 5.0 to 7.5 with item 4.

Tirofiban Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.050	mg	1	Tirofiban as tirofiban hydrochloride monohydrate	56.18	mg
45.00	mg	2	Sodium chloride	45.00	g
0.54	mg	3	Sodium citrate dihydrate	0.54	g
0.16	mg	4	Citric acid anhydrous	0.16	g
QS	mL	5	Hydrochloric acid for pH adjustment	QS	
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Fill 250 or 500 mL into plastic container; concentrate filled in 25-mL size with adjusted amounts; adjust pH to 5.5 to 6.5 with item 5 or 6.

Tobramycin Solution for Inhalation

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
60.00	mg	1	Tobramycin	60.00	g
2.25	mg	2	Sodium chloride	2.25	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	ft^3	5	Nitrogen gas	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill 5mL into a single-use ampoule; adjust pH to 6.0 with item 3 or 4. Provide item 5 cover throughout with pre- and postfill flush.

Tobramycin Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Tobramycin base, USP	10.00	g
2.92	mg	2	Sodium metabisulfite, NF	2.92	g
0.10	mg	3	Disodium edetate, USP, use disodium edetate, USP, dihydrate	0.11	g
20.98	mg	4	Sulfuric acid, reagent-grade bottle	20.98	g
QS		5	Sodium hydroxide, regent-grade bottle[a]	QS	
QS		6	Sulfuric acid, reagent-grade bottle[a]	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a]For pH adjustment, if necessary, to be used as 1 N sodium hydroxide solution, freshly prepared, by mixing 40 g of item 5 with sufficient water for injection to make 1000 mL. Use 10% sulfuric acid solution, freshly prepared, by adding 100 g or 57 mL of item 6 to sufficient water for injection to make 1000 mL.

Manufacturing Directions

1. Preparation of water.
   a. Obtain a sample from the water for injection source to be used for solution preparation and verify that it meets a conductivity limit of NMT 3 mS/cm and pH range of 5 to 7.
   b. Test the rinse draining from the tank for conductivity and oxidizable substances prior to batch preparation.
2. Preparation of solution.
   a. Add 1.1 L water for injection to a suitable tank. Sparge the water with filtered N_2 gas for not less than 30 minutes. Alternatively, heat the water to not less than 70°C and then cool to 25°C (range 20–30°C) while sparging with filtered N_2 gas.
   b. Transfer ca. 200 mL of this water for injection into another covered tank for use in step 2e. Protect the tank headspace with filtered N_2 gas.
   c. Continue N_2 sparging the bulk water for injection. While mixing with gentle agitation, add and dissolve disodium edetate, sodium metabisulfite, sulfuric acid, and tobramycin. Mix for not less than 20 minutes.
   d. Check and record pH. Adjust, if necessary, to pH 5.5 (range 5.5–6.0) with 10% sulfuric acid solution or 1 N sodium hydroxide solution. Mix thoroughly.
   e. Make up to 1 L with N_2-saturated water for injection cooled to ambient temperature from step 2b.
   f. Recheck and record pH. If necessary, readjust to pH 5.5 (range 5.3–6.0) as in step 2d.
   g. Sample for testing. Discontinue N_2 sparging and switch to N_2 gas protection of tank headspace. If the bulk solution does not meet the in-process specifications, make the necessary adjustment to the batch based on the results of testing.
   h. Prior to filtering the solution, flush the lines, filters, and the glass-lined or 316 or higher temper-grade stainless steel holding tank with filtered N_2 gas. Filter the solution through a previously rinsed filtration setup, using an approved 0.22-μm (or finer) membrane filter with an approved prefilter into the holding tank. Protect the headspace of the holding tank with filtered N_2 gas.
3. Filling. Use type I 2-mL glass ampoules.
   a. Fill specified amount into each clean, dry ampoule.
   b. Flush the headspace with filtered N_2 gas and seal the ampoule.
   c. Inspect.
   d. Sample for testing.
4. Sterilization. Steam-sterilize at 115°C and an F_0 of 8. Use product hold cycle, water spray cooling, and terminal overpressure.

Tobramycin Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Tobramycin base, USP	10.00	g
2.92	mg	2	Sodium metabisulfite, NF	2.92	g
0.10	mg	3	Disodium edetate, USP, use disodium edetate, USP, dihydrate	0.11	g
5.24	mg	4	Sulfuric acid	5.24	g
QS		5	Sodium hydroxide[a]	QS	
QS		6	Sulfuric acid[a]	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

[a]For pH adjustment, if necessary, to be used as 1 N sodium hydroxide solution, freshly prepared, by mixing 40 g of item 5 with sufficient water for injection to make 1000 mL. Use 10% sulfuric acid solution, freshly prepared, by adding 100 g or 57 mL of item 6 to sufficient water for injection to make 1000 mL.

Topotecan Hydrochloride for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.80	mg	1	Topotecan as topotecan hydrochloride	0.866	g
9.60	mg	2	Mannitol	9.60	g
4.00	mg	3	Tartaric acid	4.00	g
QS	mL	4	Hydrochloric acid for pH adjustment	QS	
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Adjust pH to 2.5 to 3.5 with item 4 or 5. Fill 5 mL and lyophilize.

Trace Element Concentrate Injection: (1- or 10-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.54	mg	1	Manganese sulfate monohydrate	1.54	g
3.93	mg	2	Copper sulfate pentahydrate	3.93	g
21.99	mg	3	Zinc sulfate heptahydrate	21.99	g
51.25	mg	4	Chromium chloride hexahydrate	51.25	mg
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Sulfuric acid for pH adjustment	QS	

Note: pH 1.5 to 2.5.

Trace Element Concentrate Injection (3- or 10-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
0.308	mg	1	Manganese sulfate monohydrate	0.308	g
1.57	mg	2	Copper sulfate pentahydrate	1.57	g
4.39	mg	3	Zinc sulfate heptahydrate	4.39	g
20.5	mg	4	Chromium chloride hexahydrate	20.50	mg
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Sodium hydroxide for pH adjustment	QS	
QS	mL	7	Sulfuric acid for pH adjustment	QS	

Tranexamic Acid Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50.00	g	1	Tranexamic acid	50.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	ft^3	3	Nitrogen gas, NF	QS	ft^3

Manufacturing Directions

1. Put approximately 0.9 L of item 2 into a stainless steel vessel, boil it for 10 minutes, and cool to room temperature.
2. Add item 1, stir to dissolve, and make up the volume.
3. Check pH (7.2–7.7)
4. Filter through previously sterilized filtration assembly by using a 0.22-μm membrane filter into a presterilized receiving vessel. Perform the bubble point test before and after filtration.
5. Sterile-fill into sterilized ampoules 5.3 mL of solution through sintered glass and seal.
6. Sample.
7. Sterilize in autoclave at 115°C for 30 minutes.
8. Sample for leak test, optical check, and complete specification testing.

Trastuzumab for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
44.00	mg	1	Trastuzumab	44.00	g
0.99	mg	2	L-Histidine hydrochloride	0.99	g
0.64	mg	3	L-Histidine	0.64	g
40.00	mg	4	Alpha, Alpha-trehalose dihydrate	40.00	g
11.00	mg	5	Benzyl alcohol	11.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill 10 mL per vial and lyophilize. Reconstitute with 20 mL water for injection for item 1 concentration of 21 mg/mL; pH ca. 6.0.

Triamcinolone Acetonide Suspension Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Triamcinolone acetonide, USP	40.00	g
0.40	mg	2	Polysorbate 80, USP	0.40	g
9.00	mg	3	Sodium chloride, USP	9.00	g
7.50	mg	4	Carboxymethylcellulose sodium, USP	7.50	g
9.00	mg	5	Benzyl alcohol, NF	9.00	g
QS	mL	6	Water for injection, USP	QS to 1.00	L
QS	mL	7	Sodium acetate for buffering	QS	
QS	mL	8	Glacial acetic acid for buffering; see item 7	QS	

Trifluprom azine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Trifluprom azine as hydrochloride salt and 5% excess	11.30	g
1.00	mg	2	Sodium acetate	1.00	g
0.0012	mL	3	Glacial acetic acid	1.20	mL
1.00	mg	4	Sodium metabisulfite	1.00	g
QS		5	Nitrogen gas, NF	QS	
QS	mL	6	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: The preparation is light sensitive. Protect and provide N_2 cover throughout.

1. In an appropriate 316 or higher temper-grade stainless steel vessel, take 1 L of freshly boiled item 6 and purge with item 5 for 20 minutes.
2. Add item 1 to ca. 0.9 L of item 6 as prepared in step 1.
3. Add items 2 and 3.
4. Check pH to 4.5 to 5.2; do not adjust.
5. Filter through a 0.45-μm prefilter and a 0.22-μm filter into a sterilized staging vessel.
6. Fill 1.1 mL into sterilized amber ampoule (200°C for 4 hours) with pre- and postflush of item 5.
7. Autoclave filled ampoules at 121°C for 30 minutes.
8. Sample for testing.

Trifluprомazine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mg	1	Triflupromazine and hydrochloride	10.80	g
15.00	mg	2	Benzyl alcohol, NF	15.00	g
3.60	mg	3	Sodium chloride, NF	3.60	g
QS		4	Nitrogen gas, NF	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

Note: The preparation is light sensitive. Protect and provide N_2 cover throughout.

1. Take 0.76 L of freshly distilled and boiled item 5 and flush with item 4 for 20 minutes.
2. Add item 3 to step 1 and stir to dissolve.
3. Add item 2 to step 2 and stir to dissolve.
4. Add item 1 to step 3 and stir to dissolve and make up volume.
5. Check pH to 4.1 to 4.3; do not adjust.
6. Filter through a 0.45-μm prefilter and a 0.22-μm filter into a sterilized staging vessel.
7. Fill 1.1 mL into a sterilized amber ampoule (200°C for 4 hours) with pre- and postflush of item 5.
8. Autoclave filled ampoules at 121°C for 30 minutes.
9. Sample for testing.

Trifluprомazine Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Trifluperazine as trifluoperazine hydrochloride	1.085	g
4.75	mg	2	Sodium tartarate	4.75	g
11.60	mg	3	Sodium biphosphate	11.60	g
0.30	mg	4	Sodium saccharin	0.30	g
7.50	mg	5	Benzyl alcohol	7.50	g
QS	mL	6	Water for injection, USP	QS to 1.00	L

Note: Fill 10-mL multidose vial.

Tripelennamine Hydrochloride Injection Veterinary

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	mg	1	Tripelennamine HCl, USP	20.00	g
5.00	mg	2	Chlorobutanol anhydrous USP	5.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Hydrochloric acid for pH adjustment	QS	

Tubocurarine Chloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
9.00	mg	1	Benzyl alcohol, NF	9.00	g
1.00	mg	2	Sodium metabisulfite, NF	1.00	g
3.00	mg	3	Tubocurarine chloride, USP	3.00	g
8.00	mg	4	Sodium chloride, USP	8.00	g
1.00	mg	5	Citric acid anhydrous powder, USP	1.00	g
0.30	mg	6	Sodium citrate dihydrate, USP	0.30	g
2.00	mg	7	Activated charcoal, USP[a]	2.00	g
QS		8	Nitrogen gas, NF	QS	
QS	mL	9	Water for injection, USP	QS to 1.00	L

Note: If necessary to remove color from solution.

Manufacturing Directions

1. Prepare the solution in a glass-lined or 316 stainless steel tank.
2. Add water for injection to ca. 90% of the final volume into the tank. Begin bubbling N_2 gas into water.
3. Add and dissolve, in order, benzyl alcohol, sodium metabisulfite, citric acid, sodium citrate, tubocurarine chloride, and sodium chloride with mixing.
4. QS to final volume with N_2-saturated water for injection and mix until all ingredients are dissolved and solution is uniform.
5. Check APHA color. The range should not exceed 15 APHA units. Use activated charcoal if necessary.
6. Check and record pH and adjust to 2.5 to 4.9 (final limit 2.5–5.0)
7. Aseptically filter the solution through a 0.22-μm or finer membrane.
8. Aseptically fill solution into type I glass vials with gray butyl rubber stoppers and flip-off cap.
9. Label and finish product.

Typhoid Vi Polysaccharide Vaccine

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
25.00	mg	1	Purified Vi polysaccharide	50.00	mg
4.15	mg	2	Sodium chloride	8.30	g
0.065	mg	3	Disodium phosphate dihydrate	0.130	g
0.023	mg	4	Monobasic sodium phosphate	0.046	g
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill in 0.5-mL syringe aseptically.

Uridine Triphosphate Injection

Prior to formulation, UTPNa_3dihydrate is kept frozen at –20°C. The UTP powder is allowed to warm to handling temperature for at least 1 hour prior to opening to minimize water absorption. The UTP raw material is dissolved in a sterile aqueous solution such as saline solution. An appropriate concentration of the saline solution is used to bring the osmolarity to ca. 300 mOsm, that is, an isotonic solution. Alternatively, UTP powder can be dissolved in sterile water and an appropriate amount of NaCl added to bring the osmolarity to ca. 300 mOsm. In either case, aqueous solution is added in sufficient volume to reach an optimum therapeutic UTP concentration level of 5 to 35 mg/mL. The pH of the liquid solution is adjusted to between 7.0 and 7.5. The resulting UTP solution is sterilized by filtration with an appropriate micrometer filter.

Urokinase for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
50,000	IU	1	Urokinase concentrate[a]	438.62	mL
9.00	mg	2	Sodium chloride	9.00	g
5.00	mg	3	Mannitol (nonpyrogenic)	5.00	g
QS		4	Water for injection	QS to 1.00	L
QS		5	Sodium hydroxide, reagent grade, for pH adjustment	QS	
QS	mL	6	Hydrochloric acid, reagent grade, for pH adjustment	QS	

[a] Quantities of ingredients adjusted based on the potency and volume of urokinase concentrate. Urokinase concentrate contains not less than 110000 IU/mL and between 9 and 22 mg/mL sodium chloride. Dilutions are made such that the two values within the specification are maintained. Mannitol is used to adjust activity and sodium chloride is used to adjust its concentration. After assay, adjust accordingly.

Manufacturing Directions

1. Add and dissolve 20 g of item 5 in water for injection in a suitable vessel. Cool and keep.
2. Prepare item 6 solution in an exhausted hood or well-ventilated area. Wear gloves.
3. Under laminar flow hood and by aseptic techniques, transfer item 1 into a clean, sterile calibrated glass container. Sample. Keep refrigerated.
4. Check pH (range 6.5–7.2) and adjust with 2% item 5 solution or 2% item 6 solution. Add water for injection to QS volume.
5. Check pH and adjust again as in step 4.
6. Under aseptic conditions, filter by using a peristaltic pump through a 0.2-μm nylon membrane disc into a sterilized glass vessel. Sample.
7. Close the container and store refrigerated until ready for filling (NMT 5 days after the preparation).
8. Target fill to be with 17% excess, 292500 IU/vial, ca. 5.85 mL.
9. Lyophilize at –46°C to –55°C; break vacuum with filtered N_2 gas. Apply stoppers after removing vials aseptically; apply aluminum overseals. Sample.

Valproate Sodium Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
100.00	mg	1	Valproic acid as valproate sodium	115.25	g
0.40	mg	2	Disodium edetate	0.40	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Water for injection, USP	QS to 1.00	L

Note: Fill 5 mL per vial as single dose.

Valrubicin for Intravesical Instillation

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
40.00	mg	1	Valrubicin	40.00	g
0.50	mL	2	Cremaphor® EL (polyoxyethyleneglycol triricinoleate)	0.50	mL
0.50	mL	3	Dehydrated alcohol	QS to 1.00	L

Note: Dilute before administration.

Vancomycin for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	g	1	Vancomycin HCl, USP	1.00[a]	g
QS	mL	2	Sodium hydroxide for pH adjustment	QS	
QS	mL	3	Hydrochloric acid for pH adjustment	QS	
QS	mL	4	Water for injection, USP	QS	
QS		5	Nitrogen gas, NF	QS	

[a] Use 0.5 g for 0.5-g strength.

Manufacturing Directions

1. Preparation of solution.
   a. Collect ca. 172 L (109 L for 0.5 g) of water for injection into a clean stainless steel tank. Cool.
   b. Add and dissolve item 1 with mixing.
   c. Check and record pH (3.0–4.0). Adjust with 10% hydrochloric acid solution or 2% sodium hydroxide solution, if necessary.
   d. QS with water for injection to bring volume to 217 L (137 L for 0.5 g). Mix slowly.
   e. Check and record pH; again adjust as in step 1c.
   f. Filter solution through a previously rinsed filter press and recirculate for approximately 30 minutes.
   g. Filter solution through a 0.2-μm filter into a clean stainless steel tank.
   h. Sample for testing.
   i. Store solution at 2°C to 8°C until ready for filling.
2. Sterile filtration and setup of initial stoppering.
   a. Connect portable tank to sterilized 0.2-mm nylon membrane disc filters. Connect the sterile lead-off hose to the outlet side of the sterile filter and the other end of the lead-off hose into the sterile bottle.
   b. Apply N_2 gas pressure to tank to provide adequate filtration rate.
   c. Transfer the sterile lead-off hose to the sterile surge bottle. Fill surge bottle with sterile-filtered solution.
   d. Sample for testing.
   e. Aseptically fill appropriate volume into each sterilized vial. Place lyophilization stoppers loosely on each vial. Place filled vials into sterilized stainless steel trays with stainless steel rings.
3. Drying/Final stoppering.
   a. Place filled vials into transport rack and transfer to lyophilizer. Start lyophilization cycle. Bring solution to 5°C. Reduce temperature to –40°C and keep at this temperature for 3.5 hours. Start vacuum and raise temperature to –20°C and keep at this temperature for 3 hours. Raise temperature to –15°C and keep at this temperature for 24 hours. Raise temperature to 15°C and keep at this temperature for 6 hours. Raise temperature to 35°C and hold for 6 hours.
   b. Stopper vials after lyophilization.
4. Oversealing and inspection.
   a. Apply aluminum overseals.
   b. Inspect each vial for defects.
   c. Sample for testing.

Varicella Virus Vaccine Live

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1350	PFU[a]	1	Varicella virus	2700,000	PFU
25.00	mg	2	Sucrose	50.00	g
12.50	mg	3	Hydrolyzed gelatin	25.00	g
3.20	mg	4	Sodium chloride	6.40	g
0.50	mg	5	Monosodium L-glutamate	1.00	g
0.45	mg	6	Sodium phosphate dibasic	0.90	g
0.08	mg	7	Potassium phosphate monobasic	0.16	g
0.08	mg	8	Potassium chloride	0.16	g
QS	mL	9	Water for injection, USP	QS to 1.00	L

[a]Plate forming units; may contain traces of EDTA, neomycin, and fetal bovine serum. Fill into 0.5-mL container. Above concentration achieved after reconstitution.

Vasopressin (8-Arginine Vasopressin) Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
20.00	U	1	Vasopressin (8-arginine vasopressin)	20,000	P Units
0.50	%	2	Chlorobutanol	5.00	g
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Glacial acetic acid for pH adjustment	QS	

Manufacturing Directions

1. Place 500 mL of water for injection into a clean compounding tank.
2. Add premeasured quantity of chlorobutanol to the compound tank and mix until a clear solution is obtained.
3. Add item 1 to the tank and mix thoroughly until a clear solution is obtained.
4. Bring the final volume QS with item 3.
5. Check the pH (2.5–4.5); adjust pH with item 4, if necessary.
6. Sample for testing.
7. After laboratory testing, sterile-filter through 0.22-μm filter membrane.
8. Fill into type I flint vials with gray stoppers without coating.

Vecuronium Bromide for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Vecuronium bromide	1.00	g
1.52	mg	2	Citric acid anhydrous	1.52	g
1.625	mg	3	Sodium phosphate dibasic	1.625	g
9.70	mg	4	Mannitol	9.70	g
QS	mL	5	Sodium hydroxide for pH adjustment	QS	
QS	mL	6	Phosphoric acid for pH adjustment	QS	
QS	mL	7	Water for injection, USP	QS to 1.00	L

Note: Fill 10 or 20 mL per vial and lyophilize; adjust to pH 4.0 with item 5 or 6. Use bacteriostatic water for injection for reconstitution (containing 0.9% benzyl alcohol); do not use bacteriostatic water for injection for newborns.

Verapamil Hydrochloride Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.50	mg	1	Verapamil hydrochloride, USP	2.50	g
85.00	mg	2	Sodium chloride, USP	85.00	g
QS	mL	3	Hydrochloric acid for pH adjustment	QS	mL
QS	mL	4	Water for injection, USP	QS to 1.00	L
QS	cy	5	Nitrogen gas, NF	QS	cy

Manufacturing Directions

Note: Fill the product in sterile conditions under N_2 cover.

1. Collect 0.99 L of item 4 in a suitable stainless steel vessel. Purge item 5 throughout processing.
2. Add and dissolve items 1 and 2. Make up volume with item 4.
3. Check pH (4.5–5.0). Adjust with item 3, if necessary (approximate volume to be used, 0–6 mL).
4. Prepare pressurized vessel with N_2 for sterile filling. Sterilize filling unit, jars, and so on at 121°C for 1 hour. Sterilize type I glass ampoule at 210°C to 220°C for 2 hours.
5. Filter solution through a 0.22-μm membrane filter. Perform bubble point test before and after filtration.
6. Fill 2.15 mL into ampoules through inline sintered glass. Flush headspace with N_2.
7. Sterilize in autoclave at 121°C for 20 minutes.
8. Sample for leak test. Perform other testing.

Vinblastine Sulfate for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
2.00	mg	1	Vinblastine sulfate, USP[a]	2.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

[a] Weight given is on anhydrous basis. Obtain water content from raw material specification and apply correction as follows: Mass required (g) = (10.60 × 100)/(100 – % water).

Manufacturing Directions

Caution: Vinblastine sulfate is a potent cytotoxic agent—handle with care.

1. Place approximately 900 mL of water for injection into a suitable stainless steel container.
2. Add item 1 to the tank stir until completely dissolved.
3. Check pH (3.5–5.0).
4. QS to volume with item 2.
5. Sample for testing.
6. After laboratory approval, filter through a 0.22-μm filter into a clean receiving vessel and proceed to fill into type I flint vials with 841 gray stoppers without coating.
7. Lyophilize the filled vials.
8. Transfer the filled vials in covered trays onto the shelves of lyophilizer.
9. Place thermocouples in representative vials.
10. Set the temperature controller to –40°C.
11. The thermocouples should register –40°C or less for at least 4 hours before starting the drying cycle.
12. Start condenser and let it cool to –50°C or less before pulling the vacuum.
13. Let the chamber achieve a level of 150 μm or less.
14. Set the temperature controller to +15°C and let it run for at least 18 hours.
15. Raise the shelf temperature to +25°C and run for approximately 10 hours till all the probes register +25°C (± 2°C) and hold for an additional 8 hours.
16. Bleed the chamber slowly with sterile dry N_2 gas.
17. Stopper vials using internal stoppering mechanism (or with depyrogenated cover in the laminar hood after withdrawing from the lyophilizer).
18. After withdrawal of the vials, clean and deice the lyophilizer.

Vincristine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Vincristine sulfate, USP[a]	1.20	g
100.00	mg	2	Mannitol, USP	120.00	g
1.30	mg	3	Methyl paraben, NF	1.56	g
0.20	mg	4	Propyl paraben, NF	0.24	g
QS	mL	5	Water for injection, USP	QS to 1.00	L
QS	mL	6	Acetic acid 5% for pH adjustment	QS	
QS	mL	7	Sodium acetate 5% for pH adjustment	QS	

[a] Weight given is on anhydrous basis. Obtain water content from raw material specification and apply correction as follows:
Mass required (g) = (1.20 × 100)/(100 – % water)

Manufacturing Directions

Caution: Vincristine sulfate is a potent cytotoxic agent—handle with care. It is also light sensitive. All solutions should be protected from light as much as possible.

1. Place approximately 800 mL item 5 into a suitable mixing tank. Heat the water to approximately 65°C.
2. Add propyl paraben to the tank and stir vigorously. With constant stirring, maintain temperature till completely dissolved.
3. Add methyl paraben to the tank. Continue stirring until completely dissolved. Maintain temperature.
4. Allow the solution to cool to less than 50°C and then add item 2 with constant stirring until dissolved.
5. Allow the solution to cool down to room temperature (25°C) and then add item 1 and stir.
6. Check pH (4.0–5.0); adjust with either item 6 or 7.
7. Check final pH.
8. QS with item 5.
9. Sample for testing.
10. After laboratory approval, filter through a 0.22-μm filter and fill into type I amber vials with gray Teflon-coated stoppers.

Vincristine Sulfate Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
1.00	mg	1	Vincristine sulfate	1.00	g
1.30	mg	2	Methyl paraben	1.30	g
0.20	mg	3	Propyl paraben	0.20	g
0.375	mg	4	Zinc sulfate heptahydrate	0.375	g
1.90	mg	5	Calcium gluconate monohydrate	1.90	g
50.00	mg	6	Ethanol USP, 95%	50.00	g
QS	mL	7	Water for injection, USP	QS to 1.00	L

Manufacturing Directions

1. Take 0.4 L of item 7 into a suitable stainless steel vessel and dissolve item 1 with agitation.
2. Dissolve item 2 separately in 50 mL of item 7 and added to step 1.
3. Dissolve item 5 separately in 0.3 L of item 7 and add to step 2.
4. Dissolve items 2 and 3 separately in item 6 and add to step 2.
5. Make up volume with item 7.
6. Filter using a 0.22-μm membrane filter and fill aseptically into type I glass ampoules.

Water for Injection

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
10.00	mL	1	Water for injection, USP	1.00	L

Manufacturing Directions

Precaution: Store all bulk water in a tightly closed container. Avoid absorption of CO_2 and other gases.

1. Preparation of water.
   a. Check the water for injection used for injection preparation and verify that it meets conductivity limit of NMT 1 μS/s and pH range of 5.0 to 7.0.
   b. Test the rinsings from the container that are used during solution preparation for conductivity (limit NMT 1.0 μS).
2. Preparation of water.
   a. Add water for injection to the final volume in the preparation tank and transfer to sterile mobile tank.
   b. Transfer the mobile tank from solution preparation area to solution room.
3. Preparation of ampoules. Use type I 10-mL clear glass ampoules, USP.
   a. Wash the ampoules according to operating procedures.
   b. Sterilize the ampoules by using a dry-heat tunnel.
   c. Set the temperature as per latest validation studies with revised cycle.
4. Sterilization. Sterilize the filtration assembly and ampoule-filling machine parts at 122°C for 30 minutes. Set parameters according to the current validated cycle.
5. Sterile filling.
   a. Aseptically connect the N_2 line through the sterile N_2 filter to the inlet of the mobile holding tank as per SOPs.
   b. Aseptically connect one end of the previously sterilized filtration assembly with a 0.22-μm pore-size filtration cartridge to the outlet of the mobile holding tank and the other end to the holding tank.
   c. Before starting the sterile filtration, check the integrity of filter cartridge according to SOPs.
   d. Operate the ampoule-filling machine according to SOPs. Bleed the dosing system as described in the operating procedures. Adjust the fill volume to 10.5 mL.
   e. Sterile-fill 10.5 mL sterile water for injection from the bulk into each sterile, dry clean ampoule and seal it.
6. Terminal sterilization. Sterilize the filled ampoules in a Finn Aqua autoclave at the current validated cycle. Set temperature at 121°C for 20 minutes.
7. Ampoule leak test. Perform the leak test according to SOPs and transfer to optical checking.
8. Optical checking. Inspect the ampoules under the optical checking machine and record and transfer to packaging.

Water for Injection, Bacteriostatic

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
15.00	mg	1	Benzyl alcohol, NF	15.00	g
QS	mL	2	Water for injection, USP	QS to 1.00	L

Zinc Sulfate Additive Injection (5-mL Vial)

Bill of Materials					
Scale/mL		Item	Material	Qty	UOM
21.95	mg	1	Zinc sulfate heptahydrate	21.95	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Zinc Sulfate Additive Injection (10-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.39	mg	1	Zinc sulfate heptahydrate	4.39	g
QS	mL	2	Water for injection, USP	QS to 1.00	L
QS	mL	3	Sodium hydroxide for pH adjustment	QS	
QS	mL	4	Sulfuric acid for pH adjustment	QS	

Zinc Sulfate Additive Injection (30-mL Vial)

Bill of Materials (Batch Size 1 L)					
Scale/mL		Item	Material	Qty	UOM
4.39	mg	1	Zinc sulfate heptahydrate	4.39	g
0.90	%	2	Benzyl alcohol, NF	0.90	%
QS	mL	3	Water for injection, USP	QS to 1.00	L
QS	mL	4	Sodium hydroxide for pH adjustment	QS	
QS	mL	5	Sulfuric acid for pH adjustment	QS	

Manufacturing Directions

1. Add approximately 850 mL of water for injection to a clean mixing tank.
2. Add accurately weighed zinc sulfate and mix until dissolved.
3. Check pH (2.0–4.0); adjust with 10% sulfuric acid (pH 4.0–7.0 used at different strengths).
4. QS to volume with water for injection.
5. Filter through a 0.22-μm filter into a clean receiving container.
6. Fill in type I glass vials with West gray stoppers and flip-off aluminum seals.

Zoledronic Acid for Injection

Bill of Materials (Batch Size 100 Vials)					
Scale/mL		Item	Material	Qty	UOM
4.00	mg	1	Zoledronic acid as zoledronic acid monohydrate	4.264	g
220.00	mg	2	Mannitol	220.00	g
24.00	mg	3	Sodium citrate	24.00	g

Note: Sterile powder for reconstitution for infusion.

COMMERCIAL PHARMACEUTICAL FORMULATIONS

- Abciximab, ReoPro®, is the Fab fragment of the chimeric human-murine monoclonal antibody 7E3. ReoPro is a clear, colorless, sterile, nonpyrogenic solution for IV use. Each single use vial contains 2 mg/mL of abciximab in a buffered solution (pH 7.2) of 0.01 M sodium phosphate, 0.15 M sodium chloride, and 0.001% polysorbate 80 in water for injection. No preservatives are added.
- AccuNeb® (albuterol sulfate) inhalation solution is a sterile, clear, colorless solution of the sulfate salt of racemic albuterol, albuterol sulfate. AccuNeb (albuterol sulfate) inhalation solution is supplied in two strengths in unit dose vials. Each unit dose vial contains either 0.75 mg of albuterol sulfate (equivalent to 0.63 mg of albuterol) or 1.50 mg of albuterol sulfate (equivalent to 1.25 mg of albuterol) with sodium chloride and sulfuric acid in a 3-mL isotonic, sterile aqueous solution. Sodium chloride is added to adjust isotonicity of the solution and sulfuric acid is added to adjust pH of the solution to 3.5.
- Actimmune® (interferon gamma-1b) is a highly purified sterile solution consisting of noncovalent dimers of two identical 16, 465 d monomers; with a specific activity of 20 million IU/mg (2×10^6 IU/0.5 mL) which is equivalent to 30 million U/mg. Actimmune is a sterile, clear colorless solution filled in a single-dose vial for subcutaneous (SC) injection. Each 0.5 mL of Actimmune contains 100 μg (2 million IU) of interferon gamma-1b formulated in 20 mg mannitol, 0.36 mg sodium succinate, 0.05 mg polysorbate 20, and sterile water for injection. Note that the above activity is expressed in international units (1 million IU/50 μg). This is equivalent to what was previously expressed as units (1.5 million U/50 μg).
- Activase (Alteplase) is a tissue plasminogen activator produced by recombinant DNA technology. It is a sterile, purified glycoprotein of 527 amino acids. Phosphoric acid and/or sodium hydroxide may be used prior to lyophilization for pH adjustment. Activase is a sterile, white to off-white, lyophilized powder for IV administration after reconstitution with sterile water for injection, USP. Quantitative composition of the lyophilized product—100-mg vial, 50-mg vial: alteplase, 100 mg (58 million IU), 50 mg (29 million IU); L-arginine, 3.5 g, 1.7 g; phosphoric acid, 1 g, 0.5 g; polysorbate 80, ≤ 11 mg, ≤ 4 mg; vacuum, no, yes.
- Adenocard® (adenosine injection) is a sterile, nonpyrogenic solution for rapid bolus IV injection. Each milliliter contains 3 mg adenosine and 9 mg sodium chloride in water for injection. The pH of the solution is between 4.5 and 7.5. The Ansyr® plastic syringe is molded from a specially formulated polypropylene. Water permeates from inside the container at an extremely slow rate, which will have an insignificant effect on solution concentration over the expected shelf life. Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the syringe material.
- Adenoscan (adenosine) vial contains a sterile, nonpyrogenic solution of adenosine 3 mg/mL and sodium chloride 9 mg/mL in water for injection, QS. The pH of the solution is between 4.5 and 7.5.
- Adriamycin (doxorubicin) is supplied in the hydrochloride form as a sterile red-orange lyophilized powder containing lactose and as a sterile, parenteral isotonic solution with sodium chloride for IV use only. Adriamycin (doxorubicin HCI) for injection, USP: each 10-mg lyophilized vial contains 10 mg of doxorubicin hydrochloride, USP, and 50 mg of lactose monohydrate, NF. Each 20-mg lyophilized vial contains 20 mg of doxorubicin hydrochloride, USP, and 100 mg of lactose monohydrate, NF. Each 50-mg lyophilized vial contains 50 mg of doxorubicin hydrochloride, USP, and 250 mg of lactose monohydrate, NF. Adriamycin (doxorubicin HCI) injection, USP: each 2 mg/mL, 5-mL (10-mg) vial contains 10 mg doxorubicin hydrochloride, USP; sodium chloride, 0.9% (to adjust tonicity) and water for injection, QS; pH adjusted to 3 using hydrochloric acid. Each 2 mg/mL, 10-mL (20-mg) vial contains 20 mg doxorubicin hydrochloride, USP; sodium chloride 0.9% (to adjust tonicity) and water for injection, QS; pH adjusted to 3 using hydrochloric acid. Each 2 mg/mL, 25-mL (50-mg) vial contains 50 mg doxorubicin hydrochloride, USP; sodium chloride 0.9% (to adjust tonicity) and water for injection, QS; pH adjusted to 3 using hydrochloric acid. Each 2 mg/mL, 100-mL (200-mg) multiple dose vial contains 200 mg doxorubicin hydrochloride, USP; sodium chloride 0.9% (to adjust tonicity) and water for injection QS; pH adjusted to 3 using hydrochloric acid.
- Aggrastat (tirofiban hydrochloride) injection premixed is supplied as a sterile solution in water for injection, for IV use only, in plastic containers of 100 or 250 mL. Each 100 mL of the premixed, isosmotic IV injection contains 5.618 mg tirofiban hydrochloride monohydrate equivalent to 5 mg tirofiban (50 μg/mL) and the following inactive ingredients: 0.9 mg sodium chloride, 54 mg sodium citrate dihydrate, and 3.2 mg citric acid anhydrous. Each 250 mL of the premixed, isosmotic IV injection contains 14.045 mg tirofiban hydrochloride monohydrate equivalent to 12.5 mg tirofiban (50 μg/mL) and the following inactive ingredients: 2.25 g sodium chloride, 135 mg sodium citrate dihydrate, and 8 mg citric acid anhydrous. Aggrastat injection is a sterile concentrated solution for IV infusion after dilution and is supplied in a 25- or a 50-mL vial. Each milliliter of the solution contains 0.281 mg of tirofiban hydrochloride monohydrate equivalent to 0.25 mg of tirofiban and the following inactive ingredients: 0.16 mg citric acid anhydrous, 2.7 mg sodium citrate dihydrate, 8 mg sodium chloride, and water for injection. The pH ranges from 5.5 to 6.5 and may have been adjusted with hydrochloric acid and/or sodium hydroxide.

- Alamast® (pemirolast potassium ophthalmic solution) is a sterile, aqueous ophthalmic solution with a pH of approximately 8 containing 0.1% of the mast cell stabilizer, pemirolast potassium, for topical administration to the eyes. Each milliliter contains the following: active ingredients: pemirolast potassium, 1 mg (0.1%); preservative—lauralkonium chloride, 0.005%. Inactives—glycerin, dibasic sodium phosphate, monobasic sodium phosphate, phosphoric acid and/or sodium hydroxide to adjust pH, and purified water. The osmolality of Alamast ophthalmic solution is approximately 240 mOsm/kg.
- Albumin (human) 25%, USP, (Plasbumin®-25) is a 25% sterile solution of albumin in an aqueous diluent. The preparation is stabilized with 0.02 M sodium caprylate and 0.02 M acetyltryptophan. The aluminum content of the product is NMT 200 μg/L. The approximate sodium content of the product is 145 mEq/L. It contains no preservative. Plasbumin-25 must be administered intravenously. Each vial of Plasbumin-25 is heat-treated at 60°C for 10 hours against the possibility of transmitting hepatitis viruses. Plasbumin-20 is a 20% sterile solution of albumin in an aqueous diluent. The preparation is stabilized with 0.016 M sodium caprylate and 0.016 M acetyltryptophan. The aluminum content of the product is NMT 200 μg/L. The approximate sodium content of the product is 145 mEq/L. It contains no preservative. Plasbumin-5 is a 5% sterile solution of albumin in an aqueous diluent. The preparation is stabilized with 0.004 M sodium caprylate and 0.004 M acetyltryptophan. The aluminum content of the product is NMT 200 μg/L. The approximate sodium content of the product is 145 mEq/L. It contains no preservative.
- Aldurazyme® (laronidase) is supplied as a sterile, nonpyrogenic, colorless to pale yellow, clear to slightly opalescent solution that must be diluted prior to administration in 0.9% sodium chloride injection, USP, containing 0.1% albumin (human). The solution in each vial contains a nominal laronidase concentration of 0.58 mg/mL and a pH of approximately 5.5. The extractable volume of 5.0 mL from each vial provides 2.9 mg laronidase, 43.9 mg sodium chloride, 63.5 mg sodium phosphate monobasic monohydrate, 10.7 mg sodium phosphate dibasic heptahydrate, and 0.05 mg polysorbate 80. Aldurazyme does not contain preservatives. Vials are for single use only.
- Alferon N Injection® [interferon alpha-n3 (human leukocyte derived)] is a sterile aqueous formulation of purified, natural, human interferon-alpha proteins for use by injection. Each milliliter contains 5 million IU of interferon alpha-n3 in phosphate-buffered saline (8.0 mg sodium chloride, 1.74 mg sodium phosphate dibasic, 0.20 mg potassium phosphate monobasic, and 0.20 mg potassium chloride) containing 3.3 mg phenol as a preservative and 1 mg albumin (human) as a stabilizer.
- Alimta® pemetrexed for injection is supplied as a sterile lyophilized powder for IV infusion available in single-dose vials. The product is a white to either light yellow or green-yellow lyophilized solid. Each 500-mg vial of Alimta contains pemetrexed disodium equivalent to 500 mg pemetrexed and 500 mg of mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust pH.
- Alkeran (melphalan) single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan and 20 mg povidone. Alkeran for injection is reconstituted using the sterile diluent provided. Each vial of sterile diluent contains sodium citrate 0.2 g, propylene glycol 6.0 mL, ethanol (96%) 0.52 mL, and water for injection to a total of 10 mL. Alkeran for injection is administered intravenously.
- Aloprim (allopurinol sodium) for injection is a sterile solution for IV infusion only. It is available in vials as the sterile lyophilized sodium salt of allopurinol equivalent to 500 mg of allopurinol. Aloprim (allopurinol sodium) for injection contains no preservatives.
- Aloxi 1 (palonosetron hydrochloride) injection is a sterile, clear, colorless, nonpyrogenic, isotonic, buffered solution for IV administration. Each 5-mL vial of Aloxi injection contains 0.25 mg palonosetron base as hydrochloride, 207.5 mg mannitol, disodium edetate, and citrate buffer in water for IV administration. The pH of the solution is 4.5 to 5.5.
- Aralast™, alpha-1 proteinase inhibitor (human), is a sterile, stable lyophilized preparation of purified human alpha-1 proteinase inhibitor [(alpha) 1-PI], also known as alpha-1—antitrypsin. Each vial of Aralast is labeled with the amount of functionally active (alpha) 1-PI expressed in milligram per vial. The formulation contains no preservative. The pH of the solution ranges from 7.2 to 7.8. Product must only be administered intravenously.
- AmBisome for injection is a sterile, nonpyrogenic lyophilized product for IV infusion. Each vial contains 50 mg of amphotericin B, USP, intercalated into a liposomal membrane consisting of approximately 213 mg hydrogenated soy phosphatidylcholine; 52 mg cholesterol, NF; 84 mg distearoylphosphatidylglycerol; 0.64 mg alpha-tocopherol, USP; together with 900 mg sucrose, NF; and 27 mg disodium succinate hexahydrate as buffer. Following reconstitution with sterile water for injection, USP, the resulting pH of the suspension is between 5 and 6. AmBisome is a true single bilayer liposomal drug delivery system.
- Amevive® (alefacept) is supplied as a sterile, white to off-white, preservative-free, lyophilized powder for parenteral administration. After reconstitution with 0.6 mL of the supplied sterile water for injection, USP, the solution of Amevive is clear, with a pH of approximately 6.9. Amevive is available in two formulations. Amevive for IM injection contains 15 mg alefacept per 0.5 mL of reconstituted solution. Amevive for IV injection contains 7.5 mg alefacept per 0.5 mL of reconstituted solution. Both formulations also contain 12.5 mg sucrose, 5.0 mg glycine, 3.6 mg sodium citrate dihydrate, and 0.06 mg citric acid monohydrate per 0.5 mL.
- Aminohippurate sodium is provided as a sterile, nonpreserved 20% aqueous solution for injection, with a pH of 6.7 to 7.6. Each 10 mL contains aminohippurate sodium, 2 g. Inactive ingredients: sodium hydroxide to adjust pH, water for injection, QS.
- Ammonul® (sodium phenylacetate and sodium benzoate) injection 10%/10% is a sterile, concentrated aqueous solution of sodium phenylacetate and sodium benzoate. The pH of the solution is between 6 and 8. Each milliliter of Ammonul contains 100 mg of sodium phenylacetate and 100 mg of sodium benzoate and water for injection. Sodium hydroxide and/or hydrochloric acid may have been used for pH adjustment.
- Antihemophilic Factor (human), Koate®-DVI, is a sterile, stable, purified, dried concentrate of human antihemophilic factor (AHF, factor VIII, AHG) which has been treated with tri-*n*-butyl phosphate (TNBP) and polysorbate 80 and heated in lyophilized form in the final container at 80°C for 72 hours. Koate-DVI is intended for use in therapy of classical hemophilia (hemophilia A).

- Antivenin (*Latrodectus mactans*) is a sterile, nonpyrogenic preparation derived by drying a frozen solution of specific venom-neutralizing globulins obtained from the blood serum of healthy horses immunized against venom of black widow spiders (*L. mactans*). Each vial contains not less than 6000 antivenin units. One unit of antivenin will neutralize one average mouse lethal dose of black widow spider venom when the antivenin and the venom are injected simultaneously in mice under suitable conditions.
- Antivenin (*Micrurus fulvius*) is a refined, concentrated, and lyophilized preparation of serum globulins obtained by fractionating blood from healthy horses that have been immunized with eastern coral snake (*M. fulvius fulvius*) venom. Prior to lyophilization, the product contains 0.25% phenol and 0.005% thimerosal (mercury derivative).
- Apokyn™ (apomorphine hydrochloride, USP) 10 mg/mL is a clear, colorless sterile solution for SC injection and is available in 2-mL ampoules and 3-mL cartridges. Each milliliter of solution contains 10 mg of apomorphine hydrochloride, USP, as apomorphine hydrochloride hemihydrate and 1 mg of sodium metabisulfite, NF, in water for injection, USP. In addition, each milliliter of solution may contain sodium hydroxide, NF, and/or hydrochloric acid, NF, to adjust the pH of the solution. In addition, the cartridges contain 5 mg/mL of benzyl alcohol.
- Aquacel® Ag with Hydrofiber® (Aquacel Ag) silver impregnated antimicrobial dressing is a soft, sterile nonwoven pad or ribbon dressing composed of sodium carboxymethylcellulose and 1.2% ionic silver which allows for a maximum of 12 mg of silver for 4 in × 4 in dressing.
- AquaMEPHYTON phytonadione is a vitamin which is a clear, yellow to amber, viscous, odorless or nearly odorless liquid. AquaMEPHYTON injection is a yellow, sterile, aqueous colloidal solution of vitamin K1, with a pH of 5.0 to 7.0, available for injection by IV, IM, and SC routes. Each milliliter contains phytonadione, 2 or 10 mg. Inactive ingredients: polyoxyethylated fatty acid derivative, 70 mg; dextrose, 37.5 mg; water for injection, QS, 1 mL; added as preservative—benzyl alcohol, 0.9%.
- Aramine, metaraminol bitartrate, contains metaraminol bitartrate equivalent to metaraminol 10 mg. Inactive ingredients: sodium chloride, 4.4 mg; water for injection, QS, add 1 mL; methyl paraben, 0.15%; propyl paraben, 0.02%; and sodium bisulfite, 0.2%, added as preservatives.
- Aranesp® is formulated as a sterile, colorless, preservative-free protein solution for IV or SC administration. Single-dose vials are available containing 25, 40, 60, 100, 150, 200, 300, or 500 μg of Aranesp. Single-dose prefilled syringes are available containing 25, 40, 60, 100, 150, 200, 300, or 500 μg of Aranesp. Single-dose vials and prefilled syringes are available in two formulations that contain excipients as follows: polysorbate solution, each milliliter contains 0.05 mg polysorbate 80, and is formulated at pH 6.2±0.2 with 2.12 mg sodium phosphate monobasic monohydrate, 0.66 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in water for injection, USP (to 1 mL); albumin solution, each milliliter contains 2.5 mg albumin (human) and is formulated at pH 6.0±0.3 with 2.23 mg sodium phosphate monobasic monohydrate, 0.53 mg sodium phosphate dibasic anhydrous, and 8.18 mg sodium chloride in water for injection, USP (to 1 mL).
- Attenuvax (measles virus vaccine live) is a live virus vaccine for vaccination against measles (rubeola). The reconstituted vaccine is for SC administration. Each 0.5-mL dose contains not less than 1000 tissue culture infectious doses (TCID) of measles virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), human albumin (0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients, and approximately 25 μg of neomycin. The product contains no preservative. Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. Attenuvax, when reconstituted as directed, is clear yellow.
- Avastin™ (Bevacizumab) is a recombinant humanized monoclonal IgG1 antibody. Avastin is a clear to slightly opalescent, colorless to pale brown, sterile, pH 6.2 solution for IV infusion. Avastin is supplied in 100- and 400-mg preservative-free, single-use vials to deliver 4 or 16 mL of Avastin (25 mg/mL). The 100-mg product is formulated in 240 mg (alpha), (alpha)-trehalose dihydrate, 23.2 mg sodium phosphate (monobasic, monohydrate), 4.8 mg sodium phosphate (dibasic, anhydrous), 1.6 mg polysorbate 20, and water for injection, USP. The 400 mg product is formulated in 960 mg (alpha), (alpha)-trehalose dihydrate, 92.8 mg sodium phosphate (monobasic, monohydrate), 19.2 mg sodium phosphate (dibasic, anhydrous), 6.4 mg polysorbate 20, and water for injection, USP.
- Avonex® (interferon beta-1a) is formulated as a sterile, white to off-white lyophilized powder for IM injection after reconstitution with supplied diluent (sterile water for injection, USP). Each vial of reconstituted Avonex contains 30 μg of interferon beta-1a; 15 mg albumin (human), USP; 5.8 mg sodium chloride, USP; 5.7 mg dibasic sodium phosphate, USP; and 1.2 mg monobasic sodium phosphate, USP, in 1 mL at a pH of approximately 7.3. A prefilled syringe of Avonex is formulated as a sterile liquid for IM injection. Each 0.5-mL (30-μg) dose of Avonex in a prefilled glass syringe contains 30 μg of interferon beta-1a; 0.79 mg sodium acetate trihydrate, USP; 0.25 mg glacial acetic acid, USP; 15.8 mg arginine hydrochloride, USP; and 0.025 mg polysorbate 20 in water for injection, USP, at a pH of approximately 4.8.
- Azopt® (brinzolamide ophthalmic suspension), 1%, is supplied as a sterile, aqueous suspension of brinzolamide which has been formulated to be readily suspended and slow settling, following shaking. It has a pH of approximately 7.5 and an osmolality of 300 mOsm/kg. Each milliliter of Azopt (brinzolamide ophthalmic suspension), 1%, contains 10 mg brinzolamide. Inactive ingredients are mannitol, carbomer 974P, tyloxapol, edetate disodium, sodium chloride, hydrochloric acid and/or sodium hydroxide (to adjust pH), and purified water. Benzalkonium chloride, 0.01%, is added as a preservative.
- BeneFIX®, coagulation factor IX (recombinant), is available in single-use vials containing the labeled amount of factor IX activity, expressed in international units. Each vial contains nominally 250, 500 or 1000 IU of coagulation factor IX (recombinant). After reconstitution of the lyophilized drug product, the concentrations of excipients in the 500- and 1000-IU dosage strengths are 10 mM L-histidine, 1% sucrose, 260 mM glycine, 0.005% polysorbate 80. The concentrations after reconstitution in the 250-IU dosage strength are half those of the other two dosage strengths. The 500- and 1000-IU dosage strengths are isotonic after reconstitution and the 250 IU dosage strength has half the tonicity of the other two dosage strengths after reconstitution.

All dosage strengths yield a clear, colorless solution upon reconstitution.

- Betadine®, povidone-iodine is a broad-spectrum microbicide. Betadine, 5%, sterile ophthalmic prep solution contains 5% povidone-iodine (0.5% available iodine) as a sterile dark brown solution stabilized by glycerin. Inactive ingredients: citric acid, glycerin, nonoxynol-9, sodium chloride, sodium hydroxide, and dibasic sodium phosphate.
- Betaseron® (interferon beta-lb) vial contains 0.3 mg of interferon beta-lb. Mannitol, USP, and albumin (human), USP (15 mg/vial), are added as stabilizers. Lyophilized Betaseron is a sterile, white to off-white powder for SC injection after reconstitution with the diluent supplied (sodium chloride, 0.54% solution).
- Betimol® (timolol ophthalmic solution), 0.25% and 0.5%, is a clear, colorless, isotonic, sterile microbiologically preserved phosphate buffered aqueous solution. It is supplied in two dosage strengths, 0.25% and 0.5%. Each milliliter of Betimol, 0.25%, contains 2.56 mg of timolol hemihydrate equivalent to 2.5 mg timolol. Each milliliter of Betimol, 0.5%, contains 5.12 mg of timolol hemihydrate equivalent to 5.0 mg timolol. Inactive ingredients: monosodium and disodium phosphate dihydrate to adjust pH (6.5–7.5) and water for injection, benzalkonium chloride, 0.01%, added as preservative. The osmolality of Betimol is 260 to 320 mOsm/kg.
- Betoptic S® ophthalmic suspension, 0.25%, contains the following in each milliliter: active—betaxolol HCl, 2.8 mg, equivalent to 2.5 mg of betaxolol base; preservative—benzalkonium chloride 0.01%; inactive—mannitol, poly(styrene-divinyl benzene) sulfonic acid, carbomer 934P, edetate disodium, hydrochloric acid or sodium hydroxide (to adjust pH), and purified water.
- Boostrix® (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine, adsorbed) (Tdap) is a noninfectious, sterile vaccine adsorbed onto aluminum hydroxide. Both toxins are detoxified with formaldehyde; concentrated by ultrafiltration; and purified by precipitation, dialysis, and sterile filtration. Each antigen is individually adsorbed onto aluminum hydroxide. All antigens are then diluted and combined to produce the final formulated vaccine. Each 0.5-mL dose is formulated to contain 2.5 Lf of diphtheria toxoid, 5 Lf of tetanus toxoid, 2.5 μg of pertactin, 8 μg of FHA, and 8 μg of inactivated PT. Each 0.5-mL dose also contains 4.5 mg of NaCl, aluminum adjuvant (NMT 0.39 mg aluminum by assay), ≤100 μg of residual formaldehyde, and ≤100 μg of polysorbate 80 (Tween 80). This vaccine does not contain a preservative.
- Buminate, 25%, albumin (human), 25% solution is a sterile, nonpyrogenic preparation of albumin in a single-dosage form for IV administration. Each 100 mL contains 25 g of albumin and is prepared from human venous plasma using the Cohn cold ethanol fractionation process. It has been adjusted to physiological pH with sodium bicarbonate and/or sodium hydroxide and stabilized with sodium acetyltryptophanate and sodium caprylate. The sodium content is 145±15 mEq/L. This solution contains no preservative and none of the coagulation factors found in fresh whole blood or plasma. Buminate 25%, albumin (human), 25% solution is a transparent or slightly opalescent solution which may have a greenish tint or may vary from a pale straw to an amber color. Buminate 5%, albumin (human), 5% solution, is a sterile, nonpyrogenic preparation of albumin in a single-dosage form for IV administration. Buminate 5%, albumin (human), 5% solution, contains no blood group isoagglutinins thereby permitting its administration without regard to the recipient's blood group. Each 100 mL contains 5 g of albumin and was prepared from human venous plasma using the Cohn cold ethanol fractionation process. Source material for fractionation may be obtained from another U.S. licensed manufacturer. It has been adjusted to physiological pH with sodium bicarbonate and/or sodium hydroxide and has been stabilized with sodium acetyltryptophanate and sodium caprylate. The sodium content is 145±15 mEq/L. The solution contains no preservative and none of the coagulation factors found in fresh whole blood or plasma. Buminate 5%, albumin (human), 5% solution, is a transparent or slightly opalescent solution which may have a greenish tint or may vary from a pale straw to an amber color.
- Byetta™ (exenatide) injection is supplied for SC injection as a sterile, preserved isotonic solution in a glass cartridge that has been assembled in a pen injector (pen). Each milliliter contains 250 μg synthetic exenatide, 2.2 mg metacresol as an antimicrobial preservative, mannitol as a tonicity-adjusting agent, and glacial acetic acid and sodium acetate trihydrate in water for injection as a buffering solution at pH 4.5. Two prefilled pens are available to deliver unit doses of 5 or 10 μg. Each prefilled pen will deliver 60 doses to provide 30 days of twice daily administration (BID).
- Calcijex® (calcitriol injection). Each milliliter contains calcitriol, 1 μg; polysorbate 20, 4 mg; sodium ascorbate, 2.5 mg added. May contain hydrochloric acid and/or sodium hydroxide for pH adjustment; pH is 6.5 (5.9–7.0). Contains no more than 1 μg/mL of aluminum.
- Calcium disodium versenate (edetate calcium disodium injection, USP) is a sterile, injectable chelating agent in concentrated solution for IV infusion or IM injection. Each 5-mL ampoule contains 1000 mg of edetate calcium disodium (equivalent to 200 mg/mL) in water for injection.
- Campath® (Alemtuzumab) single-use vial of Campath contains 30 mg alemtuzumab, 8.0 mg sodium chloride, 1.44 mg dibasic sodium phosphate, 0.2 mg potassium chloride, 0.2 mg monobasic potassium phosphate, 0.1 mg polysorbate 80, and.0187 mg disodium edetate dihydrate. No preservatives are added.
- Cancidas is a sterile, lyophilized product for IV infusion that contains a semisynthetic lipopeptide (echinocandin) compound synthesized from a fermentation product of *Glarea lozoyensis*. Cancidas, 50 mg, also contains 39 mg sucrose, 26 mg mannitol, glacial acetic acid, and sodium hydroxide. Cancidas, 70 mg, also contains 54 mg sucrose, 36 mg mannitol, glacial acetic acid, and sodium hydroxide.
- Carnitor® (levocarnitine) injection is a sterile aqueous solution containing 1 g of levocarnitine per 5 mL vial. The pH is adjusted to 6.0 to 6.5 with hydrochloric acid or sodium hydroxide.
- Cathflo® Activase® (alteplase) is a tissue plasminogen activator (t-PA) produced by recombinant DNA technology. It is a sterile, purified glycoprotein of 527 amino acids. Cathflo Activase is a sterile, white to pale yellow, lyophilized powder for intracatheter instillation for restoration of function to central venous access devices following reconstitution with sterile water for injection, USP. Each vial of Cathflo Activase contains 2.2 mg of alteplase (which includes a 10% overfill), 77 mg of L-arginine, 0.2 mg of polysorbate 80, and phosphoric acid for pH adjustment. Each reconstituted vial will deliver 2 mg of Cathflo Activase, at a pH of approximately 7.3.

- Cefoxitin sodium contains approximately 53.8 mg (2.3 mEq) of sodium per gram of cefoxitin activity. Premixed IV solution Mefoxin (cefoxitin sodium injection) is supplied as a sterile, nonpyrogenic, frozen isosmotic solution of cefoxitin sodium. Each 50 mL contains cefoxitin sodium equivalent to either 1 or 2 g of cefoxitin. Dextrose hydrous USP has been added to the above dosages to adjust osmolality (approximately 2 g and 1.1- to 1- and 2-g dosages, respectively). The pH is adjusted with sodium bicarbonate and may have been adjusted with hydrochloric acid. The pH is approximately 6.5. After thawing, the solution is intended for IV use only. Solutions of Mefoxin range from colorless to light amber.
- Cerubidine (daunorubicin hydrochloride) is the hydrochloride salt of an anthracycline cytotoxic antibiotic produced by a strain of *Streptomyces coeruleorubidus*. It is provided as a sterile, reddish lyophilized powder in vials for IV administration only. Each vial contains 21.4 mg daunorubicin hydrochloride (equivalent to 20 mg of daunorubicin) and 100 mg mannitol. It is soluble in water when adequately agitated and produces a reddish solution.
- Ciloxan® (ciprofloxacin hydrochloride ophthalmic ointment) contains the following: active—ciprofloxacin HCl, 3.33 mg, equivalent to 3-mg base; inactives—mineral oil, white petrolatum.
- Cipro IV ciprofloxacin solution is available as a sterile 1.0% aqueous concentrate, which is intended for dilution prior to administration. Ciprofloxacin solution contains lactic acid as a solubilizing agent and hydrochloric acid for pH adjustment. The pH range for the 1.0% aqueous concentrate is 3.3 to 3.9.
- Ciprodex® (ciprofloxacin, 0.3%, and dexamethasone, 0.1%) sterile otic contains ciprofloxacin hydrochloride (equivalent to 3 mg ciprofloxacin base), 1 mg dexamethasone, and 0.1 mg benzalkonium chloride as a preservative. The inactive ingredients are boric acid, sodium chloride, hydroxyethyl cellulose, tyloxapol, acetic acid, sodium acetate, edetate disodium, and purified water. Sodium hydroxide or hydrochloric acid may be added for adjustment of pH.
- Cogentin (benztropine mesylate) is supplied as a sterile injection for IV and IM use. Benztropine mesylate is a synthetic compound containing structural features found in atropine and diphenhydramine. Each milliliter of the injection contains benztropine mesylate, 1 mg; sodium chloride, 9 mg; water for injection, QS, 1 mL.
- Comvax [Haemophilus B conjugate (meningococcal protein conjugate) and hepatitis B (recombinant) vaccine] is a sterile bivalent vaccine made of the antigenic components used in producing PedvaxHIB [Haemophilus B conjugate vaccine (meningococcal protein conjugate)] and Recombivax HB [hepatitis B vaccine (recombinant)]. The individual PRP-OMPC and HBsAg adjuvanted bulks are combined to produce Comvax. Each 0.5-mL dose of Comvax is formulated to contain 7.5 μg PRP conjugated to approximately 125 μg OMPC, 5 μg HBsAg, approximately 225 μg aluminum as amorphous aluminum hydroxyphosphate sulfate, and 35 μg sodium borate (decahydrate) as a pH stabilizer, in 0.9% sodium chloride. The vaccine contains NMT 0.0004% (w/v) residual formaldehyde. The product contains no preservative. Comvax is a sterile suspension for IM injection.
- Copaxone® (glatiramer acetate) consists of the acetate salts of synthetic polypeptides, containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction of 0.141, 0.427, 0.095, and 0.338, respectively. The average molecular weight of glatiramer acetate is 5 000 to 9 000 Da. Glatiramer acetate is identified by specific antibodies. Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Copaxone injection is a clear, colorless to slightly yellow, sterile nonpyrogenic solution for SC injection. Each 1 mL of solution contains 20 mg of glatiramer acetate and 40 mg of mannitol, USP. The pH range of the solution is approximately 5.5 to 7.0
- Cosmegen dactinomycin is a sterile, yellow lyophilized powder for injection by the IV route or by regional perfusion after reconstitution. Each vial contains 0.5 mg (500 μg) of dactinomycin and 20.0 mg of mannitol.
- Cosopt (dorzolamide hydrochloride-timolol maleate ophthalmic solution) is supplied as a sterile, isotonic, buffered, slightly viscous aqueous solution. The pH of the solution is approximately 5.65 and the osmolarity is 242 to 323 mOsm. Each milliliter of Cosopt contains 20 mg dorzolamide (22.26 mg of dorzolamide hydrochloride) and 5 mg timolol (6.83 mg timolol maleate). Inactive ingredients are sodium citrate, hydroxyethyl cellulose, sodium hydroxide, mannitol, and water for injection. Benzalkonium chloride (0.0075%) is added as a preservative.
- Cubicin is supplied as a sterile, preservative-free, pale yellow to light brown lyophilized cake containing approximately 900 mg/g of daptomycin for IV use following reconstitution with 0.9% sodium chloride injection. The only inactive ingredient is sodium hydroxide which is used in minimal quantities for pH adjustment. Freshly reconstituted solutions of cubicin range in color from pale yellow to light brown.
- Curosurf® (poractant alpha) intratracheal suspension is a sterile, nonpyrogenic pulmonary surfactant intended for intratracheal use only. It is suspended in 0.9% sodium chloride solution. The pH is adjusted as required with sodium bicarbonate to a pH of 6.2 (5.5–6.5). Curosurf contains no preservatives. Curosurf is a white to creamy white suspension of poractant alpha. Each milliliter of surfactant mixture contains 80 mg of surfactant (extract) that includes 76 mg of phospholipids and 1 mg of protein of which 0.2 mg is SP-B. The amount of phospholipids is calculated from the content of phosphorus and contains 55 mg of phosphatidylcholine of which 30 mg is dipalmitoylphosphatidylcholine.
- CytoGam®, cytomegalovirus immune globulin intravenous (human) (CMV-IGIV), is an immunoglobulin G (IgG) containing a standardized amount of antibody to CMV. CMV-IGIV is formulated in final vial as a sterile liquid. The globulin is stabilized with 5% sucrose and 1% albumin (human). CytoGam contains no preservative. Each milliliter contains 50±10 mg of immunoglobulin, primarily IgG, and trace amounts of IgA and IgM; 50 mg of sucrose; 10 mg of albumin (human). The sodium content is 20 to 30 mEq/L, that is, 0.4 to 0.6 mEq/20 mL or 1.0 to 1.5 mEq/50 mL. The solution should appear colorless and translucent.
- Dantrium intravenous is a sterile, nonpyrogenic lyophilized formulation of dantrolene sodium for injection. Dantrium intravenous is supplied in 70-mL vials containing 20 mg dantrolene sodium, 3000 mg mannitol, and sufficient sodium hydroxide to yield a pH of approximately 9.5 when reconstituted with 60 mL sterile water for injection USP (without a bacteriostatic agent).

- Decadron dexamethasone sodium phosphate injection is a sterile solution (pH 7.0–8.5) of dexamethasone sodium phosphate, sealed under nitrogen, and is supplied in two concentrations: 4 mg/mL and 24 mg/mL. Each milliliter of Decadron phosphate injection, 4 mg/mL, contains dexamethasone sodium phosphate equivalent to 4 mg dexamethasone phosphate or 3.33 mg dexamethasone. Inactive ingredients per milliliter: 8 mg creatinine, 10 mg sodium citrate, sodium hydroxide to adjust pH, and water for injection, QS, with 1 mg sodium bisulfite, 1.5 mg methyl paraben, and 0.2 mg propyl paraben added as preservatives. Each milliliter of Decadron phosphate injection, 24 mg/mL, contains dexamethasone sodium phosphate equivalent to 24 mg dexamethasone phosphate or 20 mg dexamethasone. Inactive ingredients per milliliter: 8 mg creatinine, 10 mg sodium citrate, 0.5 mg disodium edetate, sodium hydroxide to adjust pH, and water for injection, QS, with 1 mg sodium bisulfite, 1.5 mg methylparaben, and 0.2 mg propylparaben added as preservatives.
- DepoDur (morphine sulfate extended-release liposome injection) is a sterile, nonpyrogenic, white to off-white, preservative-free suspension of multivesicular lipid-based particles containing morphine sulfate, USP. The median diameter of the liposome particles is in the range of 17 to 23 μm. The liposomes are suspended in a 0.9% sodium chloride solution. Each vial contains morphine sulfate (expressed as the pentahydrate) at a nominal concentration of 10 mg/mL. Inactive ingredients and their approximate concentrations are 1, 2-dioleoyl- sn-glycero-3-phosphocholine (DOPC), 4.2 mg/mL; cholesterol, 3.3 mg/mL; 1, 2-dipalmitoyl- sn -glycero-3-phospho-rac-(1-glycerol) (DPPG), 0.9 mg/mL; tricaprylin, 0.3 mg/mL; and triolein, 0.1 mg/mL. The pH of DepoDur is in the range of 5.0 to 8.0.
- Depo-Medrol sterile aqueous suspension contains methylprednisolone acetate. Depo-Medrol is an anti-inflammatory glucocorticoid for IM, intrasynovial, soft tissue, or intralesional injection. It is available as single-dose vials in two strengths: 40 and 80 mg/mL. Each mL of these preparations contains methylprednisolone acetate, 40 or 80 mg; polyethylene glycol 3350, 29 or 28 mg; myristyl-gamma-picolinium chloride, 0.195 or 0.189 mg. Sodium chloride was added to adjust tonicity. When necessary, pH was adjusted with sodium hydroxide and/or hydrochloric acid. The pH of the finished product remains within the USP specified range, that is, 3.5 to 7.0. Also available as 20 mg/mL.
- Depo-Provera contraceptive injection (CI) contains medroxyprogesterone acetate. Depo-Provera CI for IM injection is available in vials and prefilled syringes, each containing 1 mL of medroxyprogesterone acetate sterile aqueous suspension 150 mg/mL. Each milliliter contains medroxyprogesterone acetate,150 mg; polyethylene glycol 3350, 28.9 mg; polysorbate 80, 2.41 mg; sodium chloride, 8.68 mg; methyl paraben, 1.37 mg; propyl paraben, 0.150 mg; water for injection, QS. When necessary, pH is adjusted with sodium hydroxide or hydrochloric acid, or both.
- Depo-subQ provera 104 contains medroxyprogesterone acetate (MPA). Depo-subQ provera 104 for SC injection is available in prefilled syringes (160 mg/mL), each containing 0.65 mL (104 mg) of medroxyprogesterone acetate sterile aqueous suspension. Each 0.65 mL contains medroxyprogesterone acetate, 104 mg; methyl paraben, 1.040 mg; propyl paraben, 0.098 mg; sodium chloride, 5.200 mg; polyethylene glycol, 18.688 mg; polysorbate 80, 1.950 mg; monobasic sodium phosphate.H_2O, 0.451 mg; dibasic sodium phosphate.$12H_2O$, 0.382 mg; methionine, 0.975 mg; povidone, 3.250 mg; water for injection, QS. When necessary, the pH is adjusted with sodium hydroxide or hydrochloric acid, or both.
- Desferal, deferoxamine mesylate USP, is available in vials for IM, SC, and IV administration. Desferal is supplied as vials containing 500 mg and 2 g of deferoxamine mesylate USP, in sterile, lyophilized form.
- Digibind, digoxin immune Fab (ovine), is a sterile lyophilized powder of antigen-binding fragments (Fab) derived from specific antidigoxin antibodies raised in sheep. Each vial, which will bind approximately 0.5 mg of digoxin (or digitoxin), contains 38 mg of digoxin-specific Fab fragments derived from sheep plus 75 mg of sorbitol as a stabilizer and 28 mg of sodium chloride. The vial contains no preservatives. Digibind is administered by IV injection after reconstitution with sterile water for injection (4 mL/vial).
- Dilaudid (hydromorphone hydrochloride), each 1 mL of sterile solution contains 10 mg hydromorphone hydrochloride with 0.2% sodium citrate and 0.2% citric acid solution. It is also available as lyophilized Dilaudid for IV, SC, or IM administration. Each single-dose vial contains 250 mg sterile, lyophilized hydromorphone HCl to be reconstituted with 25 mL of sterile water for injection USP to provide a solution containing 10 mg/mL. Ampoules (for parenteral administration) containing 1, 2, and 4 mg hydromorphone hydrochloride per milliliter with 0.2% sodium citrate, 0.2% citric acid solution. Dilaudid ampoules are sterile. Multiple-dose vials (for parenteral administration) containing 20 mL of solution. Each milliliter contains 2 mg hydromorphone hydrochloride and 0.5 mg edetate disodium with 1.8 mg methyl paraben and 0.2 mg propyl paraben as preservatives. Sodium hydroxide or hydrochloric acid is used for pH adjustment. Dilaudid multiple-dose vials are sterile.
- Diprivan® (propofol) injectable emulsion in addition to the active component, propofol, the formulation also contains soybean oil (100 mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL), and disodium edetate (0.005%), with sodium hydroxide to adjust pH. Diprivan injectable emulsion is isotonic and has a pH of 7.0 to 8.5.
- Diuril (chlorothiazide sodium), IV sodium Diuril, is a sterile lyophilized white powder and is supplied in a vial containing chlorothiazide sodium equivalent to chlorothiazide, 0.5 g; inactive ingredients—mannitol, 0.25 g; sodium hydroxide to adjust pH.
- Doxil® (doxorubicin HCl liposome injection) is doxorubicin hydrochloride (HCl) encapsulated in Stealth® liposomes for IV administration. Doxil is provided as a sterile, translucent red liposomal dispersion in 10- or 30-mL glass single-use vials. Each vial contains 20 or 50 mg doxorubicin HCl at a concentration of 2 mg/mL and a pH of 6.5. The Stealth liposome carriers are composed of *N*-(carbonyl-methoxypolyethylene glycol 2000)-1, 2-distearoyl- sn -glycero-3-phosphoethanolamine sodium salt (MPEG-DSPE), 3.19 mg/mL; fully hydrogenated soy phosphatidylcholine (HSPC), 9.58 mg/mL; and cholesterol, 3.19 mg/mL. Each milliliter also contains ammonium sulfate, approximately 2 mg; histidine as a buffer; hydrochloric acid and/or sodium hydroxide for pH control; and sucrose to maintain isotonicity. More than 90% of the drug is encapsulated in the Stealth liposomes.
- DuoNeb® contains albuterol sulfate and ipratropium bromide. Each 3-mL vial of DuoNeb contains 3.0 mg (0.1%)

of albuterol sulfate [equivalent to 2.5 mg (0.083%) of albuterol base] and 0.5 mg (0.017%) of ipratropium bromide in an isotonic, sterile aqueous solution containing sodium chloride, hydrochloric acid to adjust to pH 4, and edetate disodium, USP (a chelating agent).

- Edex® (alprostadil for injection) is a sterile, pyrogen-free powder containing alprostadil in an alfadex [(alpha)-cyclodextrin] inclusion complex. Edex is supplied in single-dose, dual-chamber cartridges. Edex is lyophilized in single-dose, dual-chamber cartridges intended for use with the reusable Edex injection device. One chamber of the cartridge contains alprostadil, alfadex, and lactose as a sterile pyrogen-free powder. The other chamber contains 1.075 mL of sterile 0.9% sodium chloride. The Edex cartridges are supplied in three strengths: 10-μg cartridge [10.75 μg alprostadil, 347.55 μg (alpha)-cyclodextrin, 51.06 mg lactose]; 20-μg cartridge [21.5 μg alprostadil, 695.2 μg (alpha)-cyclodextrin, 51.06 mg lactose]; 40-μg cartridge [43.0 μg alprostadil, 1, 390.3 μg (alpha)-cyclodextrin, 51.06 mg lactose]. The Edex injection device is used to reconstitute the sterile powder in one chamber with the sterile 0.9% sodium chloride in the other chamber. After reconstitution, the Edex injection device is used to administer the intracavernous injection of alprostadil. After reconstitution, the active ingredient, alprostadil, immediately dissociates from the (alpha)-cyclodextrin inclusion complex. The reconstituted solution is clear and colorless and has a pH between 4 and 8. When the single-dose, dual-chamber cartridge containing either 10.75, 21.5 or 43.0 μg of alprostadil is placed into the Edex injection device and reconstituted, the deliverable amount of alprostadil in each milliliter is 10, 20 or 40 μg, respectively.
- Elestat® (epinastine HCl ophthalmic solution), 0.05%, each milliliter contains the following: active—epinastine HCl, 0.05% (0.5 mg/mL), equivalent to epinastine 0.044% (0.44 mg/mL); preservative—benzalkonium chloride, 0.01%; inactives—edetate disodium; purified water; sodium chloride; sodium phosphate, monobasic; and sodium hydroxide and/or hydrochloric acid (to adjust the pH). Elestat has a pH of approximately 7 and an osmolality range of 250 to 310 mOsm/kg.
- Elspar (Asparaginase), the specific activity of ELSPAR is at least 225 IU/mg of protein and each vial contains 10,000 IU of asparaginase and 80 mg of mannitol, an inactive ingredient, as a sterile, white lyophilized plug or powder for IV or IM injection after reconstitution.
- Enbrel® (etanercept) is supplied in a single-use prefilled 1-mL syringe as a sterile, preservative-free solution for SC injection. The solution of Enbrel is clear and colorless and is formulated at pH 6.3±0.2. Each Enbrel single-use prefilled syringe contains 0.98 mL of a 50 mg/mL solution of etanercept with 10 mg/mL sucrose, 5.8 mg/mL sodium chloride, 5.3 mg/mL L-arginine hydrochloride, 2.6 mg/mL sodium phosphate monobasic monohydrate, and 0.9 mg/mL sodium phosphate dibasic, anhydrous. Administration of one 50 mg/mL prefilled syringe of Enbrel provides a dose equivalent to two 25-mg vials of lyophilized Enbrel, when vials are reconstituted and administered as recommended. Enbrel multiple-use vials contain sterile, white, preservative-free, lyophilized powder. Reconstitution with 1 mL of the supplied sterile bacteriostatic water for injection (BWFI), USP (containing 0.9% benzyl alcohol) yields a multiple-use, clear, and colorless solution with a pH of 7.4±0.3 containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine.
- Engerix-B [hepatitis B vaccine (recombinant)] is a noninfectious recombinant DNA hepatitis B vaccine supplied as a sterile suspension for IM administration. The vaccine is ready for use without reconstitution; it must be shaken before administration since a fine white deposit with a clear, colorless supernatant may form on storage. Pediatric/Adolescent: Each 0.5-mL dose contains 10 μg of hepatitis B surface antigen adsorbed on 0.25 mg aluminum as aluminum hydroxide. The pediatric/adolescent vaccine is formulated without preservatives. The pediatric formulation contains a trace amount of thimerosal (<0.5 μg mercury) from the manufacturing process, sodium chloride (9 mg/mL), and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/mL; sodium dihydrogen phosphate dihydrate, 0.71 mg/mL). Adult: Each 1-mL adult dose contains 20 μg of hepatitis B surface antigen adsorbed on 0.5 mg aluminum as aluminum hydroxide. The adult vaccine is formulated without preservatives. The adult formulation contains a trace amount of thimerosal (<1.0 μg mercury) from the manufacturing process, sodium chloride (9 mg/mL), and phosphate buffers (disodium phosphate dihydrate, 0.98 mg/mL; sodium dihydrogen phosphate dihydrate, 0.71 mg/mL).
- EpiPen® and EpiPen Jr® autoinjectors contain 2 mL epinephrine injection for emergency IM use. Each EpiPen autoinjector delivers a single dose of 0.3 mg epinephrine from epinephrine injection, USP, 1:1000 (0.3 mL) in a sterile solution. Each EpiPen Jr autoinjector delivers a single dose of 0.15 mg epinephrine from epinephrine injection, USP, 1:2000 (0.3 mL) in a sterile solution. For stability purposes, approximately 1.7 mL remains in the autoinjector after activation and cannot be used. Each 0.3 mL in EpiPen contains 0.3 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0. Each 0.3 mL in EpiPen Jr contains 0.15 mg epinephrine, 1.8 mg sodium chloride, 0.5 mg sodium metabisulfite, hydrochloric acid to adjust pH, and water for injection. The pH range is 2.2 to 5.0.
- Epogen (erythropoietin), single-dose, preservative-free vial: Each 1 mL of solution contains 2000, 3000, 4000 or 10,000 U of epoetin alpha, 2.5 mg albumin (human), 5.8 mg sodium citrate, 5.8 mg sodium chloride, and 0.06 mg citric acid in water for injection, USP (pH 6.9±0.3). This formulation contains no preservative. Single-dose, preservative-free vial: 1 mL (40,000 U/mL). Each milliliter of solution contains 40,000 U of epoetin alpha, 2.5 mg albumin (human), 1.2 mg sodium phosphate monobasic monohydrate, 1.8 mg sodium phosphate dibasic anhydrate, 0.7 mg sodium citrate, 5.8 mg sodium chloride, and 6.8 μg citric acid in water for injection, USP (pH 6.9±0.3). This formulation contains no preservative. Multidose preserved vial: 2 mL (20,000 U; 10,000 U/mL). Each 1 mL of solution contains 10,000 U of epoetin alpha, 2.5 mg albumin (human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in water for injection, USP (pH 6.1±0.3). Multidose preserved vial: 1 mL (20,000 U/mL). Each 1 mL of solution contains 20,000 U of epoetin alpha, 2.5 mg albumin (human), 1.3 mg sodium citrate, 8.2 mg sodium chloride, 0.11 mg citric acid, and 1% benzyl alcohol as preservative in water for injection, USP (pH 6.1±0.3).
- Eraxis for injection is a sterile, lyophilized product for IV infusion that contains anidulafungin. Eraxis for injection contains the following inactive ingredients: fructose (50 mg), mannitol (250 mg), polysorbate 80 (125 mg), tartaric acid

(5.6 mg), and sodium hydroxide and/or hydrochloric acid for pH adjustment.

- Ethyol® (amifostine) is the trihydrate form of amifostine and is supplied as a sterile lyophilized powder requiring reconstitution for IV infusion. Each single-use 10-mL vial contains 500 mg of amifostine on the anhydrous basis.
- Euflexxa™ is a viscoelastic, sterile solution of highly purified, high molecular weight (2.4–3.6 million Da) hyaluronan (also known as sodium hyaluronate) in phosphate-buffered saline. Euflexxa is a highly purified product extracted from bacterial cells. Each milliliter of Euflexxa contains sodium hyaluronate, 10 mg; sodium chloride, 8.5 mg; disodium hydrogen phosphate dodecahydrate, 0.56 mg; sodium dihydrogen phosphate dihydrate, 0.05 mg; water for injection, QS.
- Faslodex® (fulvestrant) injection contains as inactive ingredients—alcohol USP, benzyl alcohol NF, and benzyl benzoate USP, as cosolvents, and castor oil, USP, as a cosolvent and release rate modifier. Faslodex is supplied in sterile single patient prefilled syringes containing 50 mg/mL fulvestrant either as a single 5-mL or two concurrent 2.5-mL injections to deliver the required monthly dose. Faslodex is administered as an IM injection of 250 mg once monthly.
- Feiba VH anti-inhibitor coagulant complex, vapor heated (AICC) is a freeze-dried sterile human plasma fraction with factor VIII inhibitor bypassing activity. Reconstituted FEIBA VH AICC contains 4 mg of trisodium citrate and 8 mg/mL of sodium chloride.
- Flolan (epoprostenol sodium) for injection is a sterile sodium salt formulated for IV administration. Each vial of Flolan contains epoprostenol sodium equivalent to either 0.5 mg (500,000 ng) or 1.5 mg (1,500,000 ng) epoprostenol, 3.76 mg glycine, 2.93 mg sodium chloride, and 50 mg mannitol. Sodium hydroxide may have been added to adjust pH. Epoprostenol (PGI 2, PGX, prostacyclin), a metabolite of arachidonic acid, is a naturally occurring prostaglandin with potent vasodilatory activity and inhibitory activity of platelet aggregation. Flolan is a white to off-white powder that must be reconstituted with sterile diluent for Flolan. Sterile diluent for Flolan is supplied in glass vials containing 50 mL of 94 mg glycine, 73.3 mg sodium chloride, sodium hydroxide (added to adjust pH), and water for injection, USP. The reconstituted solution of Flolan has a pH of 10.2 to 10.8 and is increasingly unstable at a lower pH.
- Floxin® otic (ofloxacin otic) solution, 0.3%, is a sterile aqueous anti-infective (antibacterial) solution for otic use. Floxin otic contains 0.3% (3 mg/mL) ofloxacin with benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 6.5±0.5.
- Floxin otic Singles™ (ofloxacin otic) solution, 0.3%, is a sterile aqueous antiinfective (antibacterial) solution for otic use. Floxin otic Singles contains 0.3% (3 mg/mL) ofloxacin with benzalkonium chloride (0.0025%), sodium chloride (0.9%), and water for injection. Hydrochloric acid and sodium hydroxide are added to adjust the pH to 6.5±0.5.
- Fluarix™, influenza virus vaccine for IM use, is a sterile suspension prepared from influenza viruses propagated in embryonated chicken eggs. Each 0.5-mL dose also contains octoxynol-10 (Triton® X-100), ≤0.085 mg; alpha-tocopheryl hydrogen succinate, ≤0.1 mg; and polysorbate 80 (Tween 80), ≤0.415 mg. The vaccine is formulated without preservatives. Thimerosal is used at the early stages of manufacture and is removed by subsequent purification steps to <1.25 μg mercury per dose. Each dose may also contain residual amounts of hydrocortisone, ≤0.0016 μg; gentamicin sulfate, ≤0.15 μg; ovalbumin, ≤1 μg; formaldehyde, ≤50 μg; and sodium deoxycholate, ≤50 μg, from the manufacturing process. Fluarix is supplied as a 0.5-mL dose in a prefilled syringe. Fluarix, after shaking well, is colorless to slightly opalescent.
- Flumist influenza virus vaccine live, intranasal (FluMist®) is a live trivalent nasally administered vaccine. FluMist does not contain any preservatives. Each prefilled FluMist sprayer contains a single 0.5-mL dose.
- Fluorescite injection is a sterile aqueous solution in two strengths for use intravenously as a diagnostic aid. The solution contains fluorescein sodium (equivalent to fluorescein 10% or 25%), sodium hydroxide and/or hydrochloric acid (to adjust pH), and water for injection.
- Fortaz in sterile crystalline form is supplied in vials equivalent to 500 mg, 1 g, 2 g, or 6 g of anhydrous ceftazidime and in ADD-Vantage® vials equivalent to 1 or 2 g of anhydrous ceftazidime. Solutions of Fortaz range in color from light yellow to amber, depending on the diluent and volume used. The pH of freshly constituted solutions usually ranges from 5 to 8. Fortaz is available as a frozen, isosmotic, sterile, nonpyrogenic solution with 1 or 2 g of ceftazidime as ceftazidime sodium premixed with approximately 2.2 or 1.6 g, respectively, of dextrose hydrous, USP. Dextrose has been added to adjust the osmolality. Sodium hydroxide is used to adjust pH and neutralize ceftazidime pentahydrate free acid to the sodium salt. The pH may have been adjusted with hydrochloric acid. Solutions of premixed Fortaz range in color from light yellow to amber. The solution is intended for IV use after thawing to room temperature. The osmolality of the solution is approximately 300 mOsm/kg and the pH of thawed solutions ranges from 5.0 to 7.5. The plastic container for the frozen solution is fabricated from a specially designed multilayer plastic, PL 2040.
- Forteo® is supplied as a sterile, colorless, clear isotonic solution in a glass cartridge which is preassembled into a disposable pen device for SC injection. Each prefilled delivery device is filled with 3.3 mL to deliver 3 mL. Each milliliter contains 250 μg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.10 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3.0 mg metacresol, and water for injection. In addition, hydrochloric acid solution (10%) and/or sodium hydroxide solution (10%) may have been added to adjust the product to pH 4. Each cartridge preassembled into a pen device delivers 20 μg of teriparatide per dose each day for up to 28 days.
- Fortical® calcitonin-salmon (rDNA origin) nasal spray delivers 200 IU calcitonin-salmon in a volume of 0.09 mL. Active ingredient: calcitonin-salmon 2200 IU/mL, corresponding to 200 IU per actuation (0.09 mL). Inactive ingredients: sodium chloride, USP; citric acid, USP; phenylethyl alcohol, USP; benzyl alcohol, NF; polysorbate 80, NF; hydrochloric acid, NF, or sodium hydroxide, NF (added as necessary to adjust pH); and purified water USP.
- Gama STAN™ S/D, Immune globulin (human)—Gama STAN S/D contains no preservative. Gama STAN S/D is prepared by cold ethanol fractionation from human plasma. The immune globulin is isolated from solubilized Cohn fraction II. The fraction II solution is adjusted to a final concentration of 0.3% tri-*n*-butyl phosphate (TNBP) and 0.2% sodium cholate. After the addition of solvent

(TNBP) and detergent (sodium cholate), the solution is heated to 30°C and maintained at that temperature for not less than 6 hours. After the viral inactivation step, the reactants are removed by precipitation, filtration, and finally ultrafiltration and diafiltration. Gama STAN S/D is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Gama STAN S/D is then incubated in the final container for 21 to 28 days at 20°C to 27°C.

- Gammagard S/D, immune globulin intravenous (human, IGIV) when reconstituted with the total volume of diluent (sterile water for injection, USP) supplied. This preparation contains approximately 50 mg/mL of protein (5%), of which at least 90% is gamma-globulin. The product, reconstituted to 5%, contains a physiological concentration of sodium chloride (approximately 8.5 mg/mL) and has a pH of 6.8±0.4. Stabilizing agents and additional components are present in the following maximum amounts for a 5% solution: 3 mg/mL albumin (human), 22.5 mg/mL glycine, 20 mg/mL glucose, 2 mg/mL polyethylene glycol (PEG), 1 μg/mL tri-*n*-butyl phosphate, 1 μg/mL octoxynol 9, and 100 μg/mL polysorbate 80. Gammagard S/D, immune globulin intravenous (human) contains no preservative. Gammagard liquid immune globulin intravenous (human), 10%, is a ready-for-use sterile liquid preparation of highly purified and concentrated immunoglobulin G (IgG) antibodies.
- Gamunex® is made from large pools of human plasma by a combination of cold ethanol fractionation, caprylate precipitation and filtration, and anion-exchange chromatography. The protein is stabilized during the process by adjusting the pH of the solution to 4.0 to 4.5. Isotonicity is achieved by the addition of glycine. Gamunex is incubated in the final container (at the low pH of 4.0–4.3), for a minimum of 21 days at 23°C to 27°C.
- Garamycin (gentamicin sulfate) injectable is a sterile aqueous solution for parenteral administration. Each milliliter contains gentamicin sulfate, USP, equivalent to 40 mg gentamicin base; 1.8 mg methyl paraben and 0.2 mg propyl paraben as preservatives; 3.2 mg sodium bisulfite; and 0.1 mg edetate disodium.
- Gardasil is a noninfectious recombinant, quadrivalent vaccine prepared from the highly purified virus-like particles (VLPs) of the major capsid (L1) protein of HPV types 6, 11, 16, and 18. The quadrivalent HPV VLP vaccine is a sterile liquid suspension that is prepared by combining the adsorbed VLPs of each HPV type and additional amounts of the aluminum containing adjuvant and the final purification buffer. Gardasil is a sterile preparation for IM administration. Each 0.5-mL dose contains approximately 20 μg of HPV 6 L1 protein, 40 μg of HPV 11 L1 protein, 40 μg of HPV 16 L1 protein, and 20 μg of HPV 18 L1 protein. Each 0.5-mL dose of the vaccine contains approximately 225 μg of aluminum (as amorphous aluminum hydroxyphosphate sulfate adjuvant), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 μg of polysorbate 80, 35 μg of sodium borate, and water for injection. The product does not contain a preservative or antibiotics.
- Gemzar® (gemcitabine HCl) vial contain either 200 mg or 1 g of gemcitabine HCl (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.
- Geodon for injection contains a lyophilized form of ziprasidone mesylate trihydrate. Geodon for injection is available in a single-dose vial as ziprasidone mesylate (20 mg ziprasidone/mL when reconstituted. Each millimeter of ziprasidone mesylate for injection (when reconstituted) contains 20 mg of ziprasidone and 4.7 mg of methanesulfonic acid solubilized by 294 mg of sulfobutylether (beta)-cyclodextrin sodium (SBECD).
- GlucaGen® [glucagon (rDNA origin) for injection], 1 mg (1 IU), is supplied as a sterile, lyophilized white powder in a 2-mL vial alone, or accompanied by sterile water for reconstitution (1 mL) also in a 2-mL vial. Glucagon, as supplied at pH 2.5 to 3.5, is soluble in water. Active ingredient in each vial—glucagon as hydrochloride, 1 mg (corresponding to 1 IU). Other ingredients—lactose monohydrate (107 mg). When the glucagon powder is reconstituted with sterile water for reconstitution, it forms a solution of 1 mg (1 IU)/mL glucagon for SC, IM, or IV injection.
- Glucagon for injection (rDNA origin) is a polypeptide hormone identical to human glucagon that increases blood glucose and relaxes smooth muscle of the gastrointestinal tract. Glucagon is available for use intravenously, intramuscularly, or subcutaneously in a kit that contains a vial of sterile glucagon and a syringe of sterile diluent. The vial contains 1 mg (1 U) of glucagon and 49 mg of lactose. Hydrochloric acid may have been added during manufacture to adjust the pH of the glucagon; 1 IU of glucagon is equivalent to 1 mg of glucagon. The diluent syringe contains 12 mg/mL of glycerin, water for injection, and hydrochloric acid.
- Havrix (hepatitis A vaccine, inactivated) is a noninfectious hepatitis A vaccine supplied as a sterile suspension for IM administration. Each 1-mL adult dose of vaccine consists of 1440 ELU of viral antigen, adsorbed on 0.5 mg of aluminum as aluminum hydroxide. Each 0.5-mL pediatric dose of vaccine consists of 720 ELU of viral antigen, adsorbed onto 0.25 mg of aluminum as aluminum hydroxide. The vaccine preparations also contain 0.5% (w/v) of 2-phenoxyethanol as a preservative. Other excipients are amino acid supplement (0.3% w/v) in a phosphate-buffered saline solution and polysorbate 20 (0.05 mg/mL). Residual MRC-5 cellular proteins (NMT5 μg/mL) and traces of formalin (NMT0.1 mg/mL) are present. Neomycin sulfate, an aminoglycoside antibiotic, is included in the cell growth media; only trace amounts (≤40 ng/mL) remain, following purification.
- Hemofil M, antihemophilic factor (human, AHF), method M, monoclonal purified, is a sterile, nonpyrogenic, dried preparation of antihemophilic factor (factor VIII, factor VIII:C, AHF) in concentrated form with a specific activity range of 2 to 20 AHF IU/mg of total protein. Hemofil M contains a maximum of 12.5 mg/mL albumin, and per AHF IU, 0.07 mg polyethylene glycol (3350), 0.39 mg histidine, 0.1 mg glycine as stabilizing agents, not more than 0.1 ng mouse protein, 18 ng organic solvent (tri-*n*-butyl phosphate) and 50 ng detergent (octoxynol 9). In the absence of the added albumin (human), the specific activity is approximately 2 000 AHF IU/mg of protein.
- Hepatitis B immune globulin (human), hyper Hep B™ S/D treated with solvent/detergent, is a sterile solution of hepatitis B hyperimmune immune globulin for IM administration; it contains no preservative. Hyper Hep B S/D is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Hyper Hep B S/D is then incubated in the final container for 21 to 28 days at 20°C to

27°C. Each vial contains anti-HBs antibody equivalent to 220 IU/mL.

- Herceptin (Trastuzumab) is a recombinant DNA-derived humanized monoclonal. Herceptin is a sterile, white to pale yellow, preservative-free lyophilized powder for IV administration. The nominal content of each Herceptin vial is 440 mg trastuzumab, 400 mg (alpha), (alpha)-trehalose dihydrate, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, and 1.8 mg polysorbate 20, USP. Reconstitution with 20 mL of the supplied bacteriostatic water for injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative, yields a multidose solution containing 21 mg/mL trastuzumab, at a pH of approximately 6.
- HibTITER. Haemophilus B conjugate vaccine (diphtheria CRM 197 protein conjugate) HibTITER is a sterile solution of a conjugate of oligosaccharides of the capsular antigen of *Haemophilus influenzae* type B (Haemophilus B) and diphtheria CRM 197 protein (CRM 197) dissolved in 0.9% sodium chloride. The conjugate is purified to remove unreacted protein, oligosaccharides, and reagents; sterilized by filtration; and filled into vials. HibTITER is intended for IM use. The vaccine is a clear, colorless solution. Each single dose of 0.5 mL is formulated to contain 10 μg of purified Haemophilus B saccharide and approximately 25 μg of CRM 197 protein. The potency of HibTITER is determined by chemical assay for polyribosylribitol.
- Humatrope® (somatropin, rDNA origin, for injection) is a sterile, white lyophilized powder intended for SC or IM administration after reconstitution. Phosphoric acid and/or sodium hydroxide may have been added to adjust the pH. Reconstituted solutions have a pH of approximately 7.5. This product is oxygen sensitive. Vial—Each vial of Humatrope contains 5 mg somatropin (15 IU or 225 nmol), 25 mg mannitol, 5 mg glycine, and 1.13 mg dibasic sodium phosphate. Each vial is supplied in a combination package with an accompanying 5-mL vial of diluting solution. The diluent contains water for injection with 0.3% metacresol as a preservative and 1.7% glycerin. Cartridge—The cartridges of somatropin contain either 6 mg (18 IU), 12 mg (36 IU), or 24 mg (72 IU) of somatropin. The 6-, 12-, and 24-mg cartridges contain respectively, mannitol 18, 36, and 72 mg; glycine 6, 12, and 24 mg; dibasic sodium phosphate 1.36, 2.72, and 5.43 mg. Each cartridge is supplied in a combination package with an accompanying syringe containing approximately 3 mL of diluting solution. The diluent contains water for injection; 0.3% metacresol as a preservative; and 1.7%, 0.29%, and 0.29% glycerin in the 6-, 12-, and 24-mg cartridges, respectively.
- Humira (adalimumab) is supplied in single-use 1 mL prefilled glass syringes as a sterile, preservative-free solution for SC administration. The solution of Humira is clear and colorless, with a pH of approximately 5.2. Each syringe delivers 0.8 mL (40 mg) of drug product. Each 0.8 mL of Humira contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80, and water for injection, USP. Sodium hydroxide added as necessary to adjust pH.
- Hycamtin (topotecan hydrochloride) for injection is supplied as a sterile, lyophilized, buffered, light yellow to greenish powder available in single-dose vials. Each vial contains topotecan hydrochloride equivalent to 4 mg of topotecan as free base. The reconstituted solution ranges in color from yellow to yellow-green and is intended for administration by IV infusion. Inactive ingredients are mannitol, 48 mg, and tartaric acid, 20 mg. Hydrochloric acid and sodium hydroxide may be used to adjust the pH. The solution pH ranges from 2.5 to 3.5.
- Hyper Hep B™ S/D, hepatitis B immune globulin (human)—each vial contains anti-HBs antibody equivalent to or exceeding the potency of anti-HBs in a U.S. reference hepatitis B immune globulin (Center for Biologics Evaluation and Research, FDA).
- Hyper RAB™ S/D, rabies immune globulin (human)—hyper RAB™ S/D treated with solvent/detergent is a sterile solution of antirabies immune globulin for IM administration; it contains no preservative.
- Hyper RHO S/D, Rho (D) immune globulin (human)—hyper RHO™ S/D full dose is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Hyper RHO S/D full dose is then incubated in the final container for 21 to 28 days at 20°C to 27°C. The potency is equal to or more than 1500 IU. Each single-dose vial or syringe contains sufficient anti-Rho (D) to effectively suppress the immunizing potential of 15 mL of Rho (D) positive red blood cells.
- Hyper RHO™ S/D mini dose, Rho (D) immune globulin (human), is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. One dose of Hyper RHO S/D mini dose contains not less than one-sixth the quantity of Rho (D) antibody contained in one standard dose of Rho (D) immune globulin (human) and it will suppress the immunizing potential of 2.5 mL of Rho (D) positive packed red blood cells or the equivalent of whole blood (5 mL). The quantity of Rho (D) antibody in hyper RHO S/D mini dose is not less than 250 IU.
- Hyper TET™ S/D, tetanus immune globulin (human) is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Hyper TET S/D is then incubated in the final container for 21 to 28 days at 20°C to 27°C.
- Hyperstat IV injection—each ampoule (20 mL) contains 300 mg diazoxide, USP, in a clear, sterile colorless aqueous solution; the pH is adjusted to approximately 11.6 with sodium hydroxide.
- Imitrex (sumatriptan succinate) injection is a clear, colorless to pale yellow, sterile, nonpyrogenic solution for SC injection. Each 0.5 mL of Imitrex injection (8 mg/mL solution) contains 4 mg of sumatriptan (base) as the succinate salt and 3.8 mg of sodium chloride, USP, in water for injection, USP. Each 0.5 mL of Imitrex injection (12 mg/mL solution) contains 6 mg of sumatriptan (base) as the succinate salt and 3.5 mg of sodium chloride, USP, in water for injection, USP. The pH range of both solutions is approximately 4.2 to 5.3. The osmolality of both injections is 291 mOsm.
- Immune globulin (human)—Gama STAN S/D treated with solvent/detergent is a sterile solution of immune globulin for IM administration; it contains no preservative. Gama STAN S/D is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Gama STAN S/D is then incubated in the final container for 21 to 28 days at 20°C to 27°C.
- Immune globulin intravenous (human) (IGIV), Carimune® NF, nanofiltered, is a sterile, highly purified polyvalent antibody product containing in concentrated form all the IgG antibodies which regularly occur in the donor population. The manufacturing process by which Carimune® NF is prepared from plasma consists of frac-

tionation and purification steps that comprise filtrations in the presence of filter aids. Final container lyophilized units are prepared so as to contain 1, 3, 6, or 12 g protein with 1.67 g sucrose and less than 20 mg NaCl/g of protein. The lyophilized preparation contains no preservative and may be reconstituted with sterile water, 5% dextrose or 0.9% saline to a solution with protein concentrations ranging from 3% to 12%.

- Immune globulin intravenous (human), 10% caprylate/chromatography purified (Gamunex), is a ready-to-use sterile solution of human immune globulin protein for IV administration. Gamunex consists of 9% to 11% protein in 0.16 to 0.24 M glycine. Not less than 98% of the protein has the electrophoretic mobility of gamma-globulin. Gamunex contains trace levels of fragments, IgA (average 0.046 mg/mL), and IgM. The distribution of IgG subclasses is similar to that found in normal serum. The measured buffer capacity is 35 mEq/L and the osmolality is 258 mOsm/kg solvent, which is close to physiological osmolality (285–295 mOsm/kg). The pH of Gamunex is 4.0 to 4.5. Gamunex contains no preservative.
- Increlex™ [mecasermin (rDNA origin) injection] is a sterile, aqueous, clear, and colorless solution intended for SC injection. Each multidose vial of Increlex contains 10 mg/mL mecasermin, 9 mg/mL benzyl alcohol, 5.84 mg/mL sodium chloride, 2 mg/mL polysorbate 20, and 0.05 M acetate at a pH of approximately 5.4.
- Indocin IV (indomethacin for injection) for IV administration is lyophilized indomethacin for injection. Each vial contains indomethacin for injection equivalent to 1 mg indomethacin as a white to yellow lyophilized powder or plug. Variations in the size of the lyophilized plug and the intensity of color have no relationship to the quality or amount of indomethacin present in the vial.
- Infanrix (diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed) is a noninfectious, sterile combination of diphtheria and tetanus toxoids and three pertussis antigens [inactivated pertussis toxin (PT), filamentous hemagglutinin (FHA), and pertactin (69 kDa outer membrane protein)] adsorbed onto aluminum hydroxide. Infanrix is intended for IM injection only. Each antigen is individually adsorbed onto aluminum hydroxide. Each 0.5-mL dose is formulated to contain 25 Lf of diphtheria toxoid, 10 Lf of tetanus toxoid, 25 μg of inactivated PT, 25 μg of FHA, and 8 μg of pertactin. Each 0.5-mL dose also contains 2.5 mg of 2-phenoxyethanol as a preservative, 4.5 mg of NaCl, and aluminum adjuvant (≤0.625 mg aluminum by assay). Each dose also contains ≤100 μg of residual formaldehyde and ≤100 μg of polysorbate 80 (Tween 80). Infanrix does not contain thimerosal.
- INFeD (iron dextran injection, USP) is a dark brown, slightly viscous sterile liquid complex of ferric hydroxide and dextran for IV or IM use. Each milliliter contains the equivalent of 50 mg of elemental iron (as an iron dextran complex), approximately 0.9% sodium chloride, in water for injection. Sodium hydroxide and/or hydrochloric acid may have been used to adjust pH. The pH of the solution is between 5.2 and 6.5.
- Insulin Lispro mixture. Humalog® Mix75/25™ [75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin)] is a mixture of insulin lispro solution, a rapid-acting blood glucose-lowering agent and insulin lispro protamine suspension, an intermediate-acting blood glucose-lowering agent. Humalog Mix75/25 disposable insulin delivery devices contain a sterile suspension of insulin lispro protamine suspension mixed with soluble insulin lispro for use as an injection. Each milliliter of Humalog Mix75/25 injection contains insulin lispro 100 U, 0.28 mg protamine sulfate, 16 mg glycerin, 3.78 mg dibasic sodium phosphate, 1.76 mg metacresol, zinc oxide content adjusted to provide 0.025 mg zinc ion, 0.715 mg phenol, and water for injection. Humalog Mix75/25 has a pH of 7.0 to 7.8. Hydrochloric acid, 10%, and/or sodium hydroxide, 10%, may have been added to adjust pH.
- Insulin Lispro—Humalog® (insulin lispro, rDNA origin) is a human insulin analog that is a rapid-acting parenteral blood glucose-lowering agent. The vials, cartridges, and pens contain a sterile solution of Humalog for use as an injection. Humalog injection consists of zinc-insulin lispro crystals dissolved in a clear aqueous fluid. Each milliliter of Humalog injection contains insulin lispro 100 U, 16 mg glycerin, 1.88 mg dibasic sodium phosphate, 3.15 mg metacresol, zinc oxide content adjusted to provide 0.0197 mg zinc ion, trace amounts of phenol, and water for injection. Insulin lispro has a pH of 7.0 to 7.8. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.
- Insulin. Humulin R (U-500) consists of zinc-insulin crystals dissolved in a clear fluid. Humulin R (U-500) is a sterile solution and is for SC injection. The concentration of Humulin R (U-500) is 500 U/mL. Each milliliter contains 500 U of biosynthetic human insulin, 16 mg glycerin, 2.5 mg *m*-cresol as a preservative, and zinc-oxide calculated to supplement endogenous zinc to obtain total zinc content of 0.017 mg/100 U. Sodium hydroxide and/or hydrochloric acid may be added during manufacture to adjust the pH. Humulin is available in six formulations—Regular (R), NPH (N), Lente (L), Ultralente® (U), 50% human insulin isophane suspension (NPH)/50% human insulin injection (buffered regular, 50/50), and 70% human insulin isophane suspension (NPH)/30% human insulin injection (buffered regular, 70/30). Humulin R (U-500) is the only human insulin manufactured by Eli Lilly and Company that has a concentration of 500 U/mL. The concentration of Humulin N in Humulin N Pen is 100 U/mL (U-100).
- Integrilin (eptifibatide) injection is a clear, colorless, sterile, nonpyrogenic solution for IV use. Each 10-mL vial contains 2 mg/mL of eptifibatide and each 100-mL vial contains either 0.75 mg/mL of eptifibatide or 2 mg/mL of eptifibatide. Each vial of either size also contains 5.25 mg/mL citric acid and sodium hydroxide to adjust the pH to 5.35.
- Interleukin eleven is a thrombopoietic growth factor that directly stimulates the proliferation of hematopoietic stem cells and megakaryocyte progenitor cells and induces megakaryocyte maturation resulting in increased platelet production.
- Intron® A injection is a clear, colorless solution. The 3 million IU vial of Intron A injection contains 3 million IU of interferon alpha-2b, recombinant per 0.5 mL. The 18 million IU multidose vial of Intron A injection contains a total of 22.8 million IU of interferon alpha-2b, recombinant per 3.8 mL (3 million IU/0.5 mL) to provide the delivery of six 0.5-mL doses, each containing 3 million IU of Intron A (for a label strength of 18 million IU). The 18 million IU Intron A injection multidose pen contains a total of 22.5 million IU of interferon alpha-2b, recombinant per 1.5 mL (3 million IU/0.2 mL) to provide the delivery of six 0.2-mL doses, each containing 3 million IU of Intron A (for a label strength of 18 million IU). Each milliliter also

contains 7.5 mg sodium chloride, 1.8 mg sodium phosphate dibasic, 1.3 mg sodium phosphate monobasic, 0.1 mg edetate disodium, 0.1 mg polysorbate 80, and 1.5 mg *m*-cresol as a preservative. Based on the specific activity of approximately 2.6×10^8 IU/mg protein as measured by HPLC assay, the corresponding quantities of interferon alpha-2b, recombinant in the vials and pen described above are approximately 0.012, 0.088, and 0.087 mg protein, respectively.

- Invanz (ertapenem for injection) is supplied as sterile lyophilized powder for IV infusion after reconstitution with appropriate diluent and transfer to 50 mL 0.9% sodium chloride injection or for IM injection following reconstitution with 1% lidocaine hydrochloride. Each vial contains 1.046 g ertapenem sodium, equivalent to 1 g ertapenem. The sodium content is approximately 137 mg (approximately 6 mEq). Each vial of Invanz contains the following inactive ingredients: 175 mg sodium bicarbonate and sodium hydroxide to adjust pH to 7.5.
- Iveegam EN, immune globulin intravenous (human) (IGIV), is a sterile freeze-dried concentrate of immunoglobulin G (IgG). Reconstitution of the freeze-dried powder with the accompanying quantity of sterile water for injection, USP, gives a 5% protein solution suitable for IV administration. This final solution contains, per milliliter, 50±5 mg of IgG, 50 mg of glucose as a stabilizer, and 3 mg of sodium chloride. Trace amounts of IgM and IgA are also present. The reconstituted solution is clear, colorless, and free of detectable aggregates. It contains no preservative.
- Kepivance™ (palifermin) is supplied as a sterile, white, preservative-free, lyophilized powder for IV injection after reconstitution with 1.2 mL of sterile water for injection, USP. Reconstitution yields a clear, colorless solution of Kepivance (5 mg/mL) with a pH of 6.5. Each single-use vial of Kepivance contains 6.25 mg palifermin, 50 mg mannitol, 25 mg sucrose, 1.94 mg L-histidine, and 0.13 mg polysorbate 20 (0.01% w/v).
- Kineret® (anakinra) is supplied in single-use prefilled glass syringes with 27 gauge needles as a sterile, clear, colorless to white, preservative-free solution for daily SC administration. Each prefilled glass syringe contains 0.67 mL (100 mg) of anakinra in a solution (pH 6.5) containing sodium citrate (1.29 mg), sodium chloride (5.48 mg), disodium EDTA (0.12 mg), and polysorbate 80 (0.70 mg) in water for injection, USP.
- Koate-DVI contains purified and concentrated factor VIII. When reconstituted as directed, Koate-DVI contains approximately 50 to 150 times as much factor VIII as an equal volume of fresh plasma. The specific activity, after addition of albumin (human), is in the range of 9 to 22 IU/mg protein. Koate-DVI must be administered by the IV route. The final product when reconstituted as directed contains NMT 1500 μg/mL polyethylene glycol (PEG), NMT 0.05 M glycine, NMT 25 μg/mL polysorbate 80, NMT 5 μg/g tri-*n*-butyl phosphate (TNBP), NMT 3 mM calcium, NMT 1 μg/mL aluminum, NMT 0.06 M histidine, and NMT 10 mg/mL albumin (human).
- Koate-DVI, antihemophilic factor (human), is a sterile, stable, purified, dried concentrate of human antihemophilic factor (AHF, factor VIII, AHG). The specific activity, after addition of albumin (human), is in the range of 9 to 22 IU/mg protein. The final product when reconstituted as directed contains NMT 1500 μg/mL polyethylene glycol (PEG), NMT 0.05 M glycine, NMT 25 μg/mL polysorbate 80, NMT 5 μg/g tri-*n*-butyl phosphate (TNBP), NMT 3 mM calcium, NMT 1 μg/mL aluminum, NMT 0.06 M histidine, and NMT 10 mg/mL albumin (human).
- Kogenate® FS antihemophilic factor (recombinant) is a sterile, stable, purified, nonpyrogenic, dried concentrate formulated with sucrose (0.9–1.3%), glycine (21–25 mg/mL), and histidine (18–23 mM) as stabilizers in the final container in place of albumin (human) as used in Kogenate, and is then lyophilized. The final product also contains calcium chloride (2–3 mM), sodium (27–36 mEq/L), chloride (32–40 mEq/L), polysorbate 80 (NMT 96 μg/mL), imidazole (NMT 20 μg/1000 IU), tri-*n*-butyl phosphate (NMT 5 μg/1000 IU), and copper (NMT 0.6 μg/1000 IU). The product contains no preservatives. The amount of sucrose in each vial is 28 mg. Intravenous administration of sucrose contained in Kogenate FS will not affect blood glucose levels. Each vial of Kogenate FS contains the labeled amount of recombinant FVIII in international units. One IU, as defined by the World Health Organization standard for blood coagulation FVIII, human, is approximately equal to the level of FVIII activity found in 1 mL of fresh pooled human plasma. Kogenate FS must be administered by the IV route.
- Lacrisert (hydroxypropyl cellulose ophthalmic insert) is a sterile, translucent, rod-shaped, water-soluble, ophthalmic insert made of hydroxypropyl cellulose, for administration into the inferior cul-de-sac of the eye. Each Lacrisert is 5 mg of hydroxypropyl cellulose. Lacrisert contains no preservatives or other ingredients. It is approximately 1.27 mm in diameter by approximately 3.5 mm long.
- Lanoxin (digoxin), injection pediatric, is a sterile solution of digoxin for IV or IM injection. The vehicle contains 40% propylene glycol and 10% alcohol. The injection is buffered to a pH of 6.8 to 7.2 with 0.17% sodium phosphate and 0.08% anhydrous citric acid. Each 1-mL ampoule contains 100 μg (0.1 mg) digoxin. Dilution is not required. Lanoxin injection is a sterile solution of digoxin for IV or IM injection. The vehicle contains 40% propylene glycol and 10% alcohol. The injection is buffered to a pH of 6.8 to 7.2 with 0.17% dibasic sodium phosphate and 0.08% anhydrous citric acid. Each 2-mL ampoule contains 500 μg (0.5 mg) digoxin [250 μg (0.25 mg]/mL)]. Dilution is not required.
- Lantus® [insulin glargine (rDNA origin) injection] is a sterile solution of insulin glargine for use as an injection. Each milliliter of Lantus (insulin glargine injection) contains 100 IU (3.6378 mg) insulin glargine, 30 μg zinc, 2.7 mg *m*-cresol, 20 mg glycerol 85%, and water for injection. The pH is adjusted by addition of aqueous solutions of hydrochloric acid and sodium hydroxide. Lantus has a pH of approximately 4.
- Leukine® (sargramostim) liquid is formulated as a sterile, preserved (1.1% benzyl alcohol), injectable solution (500 μg/mL) in a vial. Lyophilized Leukine is a sterile, white, preservative-free powder (250 μg) that requires reconstitution with 1 mL sterile water for injection, USP, or 1 mL bacteriostatic water for injection, USP. Liquid Leukine and reconstituted lyophilized Leukine are clear, colorless liquids suitable for SC injection or IV infusion. Liquid Leukine contains 500 μg (2.8×10^6 IU/mL) sargramostim, 1.9 mg/mL edetate disodium, and 1.1% benzyl alcohol in a 1-mL solution. The vial of lyophilized Leukine contains 250 μg (1.4×10 6 IU/vial) sargramostim. The liquid Leukine vial and reconstituted lyophilized Leukine vial also contain 40 mg/mL mannitol, USP; 10 mg/mL

sucrose, NF, and 1.2 mg/mL tromethamine, USP, as excipients.

- Lovenox injection is available in two concentrations: (1) 100 mg/mL; prefilled syringes: 30 mg/0.3 mL, 40 mg/0.4 mL; graduated prefilled syringes: 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL; multiple-dose vials: 300 mg/3.0 mL; Lovenox injection (100 mg/mL): concentration contains 10 mg enoxaparin sodium (approximate antifactor Xa activity of 1000 IU/0.1 mL water for injection; (2) 150 mg/mL; graduated prefilled syringes: 120 mg/0.8 mL, 150 mg/1 mL; Lovenox injection (150 mg/mL): concentration contains 15 mg enoxaparin sodium (approximate antifactor Xa activity of 1500 IU/0.1 mL water for injection. The Lovenox prefilled syringes and graduated prefilled syringes are preservative-free and intended for use only as a single-dose injection. The multiple-dose vial contains 15 mg/1.0 mL benzyl alcohol as a preservative. The pH of the injection is 5.5 to 7.5.
- LPVirazole®, a brand name for ribavirin for inhalation solution, is a sterile, lyophilized powder to be reconstituted for aerosol administration. Each 100 mL glass vial contains 6 g of ribavirin, and when reconstituted to the recommended volume of 300 mL with sterile water for injection or sterile water for inhalation (no preservatives added), will contain 20 mg/mL of ribavirin, pH approximately 5.5. Aerosolization is to be carried out in a small particle aerosol generator (SPAG-2) nebulizer only.
- Lupron Depot-PED, leuprolide acetate, is available in a prefilled dual-chamber syringe containing sterile lyophilized microspheres which, when mixed with diluent, become a suspension intended as a single IM injection. The front chamber of Lupron Depot-PED 7.5 mg, 11.25 mg, and 15 mg prefilled dual-chamber syringe contains leuprolide acetate (7.5/11.25/15 mg), purified gelatin (1.3/1.95/2.6 mg), D-lactic and glycolic acids copolymer (66.2/99.3/132.4 mg), and D-mannitol (13.2/19.8/26.4 mg). The second chamber of diluent contains carboxymethylcellulose sodium (5 mg), D-mannitol (50 mg), polysorbate 80 (1 mg), water for injection, USP, and glacial acetic acid, USP, to control pH. During the manufacture of Lupron Depot-PED, acetic acid is lost, leaving the peptide.
- Maxipime (cefepime hydrochloride, USP) for injection is supplied for IM or IV administration in strengths equivalent to 500 mg, 1 g, and 2 g of cefepime. Maxipime is a sterile, dry mixture of cefepime hydrochloride and L-arginine. It contains the equivalent of not less than 90% and not more than 115% of the labeled amount of cefepime. The L-arginine, at an approximate concentration of 725 mg/g of cefepime, is added to control the pH of the constituted solution at 4 to 6. Freshly constituted solutions of Maxipime will range in color from colorless to amber.
- Mefoxin (cefoxitin for injection) contains approximately 53.8 mg (2.3 mEq) of sodium per gram of cefoxitin activity. Solutions of Mefoxin range from colorless to light amber in color. The pH of freshly constituted solutions usually ranges from 4.2 to 7.0.
- Merrem® IV (meropenem for injection) is a sterile, pyrogen-free, synthetic, broad-spectrum carbapenem antibiotic for IV administration. When constituted as instructed (see Dosage and Administration; Preparation of Solution), each 1-g Merrem IV vial will deliver 1 g of meropenem and 90.2 mg of sodium as sodium carbonate (3.92 mEq). Each 500-mg Merrem IV vial will deliver 500 mg meropenem and 45.1 mg of sodium as sodium carbonate (1.96 mEq).
- Meruvax II is a sterile lyophilized preparation of the Wistar Institute RA 27/3 strain of live attenuated rubella virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), human albumin (0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients, and approximately 25 μg of neomycin. The product contains no preservative. Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. Meruvax II, when reconstituted as directed, is clear yellow.
- Miacalcin® (calcitonin-salmon) injection is provided in sterile solution for IM injection. Each milliliter contains calcitonin-salmon 200 IU; acetic acid, USP, 2.25 mg; phenol, USP, 5.0 mg; sodium acetate trihydrate, USP, 2.0 mg; sodium chloride, USP, 7.5 mg; water for injection, USP, QS to 1.0 mL.
- Mirena® (levonorgestrel-releasing intrauterine system) consists of a T-shaped polyethylene frame (T-body) with a steroid reservoir (hormone elastomer core) around the vertical stem. The reservoir consists of a cylinder, made of a mixture of levonorgestrel and silicone (polydimethylsiloxane), containing a total of 52 mg levonorgestrel. The reservoir is covered by a silicone (polydimethylsiloxane) membrane. The T-body is 32 mm in both the horizontal and vertical directions. The polyethylene of the T-body is compounded with barium sulfate, which makes it radiopaque. A monofilament brown polyethylene removal thread is attached to a loop at the end of the vertical stem of the T-body. Mirena is packaged sterile within an inserter. The inserter, which is used for insertion of Mirena into the uterine cavity, consists of a symmetric two-sided body and slider that are integrated with flange, lock, prebent insertion tube, and plunger. Once Mirena is in place, the inserter is discarded.
- Mivacron (mivacurium chloride) is a sterile, nonpyrogenic solution (pH 3.5–5.0) containing mivacurium chloride equivalent to 2 mg/mL mivacurium in water for injection. Hydrochloric acid may have been added to adjust pH. Multiple-dose vials contain 0.9% w/v benzyl alcohol.
- M-M-R II (measles, mumps, and rubella virus vaccine live) is a live virus vaccine for vaccination against measles (rubella), mumps and rubella (German measles). M-M-R II is a sterile lyophilized preparation of (1) Attenuvax (measles virus vaccine live), (2) Mumpsvax (mumps virus vaccine live), and (3) Meruvax II (rubella virus vaccine live). The reconstituted vaccine is for SC administration. Each 0.5-mL dose contains not less than 1000 TCID 50 (tissue culture infectious doses) of measles virus; 20,000 TCID 50 of mumps virus; and 1000 TCID 50 of rubella virus. Each dose of the vaccine is calculated to contain sorbitol (14.5 mg), sodium phosphate, sucrose (1.9 mg), sodium chloride, hydrolyzed gelatin (14.5 mg), human albumin (0.3 mg), fetal bovine serum (<1 ppm), other buffer and media ingredients, and approximately 25 μg of neomycin. The product contains no preservative. Before reconstitution, the lyophilized vaccine is a light yellow compact crystalline plug. M-M-R II, when reconstituted as directed, is clear yellow.
- Mycamine is a sterile, lyophilized product for IV infusion that contains micafungin sodium. Each single-use vial contains 50 mg micafungin sodium, 200 mg lactose, with citric acid, and/or sodium hydroxide (used for pH adjustment). Mycamine must be diluted with 0.9% sodium chloride injection, USP, or 5% dextrose injection, USP. Following re-

constitution with 0.9% sodium chloride injection, USP, the resulting pH of the solution is between 5 and 7.

- Mylotarg® (gemtuzumab ozogamicin for injection) is a sterile, white, preservative-free lyophilized powder containing 5 mg of drug conjugate (protein equivalent) in an amber vial. The drug product is light sensitive and must be protected from direct and indirect sunlight and unshielded fluorescent light during the preparation and administration of the infusion. The inactive ingredients are dextran 40, sucrose, sodium chloride, monobasic and dibasic sodium phosphate.
- Nabi-HB hepatitis B immune globulin (human) is a sterile solution of immunoglobulin (5±1% protein) containing antibodies to hepatitis B surface antigen (anti-HBs). Nabi-HB is formulated in 0.075 M sodium chloride, 0.15 M glycine, and 0.01% polysorbate 80, at pH 6.2. The product is supplied as a nonturbid sterile liquid in single-dose vials and appears as clear to opalescent. It contains no preservative and is intended for single use by the IM route only.
- Naropin® injection contains ropivacaine HCl is preservative-free and is available in single-dose containers in 2.0 (0.2%), 5.0 (0.5%), 7.5 (0.75%) and 10.0 mg/mL (1.0%) concentrations. The specific gravity of Naropin injection solutions ranges from 1.002 to 1.005 at 25°C.
- Natrecor® (nesiritide) is a sterile, purified preparation of human B-type natriuretic peptide (hBNP) and is manufactured from *Escherichia coli* using recombinant DNA technology. Natrecor is formulated as the citrate salt of rhBNP and is provided in a sterile, single-use vial. Each 1.5-mg vial contains a white to off-white lyophilized powder for IV administration after reconstitution. The quantitative composition of the lyophilized drug per vial is the following: nesiritide, 1.58 mg; mannitol, 20.0 mg; citric acid monohydrate, 2.1 mg; and sodium citrate dihydrate, 2.94 mg.
- Navelbine (vinorelbine tartrate) injection is for IV administration. Each vial contains vinorelbine tartrate equivalent to 10 mg (1-mL vial) or 50 mg (5-mL vial) vinorelbine in water for injection. No preservatives or other additives are present. The aqueous solution is sterile and nonpyrogenic. The aqueous solubility is >1000 mg/mL in distilled water. The pH of Navelbine injection is approximately 3.5.
- Neulasta® (pegfilgrastim) supplied in 0.6-mL prefilled syringes for SC injection. Each syringe contains 6 mg pegfilgrastim (based on protein weight), in a sterile, clear, colorless, preservative-free solution (pH 4.0) containing acetate (0.35 mg), sorbitol (30.0 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.
- Neumega. Oprelvekin, the active ingredient in Neumega, is produced in *E. coli* by recombinant DNA technology. Neumega is formulated in single-use vials containing 5 mg of oprelvekin (specific activity approximately 8×10^6 U/mg) as a sterile, lyophilized powder with 23 mg glycine, USP, 1.6 mg dibasic sodium phosphate heptahydrate, USP, and 0.55 mg monobasic sodium phosphate monohydrate, USP. When reconstituted with 1 mL of sterile water for injection, USP, the resulting solution has a pH of 7.0 and a concentration of 5 mg/mL.
- Neupogen® Filgrastim is a sterile, clear, colorless, preservative-free liquid for parenteral administration containing Filgrastim at a specific activity of $1.0 \pm 0.6 \times 10^8$ U/mg (as measured by a cell mitogenesis assay). The product is available in single-use vials and prefilled syringes. The single-use vials contain either 300 or 480 μg filgrastim at a fill volume of 1.0 or 1.6 mL, respectively. The single-use prefilled syringes contain either 300 or 480 μg filgrastim at a fill volume of 0.5 or 0.8 mL, respectively. It contains acetate, 0.59/mg; sorbitol, 50 mg/mL; sodium, 0.035/mL; and Tween 80, 0.004%.
- Nexium® IV (esomeprazole sodium) for injection is supplied as a sterile, freeze-dried, white to off-white, porous cake or powder in a 5-mL vial, intended for IV administration after reconstitution with 0.9% sodium chloride injection, USP; lactated Ringer's injection, USP, or 5% dextrose injection, USP. Nexium IV for injection contains esomeprazole sodium, 21.3 or 42.5 mg; equivalent to esomeprazole, 20 or 40 mg; edetate disodium, 1.5 mg; and sodium hydroxide, QS for pH adjustment. The pH of reconstituted solution of Nexium IV for injection depends on the reconstitution volume and is in the pH range of 9 to 11. The stability of esomeprazole sodium in aqueous solution is strongly pH dependent. The rate of degradation increases with decreasing pH.
- Infasurf® (calfactant) intratracheal suspension is a sterile, nonpyrogenic lung surfactant intended for intratracheal instillation only. It is an extract of natural surfactant from calf lungs which includes phospholipids, neutral lipids, and hydrophobic surfactant-associated proteins B and C (SP-B and SP-C). It contains no preservatives. Infasurf is an off-white suspension of calfactant in 0.9% aqueous sodium chloride solution. It has a pH of 5.0 to 6.2 (target pH 5.7). Each milliliter of Infasurf contains 35 mg total phospholipids (including 26 mg phosphatidylcholine of which 16 mg is disaturated phosphatidylcholine) and 0.65 mg proteins including 0.26 mg of SP-B.
- Nimbex (cisatracurium besylate) injection is a sterile, nonpyrogenic aqueous solution provided in 5-, 10-, and 20-mL vials. The pH is adjusted to 3.25 to 3.65 with benzenesulfonic acid. The 5- and 10-mL vials each contain cisatracurium besylate, equivalent to 2 mg/mL cisatracurium. The 20-mL vial, intended for ICU use only, contains cisatracurium besylate, equivalent to 10 mg/mL cisatracurium. The 10-mL vial, intended for multiple-dose use, contains 0.9% benzyl alcohol as a preservative. The 5- and 20-mL vials are single-use vials and do not contain benzyl alcohol. Cisatracurium besylate slowly loses potency with time at a rate of approximately 5% per year under refrigeration (5°C).
- Nipent® (pentostatin for injection) is supplied as a sterile, apyrogenic, lyophilized powder in single-dose vials for IV administration. Each vial contains 10 mg of pentostain and 50 mg of mannitol, USP. The pH of the final product is maintained between 7.0 and 8.5 by addition of sodium hydroxide or hydrochloric acid.
- Norditropin® is the Novo Nordisk A/S registered trademark for somatropin, a polypeptide hormone of recombinant DNA origin. Norditropin cartridges are supplied as solutions in ready-to-administer cartridges or prefilled pens with a volume of 1.5 mL. Each Norditropin cartridge contains the following: somatropin, 5 mg/1.5 mL, 10 mg/1.5 mL, 15 mg/1.5 mL; histidine, 1, 1.7 mg; poloxamer 188, 4.5 mg; phenol, 4.5 mg; mannitol, 60 mg, 58 mg; HCl/NaOH, QS; water for injection, add 1.5 mL.
- Norflex. Orphenadrine citrate injection contains 60 mg of orphenadrine citrate in aqueous solution in each ampoule. Norflex injection also contains sodium bisulfite NF, 2.0 mg; sodium chloride, USP, 5.8 mg; sodium hydroxide, to adjust pH; and water for injection USP, QS to 2 mL.
- NovoLog® [insulin aspart (rDNA origin) injection] is a human insulin analog that is a rapid-acting parenteral blood glucose-lowering agent. NovoLog is a sterile, aqueous, clear, and colorless solution that contains insulin aspart (B28 asp regular human insulin analog), 100 U/mL;

glycerin, 16 mg/mL; phenol, 1.50 mg/mL; metacresol, 1.72 mg/mL; zinc, 19.6 μg/mL; disodium hydrogen phosphate dihydrate, 1.25 mg/mL; and sodium chloride, 0.58 mg/mL. NovoLog has a pH of 7.2 to 7.6. Hydrochloric acid 10% and/or sodium hydroxide 10% may be added to adjust pH.

- NovoLog Mix 70/30 [70% insulin aspart protamine suspension and 30% insulin aspart injection, (rDNA origin)] is a human insulin analog suspension containing 70% insulin aspart protamine crystals and 30% soluble insulin aspart. NovoLog Mix 70/30 is a uniform, white, sterile suspension that contains insulin aspart (B28 asp regular human insulin analog), 100 U/mL; mannitol, 36.4 mg/mL; phenol, 1.50 mg/mL; metacresol, 1.72 mg/mL; zinc, 19.6 μg/mL; disodium hydrogen phosphate dihydrate, 1.25 mg/mL; sodium chloride, 0.58 mg/mL; and protamine sulfate, 0.33 mg/mL. NovoLog Mix 70/30 has a pH of 7.20 to 7.44. Hydrochloric acid or sodium hydroxide may be added to adjust pH.
- NovoSeven® is recombinant human coagulation factor VIIa (rFVIIa). NovoSeven is supplied as a sterile, white lyophilized powder of rFVIIa in single-use vials. Each vial of lyophilized drug contains the following: 1.2 mg (60 KIU), 2.4 mg (120 KIU), 4.8 mg (240 KIU) corresponding to rFVIIa, 1200 μg, 2400 μg, 4800 μg respectively; sodium chloride—5.84 mg, 11.68 mg, 23.36 mg respectively; calcium chloride dehydrate—2.94 mg, 5.88 mg, 11.76 mg respectively; glycylglycine—2.64 mg, 5.28 mg, 10.56 mg respectively; polysorbate 80—0.14 mg, 0.28 mg, 0.56 mg respectively; and mannitol—60.0 mg, 120.0 mg, 240.0 mg respectively. After reconstitution with the appropriate volume of sterile water for injection, each vial contains approximately 0.6 mg/mL NovoSeven (corresponding to 600 μg/mL). The reconstituted vials have a pH of approximately 5.5 in sodium chloride (3 mg/mL), calcium chloride dihydrate (1.5 mg/mL), glycylglycine (1.3 mg/mL), polysorbate 80 (0.1 mg/mL), and mannitol (30 mg/mL). The reconstituted product is a clear, colorless solution which contains no preservatives.
- Nutropin (hGh) is a sterile, white, lyophilized powder intended for SC administration after reconstitution with bacteriostatic water for injection, USP (benzyl alcohol preserved). The reconstituted product is nearly isotonic at a concentration of 5 mg/mL growth hormone (GH) and has a pH of approximately 7.4. Each 5-mg Nutropin vial contains 5 mg (approximately 15 IU) somatropin, lyophilized with 45 mg mannitol, 1.7 mg sodium phosphates (0.4 mg sodium phosphate monobasic and 1.3 mg sodium phosphate dibasic), and 1.7 mg glycine. Each 10-mg Nutropin vial contains 10 mg (approximately 30 IU) somatropin, lyophilized with 90 mg mannitol, 3.4 mg sodium phosphates (0.8 mg sodium phosphate monobasic and 2.6 mg sodium phosphate dibasic), and 3.4 mg glycine. Bacteriostatic water for injection, USP, is sterile water containing 0.9% benzyl alcohol per milliliter as an antimicrobial preservative packaged in a multidose vial. The diluent pH is 4.5 to 7.0.
- Nutropin AQ is a human growth hormone (hGH) produced by recombinant DNA technology. Nutropin AQ is a sterile liquid intended for SC administration. The product is nearly isotonic at a concentration of 5 mg of GH/mL and has a pH of approximately 6. The Nutropin AQ, 2-mL vial, contains 10 mg (approximately 30 IU) somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate. The Nutropin AQ 2-mL pen cartridge contains 10 mg (approximately 30 IU) somatropin, formulated in 17.4 mg sodium chloride, 5 mg phenol, 4 mg polysorbate 20, and 10 mM sodium citrate.
- Ontak® (denileukin diftitox) is supplied in single use vials as a sterile, frozen solution intended for IV administration. Each 2-mL vial of Ontak contains 300 μg of recombinant denileukin diftitox in a sterile solution of citric acid (20 mM), EDTA (0.05 mM), and polysorbate 20 (<1%) in water for injection, USP. The solution has a pH of 6.9 to 7.2.
- Optipranolol® (metipranolol ophthalmic solution), 0.3%, contains metipranolol. Each milliliter of Optipranolol contains 3 mg metipranolol. Inactives: povidone, glycerin, hydrochloric acid, sodium chloride, edetate disodium, and purified water. Sodium hydroxide and/or hydrochloric acid may be added to adjust pH. Preservative: Benzalkonium chloride, 0.004%.
- Optivar® (azelastine hydrochloride ophthalmic solution), 0.05%, is a sterile ophthalmic solution containing azelastine hydrochloride. Each milliliter of Optivar contains the following: active—0.5 mg azelastine hydrochloride, equivalent to 0.457 mg of azelastine base; preservative—0.125 mg benzalkonium chloride; inactives—disodium edetate dihydrate, hydroxypropylmethylcellulose, sorbitol solution, sodium hydroxide, and water for injection. It has a pH of approximately 5.0 to 6.5 and an osmolality of approximately 271 to 312 mOsm/L.
- Orthovisc® is a sterile, nonpyrogenic, clear, viscoelastic solution of hyaluronan contained in a single-use syringe. Orthovisc consists of high molecular weight (1.0–2.9 million Da), ultrapure natural hyaluronan dissolved in physiological saline. Hyaluronan is a natural complex sugar of the glycosaminoglycan family. The hyaluronan is extracted from chicken combs.
- Panhematin (hemin for injection) is a sterile, lyophilized powder suitable for IV administration after reconstitution. Each dispensing vial of Panhematin contains the equivalent of 313 mg hemin, 215 mg sodium carbonate, and 300 mg of sorbitol. The pH may have been adjusted with hydrochloric acid; the product contains no preservatives. When mixed as directed with sterile water for injection, USP, each 43 mL provides the equivalent of approximately 301 mg hematin (7 mg/mL).
- Patanol (olopatadine hydrochloride ophthalmic solution), 0.1%, is a sterile ophthalmic solution containing olopatadine. Each milliliter of Patanol contains active: 1.11 mg olopatadine hydrochloride equivalent to 1 mg olopatadine; preservative: benzalkonium chloride 0.01%; inactives: dibasic sodium phosphate, sodium chloride, hydrochloric acid/sodium hydroxide (adjust pH), and purified water. It has a pH of approximately 7 and an osmolality of approximately 300 mOsm/kg.
- Pediarix® [diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant) and inactivated poliovirus vaccine combined] is a noninfectious, sterile, multivalent vaccine. Each 0.5-mL dose also contains 2.5 mg of 2-phenoxyethanol as a preservative, 4.5 mg of NaCl, and aluminum adjuvant (not more than 0.85 mg aluminum by assay). Each dose also contains ≤100 μg of residual formaldehyde and ≤100 μg of polysorbate 80 (Tween 80). Thimerosal is used at the early stages of manufacture and is removed by subsequent purification steps to below the analytical limit of detection (<25 ng of mercury/20 μg HBsAg) which upon calculation is <12.5 ng mercury/dose. Neomycin sulfate and polymyxin B are used in the polio vaccine manufacturing process and may be present in the final vaccine at ≤0.05 ng neomycin and ≤0.01 ng polymyxin B/dose. The procedures used to manufacture

the HBsAg antigen result in a product that contains ≤5% yeast protein.

- PEG-Intron®, peginterferon alpha-2b, powder for injection is a covalent conjugate of recombinant alpha-2b interferon with monomethoxy polyethylene glycol (PEG). PEG-Intron is supplied in both vial and the Redipen® for SC use. Vials: Each vial contains either 74, 118.4, 177.6, or 222 μg of PEG-Intron as a white to off-white tablet-like solid, that is whole/in pieces or as a loose powder, and 1.11 mg dibasic sodium phosphate anhydrous, 1.11 mg monobasic sodium phosphate dihydrate, 59.2 mg sucrose, and 0.074 mg polysorbate 80. Following reconstitution with 0.7 mL of the supplied sterile water for injection, USP, each vial contains PEG-Intron at strengths of either 50 μg/0.5 mL, 80 μg/0.5 mL, 120 μg/0.5 mL, or 150 μg/0.5 mL.
- Redipen is a dual-chamber glass cartridge containing lyophilized PEG-Intron as a white to off-white tablet or powder that is whole or in pieces in the sterile active chamber and a second chamber containing sterile water for injection, USP. Each PEG-Intron Redipen contains either 67.5, 108, 162, or 202.5 μg of PEG-Intron, and 1.013 mg dibasic sodium phosphate anhydrous, 1.013 mg monobasic sodium phosphate dihydrate, 54 mg sucrose, and 0.0675 mg polysorbate 80. Each cartridge is reconstituted to allow for the administration of up to 0.5 mL of solution. Following reconstitution, each Redipen contains PEG-Intron at strengths of either 50 μg/0.5 mL, 80 μg/0.5 mL, 120 μg/0.5 mL, or 150 μg/0.5 mL for single use. Because a small volume of reconstituted solution is lost during preparation of PEG-Intron, each Redipen contains an excess amount of PEG-Intron powder and diluent to ensure delivery of the labeled dose.
- Plasbumin-25, albumin (human) 25%, USP (Plasbumin-25), is a 25% sterile solution of albumin in an aqueous diluent. The preparation is stabilized with 0.02 M sodium caprylate and 0.02 M acetyltryptophan. The aluminum content of the product is not more than 200 μg/L. The approximate sodium content of the product is 145 mEq/L. It contains no preservative. Plasbumin-25 must be administered intravenously. Each vial of Plasbumin-25 is heat-treated at 60°C for 10 hours against the possibility of transmitting the hepatitis viruses. Albumin (human) 5%, USP (Plasbumin®-5) is a 5% sterile solution of albumin in an aqueous diluent. The preparation is stabilized with 0.004 M sodium caprylate and 0.004 M acetyltryptophan. The aluminum content of the product is not more than 200 μg/L. The approximate sodium content of the product is 145 mEq/L. It contains no preservative. Plasbumin-5 must be administered intravenously. Each vial of Plasbumin-5 is heat-treated at 60°C for 10 hours against the possibility of transmitting the hepatitis viruses.
- Plasmanate. Each 100 mL of plasma protein fraction (human) 5%, USP–Plasmanate® contains 5 g selected plasma proteins buffered with sodium carbonate and stabilized with 0.004 M sodium caprylate and 0.004 M acetyltryptophan. The plasma proteins consist of approximately 88% normal human albumin, 12% alpha- and beta-globulins and not more than 1% gamma-globulin as determined by electrophoresis. The concentration of these proteins is such that this solution is isooncotic with normal human plasma and is isotonic. The approximate concentrations of the significant electrolytes in Plasmanate are sodium, 145 mEq/L; potassium, 0.25 mEq/L; and chloride, 100 mEq/L. Plasmanate must be administered intravenously. This product is designed to bring to the medical profession a preparation derived from human blood and similar to human plasma. Each vial of Plasmanate is sterile and heat-treated at 60°C for 10 hours against the possibility of transmitting the hepatitis viruses.
- Premarin® intravenous (conjugated estrogens, USP) for injection contains a mixture of conjugated estrogens obtained exclusively from natural sources, occurring as the sodium salts of water-soluble estrogen sulfates blended to represent the average composition of materials derived from pregnant mares' urine. It is a mixture of sodium estrone sulfate and sodium equilin sulfate. It contains as concomitant components, as sodium sulfate conjugates, 17-alpha-dihydroequilin, 17-alpha-estradiol, and 17-beta-dihydroequilin. Each Secule® vial contains 25 mg of conjugated estrogens, USP, in a sterile lyophilized cake which also contains lactose, 200 mg; sodium citrate, 12.2 mg; and simethicone, 0.2 mg. The pH is adjusted with sodium hydroxide or hydrochloric acid. A sterile diluent (5 mL) containing 2% benzyl alcohol in sterile water is provided for reconstitution. The reconstituted solution is suitable for IV or IM injection.
- Prevnar®, pneumococcal 7-valent conjugate vaccine (diphtheria CRM 197 protein), is manufactured as a liquid preparation. Each 0.5-mL dose is formulated to contain 2 μg of each saccharide for serotypes 4, 9V, 14, 18C, 19F, and 23F, and 4 μg of serotype 6B per dose (16 μg total saccharide); approximately 20 μg of CRM 197 carrier protein; and 0.125 mg of aluminum/0.5-mL dose as aluminum phosphate adjuvant.
- Prograf (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL contains polyoxyl 60 hydrogenated castor oil, 200 mg, and dehydrated alcohol, USP, 80.0% v/v. Prograf injection must be diluted with 0.9% sodium chloride injection or 5% dextrose injection before use.
- Prolastin®, alpha-1 proteinase inhibitor (human), is a sterile, stable, lyophilized preparation of purified human alpha-1 proteinase inhibitor (alpha-1 PI). When reconstituted, Prolastin has a pH of 6.6 to 7.4, a sodium content of 100 to 210 mEq/L, a chloride content of 60 to 180 mEq/L, a sodium phosphate content of 0.015 to 0.025 M, a polyethylene glycol content of not more than (NMT) 5 ppm, and NMT 0.1% sucrose.
- Prolastin, each vial of Prolastin contains the labeled amount of functionally active alpha-1–PI in milligrams per vial (mg/vial). Prolastin contains no preservative and must be administered by the IV route. The specific activity of Prolastin is ≥0.35 mg functional alpha-1–PI/mg protein and when reconstituted as directed, the concentration of alpha-1–PI is ≥20 mg/mL. When reconstituted, Prolastin has a pH of 6.6 to 7.4, a sodium content of 100 to 210 mEq/L, a chloride content of 60 to 180 mEq/L, a sodium phosphate content of 0.015 to 0.025 M, a polyethylene glycol content of NMT 5 ppm, and NMT 0.1% sucrose. Prolastin contains small amounts of other plasma proteins including alpha-2 plasmin inhibitor, alpha-1 antichymotrypsin, C 1-esterase inhibitor, haptoglobin, antithrombin III, alpha-1 lipoprotein, albumin, and IgA.
- Proleukin® (aldesleukin) for injection is a sterile, white to off-white, lyophilized cake in single-use vials intended for IV administration. When reconstituted with 1.2 mL sterile water for injection, USP, each milliliter contains 18 million IU (1.1 mg) Proleukin, 50 mg mannitol, and 0.18 mg sodium dodecyl sulfate, buffered with approximately 0.17 mg monobasic and 0.89 mg dibasic sodium phosphate to a pH of 7.5 (range 7.2–7.8). The manufacturing process for Proleukin involves fermentation in a defined medium con-

taining tetracycline hydrochloride. The presence of the antibiotic is not detectable in the final product. Proleukin contains no preservatives in the final product.

- Pulmicort Respules sterile suspension for inhalation via jet nebulizer and contains the active ingredient budesonide (micronized) and the inactive ingredients disodium edetate, sodium chloride, sodium citrate, citric acid, polysorbate 80, and water for injection. Two dose strengths are available in single-dose ampoules (Respules™ ampoules): 0.25 mg and 0.5 mg/2 mL Respule ampoule.
- Pulmozyme® (dornase alpha) inhalation solution is a sterile, clear, colorless, highly purified solution of recombinant human deoxyribonuclease I (rhDNase), an enzyme which selectively cleaves DNA. Each Pulmozyme single-use ampoule will deliver 2.5 mL of the solution to the nebulizer bowl. The aqueous solution contains 1.0 mg/mL dornase alpha, 0.15 mg/mL calcium chloride dihydrate and 8.77 mg/mL sodium chloride. The solution contains no preservative. The nominal pH of the solution is 6.3.
- Quixin® (levofloxacin ophthalmic solution) ,0.5%, is a sterile topical ophthalmic solution. Each milliliter of Quixin contains 5.12 mg of levofloxacin hemihydrate equivalent to 5 mg levofloxacin. Active: levofloxacin, 0.5% (5 mg/mL); preservative: benzalkonium chloride, 0.005%; inactives: sodium chloride and water. May also contain hydrochloric acid and/or sodium hydroxide to adjust pH. Quixin solution is isotonic and formulated at pH 6.5 with an osmolality of approximately 300 mOsm/kg. Levofloxacin is a fluorinated 4-quinolone containing a six-member (pyridobenzoxazine) ring from positions 1 to 8 of the basic ring structure.
- RabAvert® rabies vaccine is a sterile freeze-dried vaccine obtained by growing the fixed-virus strain flury LEP in primary cultures of chicken fibroblasts. The vaccine is lyophilized after addition of a stabilizer solution which consists of buffered polygeline and potassium glutamate. One dose of reconstituted vaccine contains less than 12 mg polygeline (processed bovine gelatin), less than 0.3 mg human serum albumin, 1 mg potassium glutamate, and 0.3 mg sodium EDTA. Small quantities of bovine serum are used in the cell culture process. RabAvert is intended for IM injection. The vaccine contains no preservative and should be used immediately after reconstitution with the supplied Sterile Diluent for RabAvert (water for injection). RabAvert is a white, freeze-dried vaccine for reconstitution with the diluent prior to use; the reconstituted vaccine is a clear to slightly opaque, colorless suspension.
- Raptiva® (efalizumab) is supplied as a sterile, white to off-white, lyophilized powder in single-use glass vials for SC injection. Reconstitution of the single-use vial with 1.3 mL of the supplied sterile water for injection (non-USP) yields approximately 1.5 mL of solution to deliver 125 mg/1.25 mL (100 mg/mL) of Raptiva. The sterile water for injection supplied does not comply with USP requirement for pH. After reconstitution, Raptiva is a clear to pale yellow solution with a pH of approximately 6.2. Each single-use vial of Raptiva contains 150 mg of efalizumab, 123.2 mg of sucrose, 6.8 mg of L-histidine hydrochloride monohydrate, 4.3 mg of L-histidine, and 3 mg of polysorbate 20 and is designed to deliver 125 mg of efalizumab in 1.25 mL.
- Recombinate, antihemophilic factor (recombinant, rAHF), is formulated as a sterile, nonpyrogenic, off-white to faint yellow, lyophilized powder preparation of concentrated recombinant AHF for IV injection. Recombinate (rAHF) is available in single-dose bottles which contain nominally 250, 500, and 1000 IU/bottle. When reconstituted with the appropriate volume of diluent, the product contains the following stabilizers in maximum amounts: 12.5 mg/mL albumin (human), 0.20 mg/mL calcium, 1.5 mg/mL polyethylene glycol (3350), 180 mEq/L sodium, 55 mM histidine, 1.5 μg/AHF IU polysorbate-80. Von Willebrand Factor (vWF) is coexpressed with the antihemophilic factor (recombinant) and helps to stabilize it. The final product contains not more than 2 ng vWF/IU rAHF which will not have any clinically relevant effect in patients with von Willebrand's disease. The product contains no preservative.
- Refludan [lepirudin (rDNA) for injection] is supplied as a sterile, white, freeze-dried powder for injection or infusion and is freely soluble in sterile water for injection USP or 0.9% sodium chloride injection USP. Each vial of Refludan contains 50 mg lepirudin. Other ingredients are 40 mg mannitol and sodium hydroxide for adjustment of pH to approximately 7.
- Remicade is a chimeric IgG1-kappa monoclonal antibody supplied as a sterile, white, lyophilized powder for IV infusion. Following reconstitution with 10 mL of sterile water for injection, USP, the resulting pH is approximately 7.2. Each single-use vial contains 100 mg infliximab, 500 mg sucrose, 0.5 mg polysorbate 80, 2.2 mg monobasic sodium phosphate, monohydrate, and 6.1 mg dibasic sodium phosphate, dihydrate. No preservatives are present.
- Repliva 21/7™ tablets for oral administration provide 28-day iron supplement therapy. Each red film-coated tablet contains Iron Ferrochel® (elemental iron), 70 mg; ferrous fumarate (elemental iron), 81 mg; succinic acid, 150 mg; vitamin C (ascorbic acid), 140 mg; vitamin C as Ester-C®; ascorbic acid (as calcium ascorbate), 60 mg; threonic acid (as calcium threonate), 0.8 mg; folic acid USP, 1 mg; vitamin B_{12} (cyanocobalamin), 10 μg; inactive ingredients: citric acid, croscarmellose sodium, FD&C red No. 40 aluminum lake, FD&C yellow No. 6 aluminum lake, fumed silica, hypromellose, lactose monohydrate, lecithin, magnesium stearate, maltodextrin, microcrystalline cellulose, polydextrose, polyethylene glycol, polyvinyl alcohol, povidone, silicon dioxide, sodium benzoate, sodium citrate, sorbic acid, starch, talc, titanium dioxide, triacetin. Each purple film-coated tablet contains inert ingredients: croscarmellose sodium, D&C red No. 27 aluminum lake, FD&C blue No. 1 aluminum lake, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, silicon dioxide, stearic acid, talc, titanium dioxide.
- Repronex® (menotropins for injection, USP) is a purified preparation of gonadotropins extracted from the urine of postmenopausal women. Each vial of Repronex contains 75 or 150 IU of follicle-stimulating hormone (FSH) activity and 75 or 150 IU of luteinizing hormone (LH) activity, respectively, plus 20 mg lactose monohydrate in a sterile, lyophilized form. The final product may contain sodium phosphate buffer (sodium phosphate tribasic and phosphoric acid).
- Retisert™ (fluocinolone acetonide intravitreal implant), 0.59 mg, is a sterile implant designed to release fluocinolone acetonide locally to the posterior segment of the eye at a nominal initial rate of 0.6 μg/day, decreasing over the first month to a steady state between 0.3 and 0.4 μg/day over approximately 30 months. Retisert consists of a tablet containing 0.59 mg of the active ingredient,

fluocinolone acetonide, USP, and the following inactives: microcrystalline cellulose, polyvinyl alcohol, and magnesium stearate.

- Retrovir (zidovudine) IV infusion is a sterile solution for IV infusion only. Each milliliter contains 10 mg zidovudine in water for injection. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH to approximately 5.5. Retrovir IV Infusion contains no preservatives.
- Rev-Eyes™ (dapiprazole hydrochloride ophthalmic solution) ophthalmic eye drops is a clear, colorless, slightly viscous solution for topical application. Each milliliter (when reconstituted as directed) contains 5 mg of dapiprazole hydrochloride as the active ingredient. The reconstituted solution has a pH of approximately 6.6 and an osmolarity of approximately 415 mOsm. The inactive ingredients include mannitol (2%), sodium chloride, hydroxypropyl methylcellulose (0.4%), edetate sodium (0.01%), sodium phosphate dibasic, sodium phosphate monobasic, water for injection, and benzalkonium chloride (0.01%) as a preservative. Rev-Eyes ophthalmic eye drops, 0.5%, is supplied in a kit consisting of one vial of dapiprazole hydrochloride (25 mg), one vial of diluent (5 mL), and one dropper for dispensing.
- Rho (D) immune globulin (human)—Hyper RHO™ S/D full dose treated with solvent/detergent is a sterile solution of immune globulin containing antibodies to Rho (D) for IM administration; it contains no preservative. The fraction II solution is adjusted to a final concentration of 0.3% tri-*n*-butyl phosphate (TNBP) and 0.2% sodium cholate. After the addition of solvent (TNBP) and detergent (sodium cholate), the solution is heated to 30°C and maintained at that temperature for not less than 6 hours. Hyper RHO S/D Full Dose is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Hyper RHO S/D full dose is then incubated in the final container for 21 to 28 days at 20°C to 27°C. The potency is equal to or greater than 1500 IU. Hyper RHO S/D mini dose is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. The quantity of Rho (D) antibody in Hyper RHO S/D mini dose is not less than 250 IU.
- Rhophylac® contains a maximum of 30 mg/mL of human plasma proteins of which 10 mg/mL is human albumin, which is added as a stabilizer. Prior to the addition of the stabilizer, the product purity is greater than 95% IgG. The product contains less than 5 μg/mL IgA. Additional excipients are approximately 20 mg/mL of glycine and up to 0.25 M sodium chloride. Rhophylac contains no preservative.
- Rhophylac is a sterile Rho (D) immune globulin intravenous (human) solution in a prefilled, ready-to-use syringe for either IV or IM injection. One syringe contains at least 1500 IU (300 μg) of IgG antibodies to Rho (D) in a 2-mL solution. The manufacturing process includes a solvent detergent (S/D) treatment step (using tri-*n*-butyl phosphate and Triton X-100) that is effective in inactivating enveloped viruses such as HBV, HCV, and HIV.
- Rituxan® (rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and water for injection. The pH is adjusted to 6.5.
- Rozerem™ (ramelteon) tablet includes the following inactive ingredients: lactose monohydrate, starch, hydroxypropyl cellulose, magnesium stearate, hypromellose, copovidone, titanium dioxide, yellow ferric oxide, polyethylene glycol 8000, and ink containing shellac and synthetic iron oxide black.
- Sandimmune® injection (cyclosporine injection, USP) is available in a 5-mL sterile ampoule for IV administration. Each milliliter contains cyclosporine USP, 50 mg; Cremophor EL (polyoxyethylated castor oil), 650 mg; alcohol, 32.9% by volume; nitrogen, QS, which must be diluted further with 0.9% sodium chloride injection or 5% dextrose injection before use.
- Sandostatin® (octreotide acetate) injection, a cyclic octapeptide prepared as a clear sterile solution of octreotide, acetate salt, in a buffered lactic acid solution for administration by deep SC (intrafat) or IV injection. Sandostatin (octreotide acetate) injection is available as sterile 1-mL ampoules in three strengths, containing 50, 100, or 500 μg octreotide (as acetate) and sterile 5-mL multidose vials in two strengths, containing 200 and 1000 μg/mL of octreotide (as acetate). Each ampoule also contains lactic acid, USP, 3.4 mg; mannitol, USP, 45 mg; sodium bicarbonate, USP, QS to pH 4.2±0.3; water for injection, USP, QS to 1 mL. Each milliliter of the multidose vials also contains lactic acid, USP, 3.4 mg; mannitol, USP, 45 mg; phenol, USP, 5.0 mg; sodium bicarbonate, USP, QS to pH 4.2±0.3; water for injection, USP, QS to 1 mL.
- Sandostatin LAR® depot. Octreotide is the acetate salt of a cyclic octapeptide. Sandostatin LAR depot (octreotide acetate for injectable suspension) is available in a vial containing the sterile drug product, which when mixed with diluent, becomes a suspension that is given as a monthly intragluteal injection. The octreotide is uniformly distributed within the microspheres which are made of a biodegradable glucose star polymer, D,L-lactic and glycolic acids copolymer. Sterile mannitol is added to the microspheres to improve suspendability. Sandostatin LAR depot is available as sterile 5-mL vials in three strengths delivering 10, 20, or 30 mg octreotide free peptide. Each vial of Sandostatin LAR depot contains octreotide acetate, 11.2 mg, 22.4 mg, 33.6 mg; D,L-lactic and glycolic acids copolymer, 188.8 mg, 377.6 mg, 566.4 mg; mannitol, 41.0 mg, 81.9 mg, 122.9 mg. Each syringe of diluent contains carboxymethylcellulose sodium, 12.5 mg; mannitol, 15.0 mg, water for injection, 2.5 mL.
- Simulect® (basiliximab) is a sterile lyophilisate which is available in 6-mL colorless glass vials and is available in 10- and 20-mg strengths. Each 10-mg vial contains 10 mg basiliximab, 3.61 mg monobasic potassium phosphate, 0.50 mg disodium hydrogen phosphate (anhydrous), 0.80 mg sodium chloride, 10 mg sucrose, 40 mg mannitol, and 20 mg glycine, to be reconstituted in 2.5 mL of sterile water for injection, USP. No preservatives are added. Each 20-mg vial contains 20 mg basiliximab, 7.21 mg monobasic potassium phosphate, 0.99 mg disodium hydrogen phosphate (anhydrous), 1.61 mg sodium chloride, 20 mg sucrose, 80 mg mannitol and 40 mg glycine to be reconstituted in 5 mL of sterile water for injection, USP. No preservatives are added.
- Symlin® (pramlintide acetate) injection is formulated as a clear, isotonic, sterile solution for SC administration. Symlin vials contain 0.6 mg/mL of pramlintide (as acetate),

2.25 mg/mL of metacresol as a preservative, D-mannitol as a tonicity modifier, and acetic acid and sodium acetate as pH modifiers. Symlin has a pH of approximately 4.0.

- Synagis® is available in two formulations: a lyophilized powder and a liquid solution. Lyophilized powder: Synagis is supplied as a sterile lyophilized product for reconstitution with sterile water for injection. Reconstituted Synagis (100 mg/mL) is to be administered by IM injection only. The reconstituted solution should appear clear or slightly opalescent with pH of 6.0. Each 100-mg single-use vial of Synagis lyophilized powder is formulated in 67.5 mg of mannitol, 8.7 mg histidine, and 0.3 mg of glycine and is designed to deliver 100 mg of Synagis in 1 mL when reconstituted with 1 mL of sterile water for injection. Each 50-mg single-use vial of Synagis lyophilized powder is formulated in 40.5 mg mannitol, 5.2 mg of histidine, and 0.2 mg of glycine and is designed to deliver 50 mg of Synagis in 0.5 mL, when reconstituted with 0.6 mL of sterile water for injection. Liquid solution: Synagis (100 mg/mL) is supplied as a sterile, preservative-free solution to be administered by IM injection only. The solution should appear clear or slightly opalescent with pH of 6.0. Each 100-mg single-use vial of Synagis liquid solution is formulated in 4.7 mg of histidine and 0.1 mg of glycine in a volume of 1.2 mL and is designed to deliver 100 mg of Synagis in 1 mL. Each 50-mg single-use vial of Synagis liquid solution is formulated in 2.7 mg of histidine and 0.08 mg of glycine in a volume of 0.7 mL and is designed to deliver 50 mg of Synagis in 0.5 mL.
- Systane®. Active ingredients: polyethylene glycol 400, 0.4%, and propylene glycol, 0.3%, as lubricants. Inactive ingredients: boric acid, calcium chloride, hydroxypropyl guar, magnesium chloride, polyquaternium-1 as a preservative, potassium chloride, purified water, sodium chloride, zinc chloride.
- Tenecteplase is a tissue plasminogen activator (tPA) produced by recombinant DNA technology using an established mammalian cell line (Chinese hamster ovary cells). TNKase is a sterile, white to off-white, lyophilized powder for single IV bolus administration after reconstitution with sterile water for injection (SWFI), USP. Each vial of TNKase nominally contains 52.5 mg tenecteplase, 0.55 g L-arginine, 0.17 g phosphoric acid, and 4.3 mg polysorbate 20, which includes a 5% overfill. Each vial will deliver 50 mg of tenecteplase.
- Tenormin® (atenolol) for parenteral administration is available as Tenormin IV injection containing 5 mg atenolol in 10 mL sterile, isotonic, citrate-buffered, aqueous solution. The pH of the solution is 5.5 to 6.5. Inactive ingredients: sodium chloride for isotonicity, and citric acid and sodium hydroxide to adjust pH.
- Tetanus immune globulin (human) – Hyper TET™ S/D treated with solvent/detergent is a sterile solution of tetanus hyperimmune immune globulin for IM administration; it contains no preservative. Hyper TET S/D is formulated as a 15% to 18% protein solution at a pH of 6.4 to 7.2 in 0.21 to 0.32 M glycine. Hyper TET S/D is then incubated in the final container for 21 to 28 days at 20°C to 27°C. The product is standardized against the US standard antitoxin and the U.S. control tetanus toxin and contains not less than 250 tetanus antitoxin units per container.
- Tev-Tropin™ (somatropin, rDNA origin, for injection) is a sterile, white, lyophilized powder, intended for SC administration, after reconstitution with bacteriostatic 0.9% sodium chloride injection, USP, (normal saline) (benzyl alcohol preserved). The quantitative composition of the lyophilized drug per vial is 5 mg (15 IU) vial: somatropin, 5 mg (15 IU); mannitol, 30 mg. The diluent contains bacteriostatic 0.9% sodium chloride injection, USP, (normal saline), 0.9% benzyl alcohol as a preservative, and water for injection. A 5-mL vial of the diluent will be supplied with each dispensed vial of Tev-Tropin. Tev-Tropin is a highly-purified preparation. Reconstituted solutions have a pH in the range of 7.0 to 9.0.
- The Bexxar therapeutic regimen (tositumomab and iodine I 131 tositumomab) is an antineoplastic radioimmunotherapeutic monoclonal antibody-based regimen composed of the monoclonal antibody, Tositumomab, and the radiolabeled monoclonal antibody, iodine I 131 tositumomab. Tositumomab is supplied as a sterile, pyrogen-free, clear to opalescent, colorless to slightly yellow, preservative-free liquid concentrate. It is supplied at a nominal concentration of 14 mg/mL tositumomab in 35- and 225-mg single-use vials. The formulation contains 10% (w/v) maltose, 145 mM sodium chloride, 10 mM phosphate, and water for injection, USP. The pH is approximately 7.2. iodine I 131 tositumomab is supplied as a sterile, clear, preservative-free liquid for IV administration. The dosimetric dosage form is supplied at nominal protein and activity concentrations of 0.1 mg/mL and 0.61 mCi/mL (at date of calibration), respectively. The therapeutic dosage form is supplied at nominal protein and activity concentrations of 1.1 mg/mL and 5.6 mCi/mL (at date of calibration), respectively. The formulation for the dosimetric and the therapeutic dosage forms contains 4.4 to 6.6% (w/v) povidone, 1 to 2 mg/mL maltose (dosimetric dose) or 9 to 15 mg/mL maltose (therapeutic dose), 0.85 to 0.95 mg/mL sodium chloride, and 0.9 to 1.3 mg/mL ascorbic acid. The pH is approximately 7.0.
- Rituxan (Rituximab) antibody, a genetically engineered chimeric murine/human monoclonal antibody, is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and water for injection. The pH is adjusted to 6.5.
- Thrombate III®, antithrombin III (human), is a sterile, nonpyrogenic, stable, lyophilized preparation of purified human antithrombin III. When reconstituted with sterile water for injection, USP, thrombate III has a pH of 6.0 to 7.5, a sodium content of 110 to 210 mEq/L, a chloride content of 110 to 210 mEq/L, an alanine content of 0.075 to 0.125 M, and a heparin content of not more than 0.004 U/IU AT-III. Thrombate III contains no preservative and must be administered by the IV route. In addition, thrombate III has been heat-treated in solution at 60°C±0.5°C for not less than 10 hours. Each vial of thrombate III contains the labeled amount of antithrombin III in international units per vial. The potency assignment has been determined with a standard calibrated against a World Health Organization (WHO) antithrombin III reference preparation.
- Tobi® is a tobramycin solution for inhalation. It is a sterile, clear, slightly yellow, nonpyrogenic aqueous solution with the pH and salinity adjusted specifically for administration by a compressed air-driven reusable nebulizer. Each single-use 5-mL ampoule contains 300 mg tobramycin and 11.25 mg sodium chloride in sterile water for injection. Sulfuric acid and sodium hydroxide are added to adjust the pH to 6.0. Nitrogen is used for sparging.

- Tobradex® (tobramycin and dexamethasone ophthalmic ointment) is a sterile, multiple-dose antibiotic and steroid combination for topical ophthalmic use. Each gram of Tobradex (tobramycin and dexamethasone ophthalmic ointment) contains the following: actives—tobramycin, 0.3%, (3 mg) and dexamethasone, 0.1% (1 mg); preservative—chlorobutanol, 0.5%; inactives—mineral oil and white petrolatum.
- Tobradex (tobramycin and dexamethasone ophthalmic suspension) suspension contains actives—tobramycin, 0.3% (3 mg), and dexamethasone, 0.1% (1 mg). Preservative: benzalkonium chloride, 0.01%. Inactives: tyloxapol, edetate disodium, sodium chloride, hydroxyethyl cellulose, sodium sulfate, sulfuric acid and/or sodium hydroxide (to adjust pH), and purified water.
- Trasylol® (aprotinin injection is supplied as a clear, colorless, sterile isotonic solution for IV administration. Each milliliter contains 10,000 KIU (Kallikrein inhibitor units) (1.4 mg/mL) and 9 mg sodium chloride in water for injection. Hydrochloric acid and/or sodium hydroxide is used to adjust the pH to 4.5 to 6.5.
- Traumeel® injection solution is officially classified as a homeopathic combination remedy. (1) Botanical ingredients: *Arnica montana*, radix (mountain arnica); *Calendula officinalis* (marigold); *Hamamelis virginiana* (witch hazel); Millefolium (milfoil); *Belladonna* (deadly nightshade); *Aconitum napellus* (monkshood); Chamomilla (chamomile); *Symphytum officinale* (comfrey); *Bellis perennis* (daisy); *Echinacea angustifolia* (narrow-leafed cone flower); *Echinacea purpurea* (purple cone flower); *Hypericum perforatum* (St. John's wort). (2) Mineral ingredients: Hepar sulphuris calcareum (calcium sulfide). Injection solution: each 2-mL ampoule contains as active ingredients Hepar sulphuris calcareum 8X. 200.0 μL; *Belladonna* 3X, 20.0 μL; *Calendula officinalis* 3X, 20.0 μL; Chamomilla 4X, 20.0 μL; Millefolium 4X, 20.0 μL; *Aconitum napellus* 3X, 12.0 μL; *Bellis perennis* 3X, 10.0 μL; *Hypericum perforatum* 3X, 6.0 μL; *E. angustifolia* 3X, 5.0 μL; *E. purpurea* 3X, 5.0 μL; *Arnica montana*, radix 2X, 2.0 μL; *Hamamelis virginiana* 2X, 2.0 μL; *Symphytum officinale* 6X, 2.0 μL. Each 2-mL ampoule contains as an inactive ingredient—sterile isotonic sodium chloride solution.
- Travoprost is a synthetic prostaglandin F 2(alpha) analogue. Travatan® ophthalmic solution, 0.004%, is supplied as sterile, buffered aqueous solution of travoprost with a pH of approximately 6.0 and an osmolality of approximately 290 mOsm/kg. Each milliliter of Travatan ophthalmic solution, 0.004%, contains 40 μg travoprost. Benzalkonium chloride, 0.015%, is added as a preservative. Inactive ingredients are polyoxyl-40 hydrogenated castor oil, tromethamine, boric acid, mannitol, edetate disodium, sodium hydroxide and/or hydrochloric acid (to adjust pH), and purified water.
- Trelstar LA contains a pamoate salt of triptorelin, is a sterile, lyophilized biodegradable microgranule formulation supplied as a single-dose vial containing triptorelin pamoate (11.25 mg as the peptide base); 145 mg poly-D,L -lactide-co-glycolide; 85 mg mannitol, USP; 30 mg carboxymethylcellulose sodium, USP; 2 mg polysorbate 80, NF. When 2 mL sterile water for injection is added to the vial containing Trelstar LA and mixed, a suspension is formed which is intended as an IM injection to be administered every 84 days (i.e., every 12 weeks). Trelstar LA is available in two packaging configurations: (a) Trelstar LA vial alone or (b) Trelstar LA vial plus a separate prefilled syringe that contains sterile water for injection, USP, 2 mL, pH 6 to 8.5 (Clip'n'Ject®). Trelstar depot contains a pamoate salt of triptorelin and triptorelin is a synthetic decapeptide agonist analog of luteinizing hormone-releasing hormone (LHRH or GnRH) with greater potency than the naturally occurring LHRH. Trelstar depot is a sterile, lyophilized biodegradable microgranule formulation supplied as a single-dose vial containing triptorelin pamoate (3.75 mg as the peptide base), 170 mg poly- D, L-lactide-co-glycolide, 85 mg mannitol, USP, 30 mg carboxymethylcellulose sodium, USP, 2 mg polysorbate 80, NF. When 2 mL sterile water for injection is added to the vial containing Trelstar depot and mixed, a suspension is formed which is intended as a monthly IM injection.
- Trisenox® is a sterile injectable solution of arsenic trioxide. Trisenox is available in 10-mL single-use ampoules containing 10 mg of arsenic trioxide. Trisenox is formulated as a sterile, nonpyrogenic, clear solution of arsenic trioxide in water for injection using sodium hydroxide and dilute hydrochloric acid to adjust to pH 8. Trisenox is preservative-free. Arsenic trioxide, the active ingredient, is present at a concentration of 1.0 mg/mL. Inactive ingredients and their respective approximate concentrations are sodium hydroxide (1.2 mg/mL) and hydrochloric acid, which is used to adjust the pH to 7.5 to 8.5.
- Tygacil (tigecycline) is an orange lyophilized powder or cake. Each Tygacil vial contains 50 mg tigecycline lyophilized powder for IV infusion. The product does not contain excipients or preservatives.
- Ultane (sevoflurane) is a clear, colorless liquid containing no additives. Sevoflurane is nonpungent. It is miscible with ethanol, ether, chloroform, and benzene and it is slightly soluble in water. Sevoflurane is stable when stored under normal room lighting conditions according to instructions. Sevoflurane is not corrosive to stainless steel, brass, aluminum, nickel-plated brass, chrome-plated brass, or copper beryllium.
- Vancocin® HCl (vancomycin hydrochloride capsules, USP) contain vancomycin hydrochloride equivalent to 125 mg (0.08 mmol) or 250 mg (0.17 mmol) vancomycin. The capsule also contain FD&C blue No. 2, gelatin, iron oxide, polyethylene glycol, titanium dioxide, and other inactive ingredients.
- Vantas™ (histrelin implant) is a sterile, nonbiodegradable, diffusion-controlled reservoir drug delivery system designed to deliver histrelin continuously for 12 months upon SC implantation. The Vantas implant contains 50 mg of histrelin acetate. The sterile Vantas implant consists of a 50-mg histrelin acetate drug core inside a nonbiodegradable, 3 cm × 3.5 mm cylindrically shaped hydrogel reservoir. The drug core also contains the inactive ingredient stearic acid NF. The hydrogel reservoir is a hydrophilic polymer cartridge composed of 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, trimethylolpropane trimethacrylate, benzoin methyl ether, Perkadox-16, and Triton X-100. The hydrated implant is packaged in a glass vial containing 2 mL of 1.8% NaCl solution. The implant is primed for release of the drug upon insertion.
- Vaprisol (conivaptan hydrochloride injection) is supplied as a sterile liquid in an ampoule. Each ampoule will deliver 20 mg conivaptan hydrochloride, 1.2 g propylene glycol, 0.4 g ethanol, and water for injection, QS. Lactic acid is added for pH adjustment to 3.0.
- Velcade® (bortezomib) for injection is an antineoplastic agent available for IV injection use only. Each single-dose vial contains 3.5 mg of bortezomib as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol, USP. The sol-

ubility of bortezomib, as the monomeric boronic acid, in water is 3.3 to 3.8 mg/mL in a pH range of 2.0 to 6.5.

- Ventavis (iloprost) inhalation solution is a clear, colorless sterile solution containing 10 μg/mL iloprost formulated for inhalation via the Prodose® AAD® (adaptive aerosol delivery) system, a pulmonary drug delivery device. Each single-use glass ampoule contains 2 mL (20 μg) of the solution to be added to the Prodose AAD system medication chamber. Each milliliter of the aqueous solution contains 0.01 mg iloprost, 0.81 mg ethanol, 0.121 mg tromethamine, 9.0 mg sodium chloride, and approximately 0.51 mg hydrochloric acid (for pH adjustment to 8.1) in water for injection. The solution contains no preservatives.
- Vfend® (voriconazole is available as a lyophilized powder for solution for IV infusion, film-coated tablets for oral administration, and as a powder for oral suspension. Vfend IV is a white lyophilized powder containing nominally 200 mg voriconazole and 3200 mg sulfobutyl ether beta-cyclodextrin sodium in a 30-mL type I clear glass vial. Vfend IV is intended for administration by IV infusion. It is a single-dose, unpreserved product. Vials containing 200 mg lyophilized voriconazole are intended for reconstitution with water for injection to produce a solution containing 10 mg/mL Vfend and 160 mg/mL of sulfobutyl ether beta-cyclodextrin sodium. The resultant solution is further diluted prior to administration as an IV infusion.
- Viadur® (leuprolide acetate implant) is a sterile, nonbiodegradable, osmotically driven miniaturized implant designed to deliver leuprolide acetate for 12 months at a controlled rate. Viadur contains 72 mg of leuprolide acetate (equivalent to 65 mg leuprolide free base) dissolved in 104 mg dimethyl sulfoxide. The 4 mm × 45 mm titanium alloy reservoir houses a polyurethane rate-controlling membrane, an elastomeric piston, and a polyethylene diffusion moderator. The reservoir also contains the osmotic tablets, which are not released with the drug formulation. The osmotic tablets are composed of sodium chloride, sodium carboxymethyl cellulose, povidone, magnesium stearate, and sterile water for injection. Polyethylene glycol fills the space between the osmotic tablets and the reservoir. A minute amount of silicone medical fluid is used during manufacture as a lubricant. The weight of the implant is approximately 1.1g.
- Visudyne® (verteporfin for injection) is a light activated drug used in photodynamic therapy. The finished drug product is a lyophilized dark green cake. Verteporfin is a 1:1 mixture of two regioisomers (I and II). Each milliliter of reconstituted Visudyne contains active—verteporfin, 2 mg; Inactives—lactose, egg phosphatidylglycerol, dimyristoyl phosphatidylcholine, ascorbyl palmitate, and butylated hydroxytoluene.
- VISUtein provides 18 mg of lutein, along with 200 mg of *N*-acetyl cysteine and 60 mg anthocyanidins from bilberry. Other ingredients are mixed carotenoids, vitamins A, B_2, and zinc.
- Viva® lubricating eye drops are 1% polysorbate 80 preservative-free in a multidose bottle. It is a patented, nonoily/glycerin free (no blurring of vision) sterile ophthalmic lubricant that is designed to provide instant moisturizing. Inactive ingredients: citric acid, edetate disodium, purified water, sodium chloride and the antioxidants: mannitol, pyruvate, retinyl palmitate, and sodium citrate.
- Vivotif® (typhoid vaccine live oral Ty21a) is a live attenuated vaccine. The lyophilized bacteria are mixed with lactose and magnesium stearate and filled into gelatin capsules which are coated with an organic solution to render them resistant to dissolution in stomach acid. The enteric-coated, salmon/white capsules are then packaged in four-capsule blisters for distribution. The contents of each enteric-coated capsule are viable *Salmonella typhi* Ty21a, 2 to 6 × 10^9 CFU (colony-forming unit); nonviable *S. typhi* Ty21a, 5 to 50 × 10^9 bacterial cells; sucrose, 26 to 130 mg; ascorbic acid, 1 to 5 mg; amino acid mixture, 1.4 to 7 mg; lactose, 100 to 180 mg; magnesium stearate, 3.6 to 4.4 mg.
- Voltaren ophthalmic (diclofenac sodium ophthalmic solution), 0.1%, solution is a sterile, topical, nonsteroidal, anti-inflammatory product for ophthalmic use. Inactive ingredients: polyoxyl 35 castor oil, boric acid, tromethamine, sorbic acid (2 mg/mL), edetate disodium (1 mg/mL), and purified water.
- WinRho® SDF is a sterile, freeze-dried gamma-globulin (IgG) fraction containing antibodies to the Rho (D) antigen (D antigen). The product is stabilized with 0.1 M glycine, 0.04 M sodium chloride, and 0.01% polysorbate 80. It contains no preservative.
- Xigris® [drotrecogin-alpha (activated)] is a recombinant form of human activated protein C. Xigris is supplied as a sterile, lyophilized, white to off-white powder for IV infusion. The 5- and 20-mg vials of Xigris contain 5.3 and 20.8 mg of drotrecogin-alpha (activated), respectively. The 5- and 20-mg vials of Xigris also contain 40.3 and 158.1 mg of sodium chloride, 10.9 and 42.9 mg of sodium citrate, and 31.8 and 124.9 mg of sucrose, respectively.
- Xolair (omalizumab) is a recombinant DNA-derived humanized IgG1(kgr) monoclonal antibody that selectively binds to human immunoglobulin E (IgE). Xolair is a sterile, white, preservative-free, lyophilized powder contained in a single-use vial that is reconstituted with sterile water for injection (SWFI), USP, and administered as an SC injection. A Xolair 75-mg vial contains 129.6 mg of omalizumab, 93.1 mg sucrose, 1.8 mg L-histidine hydrochloride monohydrate, 1.2 mg L-histidine, and 0.3 mg polysorbate 20 and is designed to deliver 75 mg of omalizumab in 0.6 mL after reconstitution with 0.9 mL SWFI, USP. A Xolair 150 mg vial contains 202.5 mg of omalizumab, 145.5 mg sucrose, 2.8 mg L-histidine hydrochloride monohydrate, 1.8 mg L-histidine, and 0.5 mg polysorbate 20, and is designed to deliver 150 mg of omalizumab in 1.2 mL after reconstitution with 1.4 mL SWFI, USP.
- Zaditor™ is a sterile ophthalmic solution containing ketotifen for topical administration to the eyes. Each milliliter of Zaditor contains active—0.345 mg ketotifen fumarate equivalent to 0.25 mg ketotifen. Inactives—glycerol, sodium hydroxide/hydrochloric acid (to adjust pH), and purified water. Preservative: benzalkonium chloride, 0.01%. It has a pH of 4.4 to 5.8 and an osmolality of 210 to 300 mOsm/kg.
- Zeel® injection solution is a combination formulation consisting of five botanical substances, five mineral substances, and four animal-derived substances. Zeel injection solution is officially classified as a homeopathic combination remedy. (1) Botanical ingredients: *Arnica montana*, radix (mountain arnica), Dulcamara (bittersweet), *Rhus toxicodendron* (poison oak), *Sanguinaria canadensis* (blood root), *Symphytum officinale* (comfrey). (2) Mineral ingredients: sulfur, (alpha)-lipoicum acid (thioctic acid), coenzyme A, nadidum (nicotinamide adenine dinucleotide), Natrum oxalaceticum (sodium oxalacetate). (3) Animal-derived ingredients: Cartilago suis (porcine cartilage), Embryo totalis suis (porcine embryo), Funiculus umbilicalis suis (porcine umbilical cord), Placenta suis (porcine placenta). Injection solution: each 2-mL ampoule contains as active ingredi-

ents *Arnica montana*, radix, 4 × 200 μL; *Rhus toxicodendron* 2 × 10 μL; Dulcamara, 3 × 10 μL; *Symphytum officinale*, 6 × 10 μL; sulfur, 6 × 3.6 μL; *Sanguinaria canadensis*, 4 × 3 μL; Cartilago suis, 6 × 2 μL; Embryo totalis suis, 6 × 2 μL; Funiculus umbilicalis suis, 6 × 2 μL; Placenta suis, 6 × 2 μL; coenzyme A, 8 × 2 μL; (alpha)-Lipoicum acidum, 8 × 2 μL; Nadidum, 8 × 2 μL; Natrum oxalaceticum, 8 × 2 μL. Each 2.0 mL ampoule contains as an inactive ingredient sterile isotonic sodium chloride solution.

- Zemaira®, alpha-1 proteinase inhibitor (human), is a sterile, stable, lyophilized preparation of highly purified human alpha-1 proteinase inhibitor (A1-PI), also known as alpha-1 antitrypsin, is supplied as a sterile, white, lyophilized powder to be administered by the IV route. The specific activity of Zemaira ≥0.7 mg of functional A1-PI per milligram of total protein. The purity is ≥90% A1-PI. Following reconstitution with 20 mL of sterile water for injection, USP, each vial contains approximately 1000 mg of functionally active A1-PI, 81 mM sodium, 38 mM chloride, 17 mM phosphate, and 144 mM mannitol. Hydrochloric acid and/or sodium hydroxide may have been added to adjust the pH. Zemaira contains no preservatives. Each vial of Zemaira contains the labeled amount of functionally active A1-PI in milligrams as stated on the vial label as determined by its capacity to neutralize human neutrophil elastase.
- Zemplar® (paricalcitol injection, USP). Each mL contains paricalcitol, USP, 5 μg, propylene glycol, 30% (v/v), and alcohol, 20% (v/v).
- Zevalin (ibritumomab tiuxetan) is ibritumomab, is supplied as two separate and distinctly labeled kits that contain all of the nonradioactive ingredients necessary to produce a single dose of In-111 Zevalin and a single dose of Y-90 Zevalin, both essential components of the Zevalin therapeutic regimen. Each of the two Zevalin kits contains four vials that are used to produce a single dose of either In-111 Zevalin or Y-90 Zevalin, as indicated on the outer container label: One Zevalin vial containing 3.2 mg of ibritumomab tiuxetan in 2 mL of 0.9% sodium chloride solution; a sterile, pyrogen-free, clear, colorless solution that may contain translucent particles; no preservative present. One 50 mM sodium acetate vial containing 13.6 mg of sodium acetate trihydrate in 2 mL of water for injection; a sterile, pyrogen-free, clear, colorless solution; no preservative present. One formulation buffer vial containing 750 mg of albumin (human), 76 mg of sodium chloride, 28 mg of sodium phosphate dibasic dodecahydrate, 4 mg of pentetic acid, 2 mg of potassium phosphate monobasic, and 2 mg of potassium chloride in 10 mL of water for injection adjusted to pH 7.1 with either sodium hydroxide or hydrochloric acid; a sterile, pyrogen-free, clear yellow to amber-colored solution; no preservative present. One empty reaction vial, sterile, pyrogen-free.
- Zithromax (azithromycin for injection) contains the active ingredient azithromycin. Zithromax (azithromycin for injection) is supplied in lyophilized form in a 10-mL vial equivalent to 500 mg of azithromycin for IV administration. Reconstitution, according to label directions, results in approximately 5 mL of Zithromax for IV injection with each milliliter containing azithromycin dihydrate equivalent to 100 mg of azithromycin.
- Zoladex® (goserelin acetate implant) 10.8-mg implant is supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 10.8 mg of goserelin. Zoladex is designed for SC implantation with continuous release over a 12-week period. Goserelin acetate is dispersed in a matrix of D,L-lactic and glycolic acids copolymer (12.82–14.76 mg/dose) containing less than 2% acetic acid and up to 10% goserelin-related substances and presented as a sterile, white to cream-colored 1.5-mm diameter cylinder, preloaded in a special single-use syringe with a 14-gauge × 0.5 mm needle and protective needle sleeve (SafeSystem™ Syringe) in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule. Studies of the D,L-lactic and glycolic acids copolymer have indicated that it is completely biodegradable and has no demonstrable antigenic potential. Zoladex is also supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 3.6 mg of goserelin designed for administration every 28 days. Zoladex is also supplied as a sterile, biodegradable product containing goserelin acetate equivalent to 3.6 mg of goserelin. Zoladex is designed for SC injection with continuous release over a 28-day period. Goserelin acetate is dispersed in a matrix of D,L-lactic and glycolic acids copolymer (13.3–14.3 mg/dose) containing less than 2.5% acetic acid and up to 12% goserelin-related substances and presented as a sterile, white to cream-colored 1-mm diameter cylinder, preloaded in a special single use syringe with a 16-gauge needle × 0.5 mm needle and protective needle sleeve (SafeSystem Syringe) in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule.
- Zometa® contains zoledronic acid. Zometa (zoledronic acid) injection is available in vials as a sterile liquid concentrate solution for IV infusion. Each 5-mL vial contains 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid on an anhydrous basis. Inactive ingredients: mannitol, USP, as bulking agent; water for injection; and sodium citrate, USP, as buffering agent.
- Zosyn (piperacillin and tazobactam for injection) formulation also contains edetate disodium dihydrate (EDTA) and sodium citrate. Each Zosyn 2.25 g single-dose vial or ADD-Vantage vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 2 g of piperacillin and tazobactam sodium equivalent to 0.25 g of tazobactam. The product also contains 0.5 mg of EDTA per vial. Each Zosyn 3.375 g single-dose vial or ADD-Vantage vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 3 g of piperacillin and tazobactam sodium equivalent to 0.375 g of tazobactam. The product also contains 0.75 mg of EDTA per vial. Each Zosyn 4.5 g single-dose vial or ADD-Vantage vial contains an amount of drug sufficient for withdrawal of piperacillin sodium equivalent to 4 g of piperacillin and tazobactam sodium equivalent to 0.5 g of tazobactam. The product also contains 1 mg of EDTA per vial.
- Zylet (loteprednol etabonate and tobramycin ophthalmic suspension) contains (per milliliter) actives—loteprednol etabonate, 5 mg (0.5%), and tobramycin, 3 mg (0.3%); inactives—edetate disodium, glycerin, povidone, purified water, tyloxapol, and benzalkonium chloride 0.01% (preservative). Sulfuric acid and/or sodium hydroxide may be added to adjust the pH to 5.7 to 5.9. The suspension is essentially isotonic with a tonicity of 260 to 320 mOsm/kg.
- Zymar® (gatifloxacin ophthalmic solution), 0.3%, is a sterile ophthalmic solution. Active: gatifloxacin 0.3% (3 mg/mL). Preservative: benzalkonium chloride, 0.005%. Inactives: edetate disodium, purified water, and sodium chloride. May contain hydrochloric acid and/or sodium

hydroxide to adjust pH to approximately 6. Zymar is a sterile, clear, pale yellow colored isotonic unbuffered solution. It has an osmolality of 260 to 330 mOsm/kg.

- Zyprexa IM (olanzapine for injection) is intended for IM use only. Each vial provides for the administration of 10 mg (32 μmol) olanzapine with inactive ingredients 50 mg lactose monohydrate and 3.5 mg tartaric acid. Hydrochloric acid and/or sodium hydroxide may have been added during manufacturing to adjust pH.

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Pharmaceutical Science

about the book...

No other area of regulatory compliance receives more attention and scrutiny by regulatory authorities than the regulation of sterile products, for obvious reasons. With the increasing number of potent products, particularly the new line of small protein products, joining the long list of proven sterile products, the technology of manufacturing sterile products has evolved into a very sophisticated industry.

Highlights from ***Sterile Products, Volume Six*** include:

- formulations of sterile dosage forms, regulatory filing requirements of sterile preparations, and cGMP compliance, all of which are tied together in the final preparation of the CMC sections of regulatory applications
- specifications of a manufacturing facility to manufacture compliant sterile products
- NDA or aNDA filing requirements of sterile products
- an alphabetical presentation of formulations of pharmaceutical products based on their generic names

about the author...

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